

**ENVIRONMENTALLY BENIGN SOLVENT SYSTEMS: TOWARD A GREENER [4+2]
CYCLOADDITION PROCESS**

by

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I would like to dedicate this work to the happiness and welfare of all sentient beings.

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Abstract

Green chemistry is a field that encompasses a wide range of environmentally benign technologies. This review discusses the principles of green chemistry, as well as recent applications of these principles to the Diels-Alder reaction with a focus on benign solvent systems. Specifically, Diels-Alder reactions in water, ionic liquids, supercritical carbon dioxide, and solvent-free systems will be reviewed up to February 2006.

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ABBREVIATIONS

Boc ₂ O	di- <i>tert</i> -butyl dicarbonate
bmim ⁺	1-butyl-3-methylimidazolium
[bmim][BF ₄]	1-butyl-3-methylimidazolium tetrafluoroborate
[bm ₂ im][BF ₄]	1-butyl-2,3-dimethylimidazolium tetrafluoroborate
[bmim][Cl]	1-butyl-3-methylimidazolium chloride
[bmim][OTf]	1-butyl-3-methylimidazolium triflate
[bmim][PF ₆]	1-butyl-3-methylimidazolium hexafluorophosphate
CPD	cyclopentadiene
DDQ	2,3-dichloro-5,6-dicyano- <i>p</i> -benzoquinone
DEAD	diethyl azodicarboxylate
[DiBuIm][BF ₄]	1,3-dibutylimidazolium tetrafluoroborate
DMU	dimethylurea
EAN	ethylammonium nitrate
[EMIC]AlCl ₃	1-ethyl-3-methyl-1 <i>H</i> -imidazolium aluminum trichloride
emim ⁺	1-ethyl-3-methylimidazolium
Fur	furanyl
[HMI][BF ₄]	1-hexyl-3-methylimidazolium tetrafluoroborate
[HO(CH ₂) ₂ mim][N(Tf) ₂]	1-(2-hydroxyethyl)-3-methylimidazolium triflamide
LiOPf	lithium heptadecafluorooctanesulfonate

MW	microwave
Py	pyridinyl
Py ⁺	pyridinium
Sc	supercritical

1.0 INTRODUCTION

Technological advancement often comes with costs, and in the case of the chemical industries a significant share of those costs originates from the production of waste, for chemical waste must be handled and disposed of with care and insight.¹ The aforementioned context of ‘cost’ implies an economic burden for companies that produce excessive waste. This burden is indeed large for U.S. industries, which spend about 100 to 150 billion dollars a year to adhere to environmental regulations.²

But it would be unwise to disregard the other, eventually more important side of the waste issue, and that is the considerably negative impact that chemical wastes have on our precious environment. Of course environmental problems are not solely the result of the chemical industries, but chemical industries must take some responsibility. For example, according to the United States EPA of the 4.44 billion pounds of waste disposed of or released in the United States in 2003, 12% originated from the chemical sector. This is a significant amount.³

Clearly chemist’s play a substantial role, and in doing so must share in the duty of considering the environmental consequences of their technologies. This includes developing ways to confront the waste problem. Throughout history there have been three general approaches to dealing with this issue.¹ In the middle of the twentieth century, before the

environmental impact of the chemical industries was seriously considered, waste was simply diluted and released. The near-sightedness of this practice became evident over the next 30 years with the rise of environmental issues such as pesticide bioaccumulation, as well as catastrophes like those at the towns of Times Beach and Love Canal.^{1,4} Waste can also be treated and then released into the environment. Emissions cleaned via smoke stack scrubbers, for example, or acids neutralized. Such an approach is a great improvement, though it still suffers from costs associated with handling and disposing of waste (*vide supra*). The third and most efficient strategy for dealing with waste is also the most obvious—don't generate it!

This last approach is the foundational pillar of a movement within the chemical sciences that originated in the early 1990s. Its name is *green chemistry*. The chemists Paul Anastas and John Warner have laid down its philosophy in 12 principles (Figure 1).^{1,5}

1. Prevention is the best policy
2. Utilize syntheses of high atom economy
3. Design less hazardous chemical syntheses (i.e. reagents and products should have little to no toxicity)
4. Design products to have little to no toxicity
5. Eliminate solvents and auxiliaries whenever possible, or else utilize safer solvents and auxiliaries
6. Design syntheses to be energy efficient
7. Use renewable feedstocks
8. Eliminate or reduce the use of derivatives (i.e. protecting groups)
9. Design catalytic versions of reactions whenever possible
10. Design products that break down into environmentally innocuous chemicals
11. Use analytical methodologies to monitor chemical reactions
12. Design safer chemical syntheses (i.e. avoiding explosions or fires)

Figure 1. The 12 principles of green chemistry.

Taken together, these principles tell us that chemistry should be efficient, non-wasteful, and non-hazardous. Instead of producing unwanted and hazardous materials, only to expend energy in dealing with them at a later point in time, every effort should be taken to circumvent their appearance from the very beginning. While our discussion thus far has concerned only waste, note that green chemistry addresses all environmental implications of synthetic processes, from bioavailability of starting materials, to energy efficiency, to biodegradability of products. For detailed elaborations of the twelve principles the reader is encouraged to reference Anasta's and Warner's book, *Green Chemistry: Theory and Practice*.¹

The 12 principles provide a blueprint for the design of new chemical technologies. Much like a blueprint for a home or office building the principles are very precise. They are also very demanding, though in a very positive way as strict guidelines are often needed for progress. Ideally, chemists should embrace each of these principles and adopt them to the fullest extent. They very much suit the synthetic community, though other areas of chemistry, including polymer science and analytical chemistry, can and do make use of the green philosophy.⁶

For synthetic chemistry assimilation of these principles needs to happen in both academia and industry. In fact, for green chemistry to have a significant impact it *must* be practiced in industry;⁵ the previously mentioned statistics concerning waste generation by industry serve well to highlight this point.² Synthetic chemists at the university level may design their routes with the green chemistry philosophy in mind, but without proper thought given to scale up and industrial application significant change can never be made.

To help overcome the aforementioned obstacle Neil Winterton has proposed 12 additional principles of green chemistry (Figure 2).⁷ These are designed to lessen the gap between academic and industrial green chemistry, to allow for a smoother transition between

research and practice. Some of the principles are very similar to those laid out by Anastas and Warner while others (i.e. principles 4-7, 10, 11) act like the conscience of the chemist, forcing the researcher to gather data concerning the scalability and applicability of his or her reactions.

1. Identify and quantify by-products
2. Report conversions, selectivities and productivities
3. Establish full mass-balance for processes
4. Measure catalyst and solvent losses in air and aqueous effluent
5. Investigate basic thermochemistry
6. Anticipate heat and mass transfer limitations
7. Consult a chemical or process engineer
8. Consider the effect of overall process on choice of chemistry
9. Help develop and apply sustainability measures
10. Quantify and minimize use of utilities
11. Recognize where safety and waste minimization are incompatible
12. Monitor, report and minimize laboratory waste emitted

Figure 2. 12 additional principles of green chemistry.

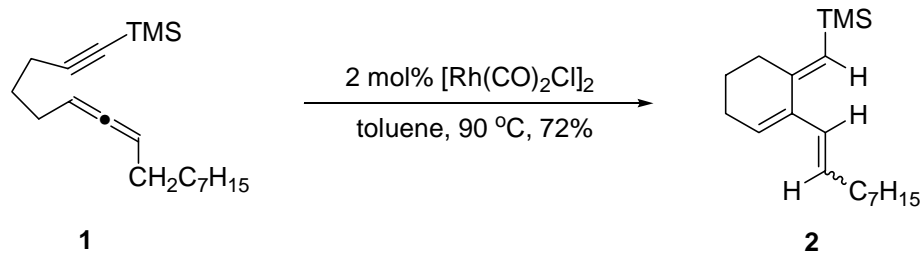
As mentioned before, the principles of green chemistry are precise and demanding. Is it possible to design a synthetic process that meets all of these requirements, both on the academic and industrial level? From the green chemist's point of view such a reaction would be perfect, yet intuition tells us that this is a very tall order. First, all of the principles would have to fall into place. Second, the reaction must be cost-efficient. For industry this is a very important concern; a company can develop a green reaction but can't use it if they lose money in the process. Thus in designing green processes there is a trade-off between what is the best for the environment and what is feasible, both from a chemical and economic viewpoint. As a result

many reactions that fall under the category of green chemistry do not follow every principle and are not 100% green.

Bearing these factors in mind, there are many things to consider when designing a green synthetic process, and to help determine what reactions are the best candidates for green processes it is useful to consider what classes of reactions are inherently green. One criterion for inherent greenness is atom economy. Simply put, an atom economical reaction is one in which most, if not all, of the molecular weight of the reactants ends up in the products.⁸ Note that this definition precludes loss of mass via incomplete conversion or decomposition, and thus is applied without consideration of chemical yield. In other words a reaction can yield less than 100% of products and still be highly atom economical.

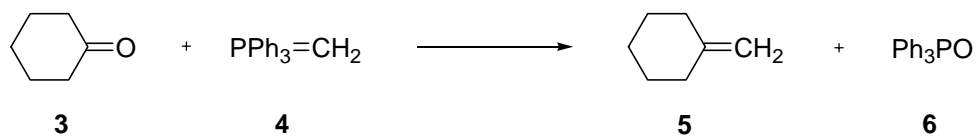
The definition also precludes the notion of a reaction medium, and this is quite significant. Most chemical reactions are performed in a solvent. The concentrations of reactants are typically so low that solvent molecules far outnumber substrate molecules. In the end solvents are discarded as waste, so that when viewed from this perspective no solvated reaction comes close to being atom economical.

A 100% atom economical reaction is one in which every atom of reactant becomes incorporated into the product. Rearrangement reactions are good examples of completely atom economical processes; the bonds in the reactants are simply broken and reassembled differently and no atoms are lost to unwanted products. Our group has provided an example of this with the development of a rhodium(I) catalyzed allenic alder ene reaction (Scheme 1).⁹



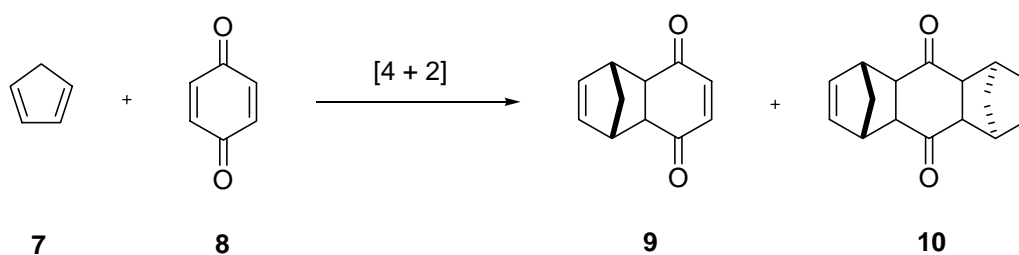
Scheme 1

Bonds in substrate **1** are broken and formed to give a cross conjugated triene **2**, but no molecular weight is lost to side products. The fact that this reaction is catalyzed makes it particularly environmentally friendly. Compare this reaction to the notoriously wasteful Wittig reaction (Scheme 2), where only 17% of the reactant mass is incorporated into the product **5**. The remaining mass is lost as useless triphenylphosphine oxide (**6**).^{1,8}



Scheme 2

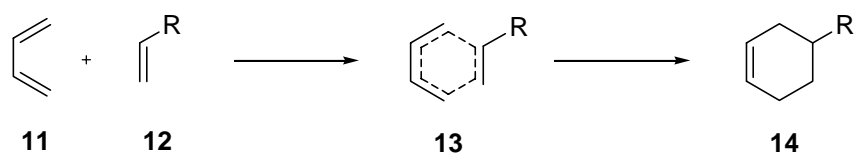
There are other classes of completely atom economical reactions. Included among these are the cycloaddition reactions. The focus of the following review is on the most famous of cycloaddition processes, the [4 + 2] cycloaddition reaction, also commonly known as the Diels-Alder reaction. The history of this reaction goes back over 100 years, but credit for its discovery can be traced to 1928 when the German chemists Otto Diels and Kurt Alder published the seminal article “Synthesen in der hydroaromatischen Reihe” in the journal *Annalen der Chemie*.^{10,11} The reaction studied by Diels and Alder is depicted in Scheme 3.



Scheme 3

Product **9** is a result of one molecule of CPD (**7**) reacting with one molecule of quinone (**8**). Product **10** is a result of two molecules of CPD reacting with one molecule of quinone. In either case we can see how the process is 100% atom economical; all of the reacting atoms ending up in the products.

Scheme 4 presents a stripped-down view of the Diels-Alder reaction, making it easy to appreciate the simplicity of the process.¹² At the outset there is a conjugated 1,3-diene **11** and an alkene **12** (the dienophile). These two come together in a concerted manner, meaning that all bonds are broken and formed at the same time, and that there is no intermediate and only one transition state **13**.^{12,13} The final product is ring **14** with up to four possible stereocenters. The formal classification given to the Diels-Alder reaction denotes either how many atoms are reacting or how many pi electrons are reacting.^{12,13}



Scheme 4

In other words, with regard to the diene four atoms are involved, and with regard to the dienophile there are two atoms reacting, hence the classification [4 + 2]. It is also equally correct to say that four pi electrons from the diene are reacting with two pi electrons from the dienophile, resulting in the same classification.

The Diels-Alder reaction starts out with two very simple substrates and furnishes products of potentially high complexity. The ability to assemble a six-membered ring with four stereocenters in one reaction makes this process extremely useful; nobody can deny this fact, and for those who seek evidence they need only glance at the number of biologically relevant

molecules that contain six-membered rings, or the number of complex natural product synthesis involving the reaction.¹⁴ The significance of the Diels-Alder reaction was recognized early on, as Otto Diels and Kurt Alder received the Nobel Prize in chemistry for their discovery in 1950.¹⁵

As it turns out, the ability of the Diels-Alder reaction to set four stereocenters in its products is both a blessing and a bane, for these stereocenters are not always easily controlled. A Diels-Alder reaction will typically yield a mixture of two products, an *endo* isomer and an *exo* isomer. Figure 3 gives a representation of these two types of products.¹²

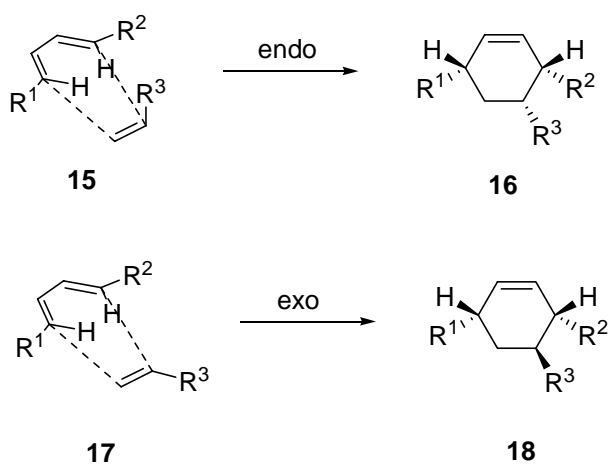
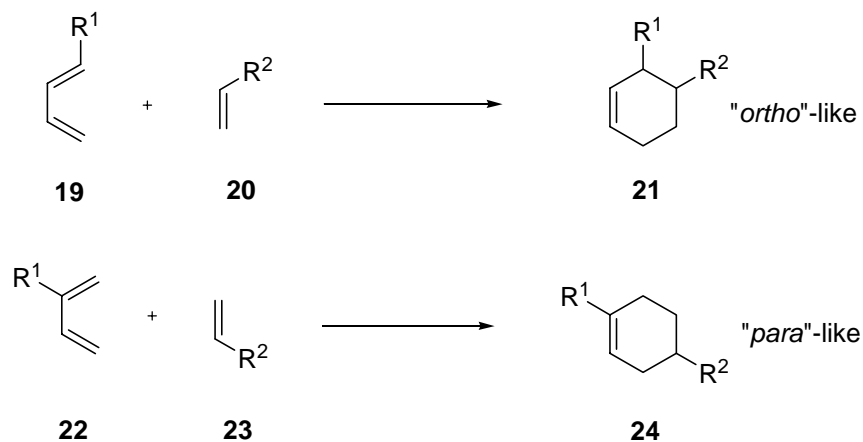


Figure 3. *Endo* and *exo* products resulting from the Diels-Alder reaction.

The *endo* product **16**, which is typically favored in most Diels-Alder reactions, includes all R groups on the same side of the molecule. The *exo* product **18** has R³ opposite the other R groups.¹² Much work has gone into the study of *endo/exo* selectivity in the Diels-Alder reaction.

In addition to issues of stereochemistry, issues of regiochemistry come into play when un-symmetrical dienes are used (Scheme 5).¹² In this case two types of adducts are possible. Adduct **21**, with R¹ and R² adjacent to each other, is called the “ortho”-like product.

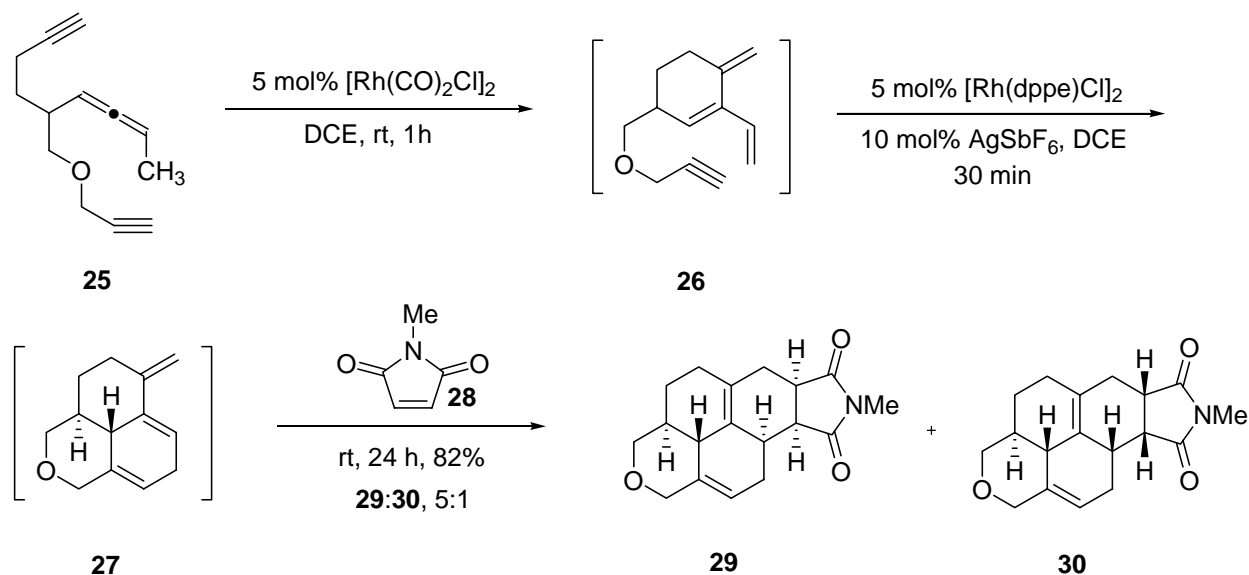


Scheme 5

Adduct **24**, with R¹ and R² opposite each other, is known as the “para”-like product. We will come across such issues of regiochemistry later on.

Considerable effort has been devoted to understanding and controlling the regio- and stereochemistry of the Diels-Alder reaction. As such the process remains extremely useful and is most worthy of a niche within the world of green chemistry. Accordingly, it has been afforded one. There are several ways to make the Diels-Alder reaction more environmentally friendly. Recent work in our group showcases the benefits of transition metal catalysis (Scheme 6).¹⁶ In a one pot, three step procedure, substrate **25** is treated with [Rh(CO)₂Cl]₂ to give cross conjugated

triene **26**. $[\text{Rh}(\text{dppf})\text{Cl}]_2$ and AgSbF_6 then catalyze a Diels-Alder reaction. The addition of *N*-methylmaleimide **28** affects another cycloaddition to give the products **29** and **30**. The entire process encompasses green principles 1, 2, 6, and 9 by virtue of minimizing solvent usage, being highly atom efficient, minimizing energy usage, and utilizing catalysis.



Scheme 6

There are numerous other examples of green Diels-Alder processes. It is the aim of this paper to review some of these reactions. Since green processes are rarely 100 percent so, it follows that many are green only by degree, with some adhering more to the green philosophy than others. An important task is therefore to define ‘green’ for the present application. To limit

the scope of this project to a reasonable size we will adopt green principle 5 as our base definition. The focus will therefore be placed upon Diels-Alder reactions that eliminate solvents when possible or otherwise use benign solvents.

Other green chemistry principles will be considered as well, specifically the issues of safety, atom economy, and energy efficiency. These have all been used as criteria for deciding which reactions to include and which to leave out, and when such aspects of the reactions discussed herein warrant attention, those aspects are elaborated upon and used as an evaluation of overall greenness. This review will discuss developments in solvent-free Diels-Alder chemistry, Diels-Alder chemistry performed in ionic liquids, Diels-Alder chemistry performed in water, and Diels-Alder chemistry performed in supercritical CO₂.

2.0 SOLVENT-FREE DIELS-ALDER REACTIONS

Common organic solvents (benzene, CH₂Cl₂, acetonitrile, THF), while providing excellent environments for the majority of organic reactions, are nevertheless toxic and harmful to the environment. Replacing them with benign solvents is a major step in designing greener reactions. Yet performing reactions without the use of any solvent is optimal, as two principles of the green chemistry philosophy are addressed instead of just one—harmful materials are eliminated *and* the reactions are more atom economical. As early as 1966 the Diels-Alder reaction has been run with success in a solvent-free environment.¹⁷ After the realization in 1986 that microwaves are a viable energy source for synthetic chemistry, chemists also realized that solvent-free Diels-Alder reactions could benefit from this technology;¹⁸ below we will see many examples of such reactions performed in the microwave oven.

Care must be taken with the term ‘solvent-free.’ By definition this term does not apply to the entirety of the chemical processes described below. The reactions are solvent-free only in that solvents are not used during the desired chemical transformations; solvents are applied at other times, most often during the work-up of the reactions, or occasionally before the reactions are initiated. This latter application of solvents concerns us especially when reactants are

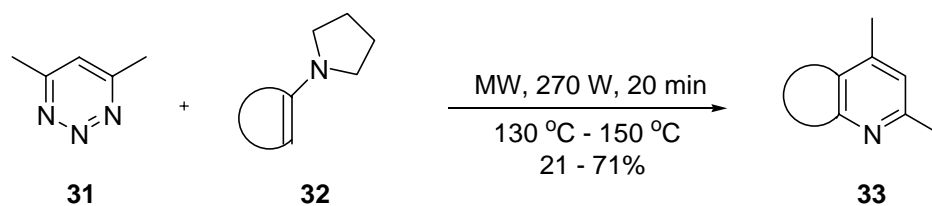
adsorbed onto a solid surface such as silica gel or alumina. Still, even if solvent-free reactions are not 100 percent so they undoubtedly represent green technologies as solvent usage is reduced.

2.1 NEAT DIELS-ALDER REACTIONS

2.1.1 Synthesis of Pyridines

Pyridines have been of interest to synthetic chemists for over 100 years.¹⁹ Thus, a large and varied pool of methods to prepare these types of compounds is at the chemist's disposal. Of the many ways to prepare the pyridine skeleton, methods utilizing inverse-electron-demand Diels-Alder reactions of triazenes are very amenable to green synthesis. Both 1,2,3-triazenes and 1,2,4-triazenes react with enamines in this fashion. Using neat conditions and microwave irradiation provides a particularly green route to these heterocycles.

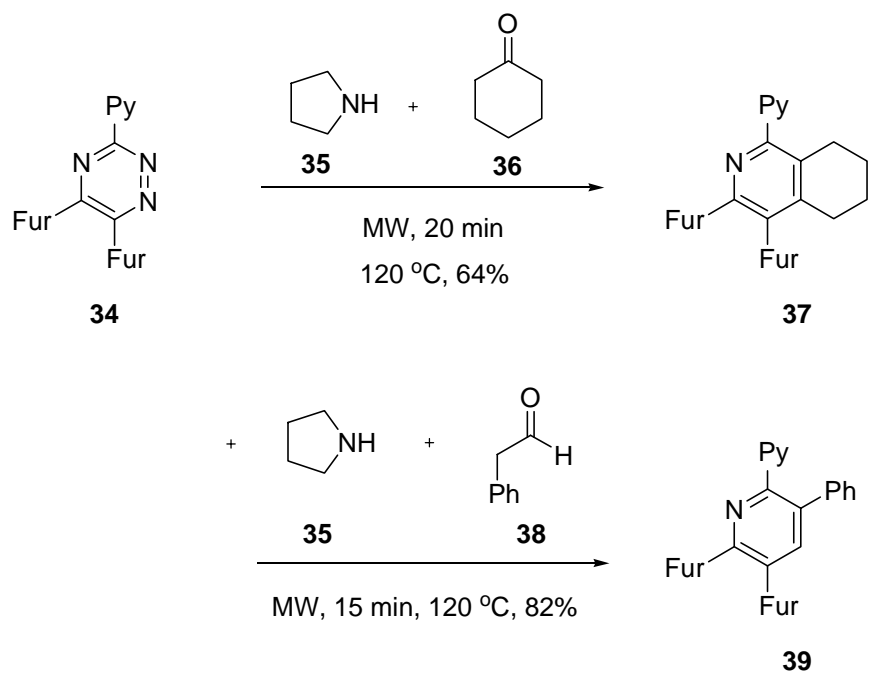
Díaz-Ortiz and coworkers have performed the Diels-Alder reactions of 4,6-dimethyl-1,2,3-triazene **31** with a variety of enamines **32** under microwave irradiation to give the corresponding pyridines **33** (Scheme 7).²⁰ The yields of products ranged from poor to good and these microwave conditions are an improvement over classical conditions, which give much lower yields (0 – 27%).²¹ For some cases, the authors successfully effected *in situ* formation of the enamines under the microwave conditions, though product yields were generally lower when compared to reactions with pre-formed enamines.



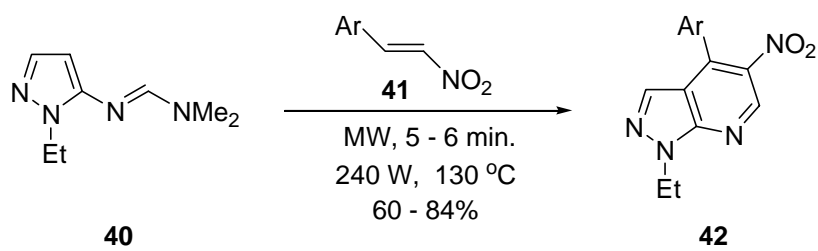
Scheme 7

The *in situ* formation of enamines has also been used as a strategy in the preparation of pyridines by Sainz and coworkers, who utilized inverse-electron-demand Diels-Alder reactions of 1,2,4-triazenes.¹⁹ Pyrrolidine (**35**) was used as it was found that cyclic amines worked better than acyclic amines (Scheme 8). And, once again the benefits of microwave irradiation are evident; considering cyclohexanone (**36**) as a substrate, prolonged heating with pyrrolidine and triazene **34** under classical conditions (96 h) affords only 25% of the desired product **37**. Microwave irradiation affords this cycloadduct in 64% yield in only 20 minutes. Unsymmetrical dienophiles react with triazenes with moderate to high regioselectivity, as is illustrated by the completely selective production of pyridine **39**.

Pyrazolo[3,4-*b*]pyridines have been prepared in moderate to good yields from the Diels-Alder reactions of pyrazolyl imine **40** and aromatic nitroalkenes **41**.²² Pyrazolyl imines such as compound **40** are typically difficult substrates to use in Diels-Alder cycloadditions because the molecules lose aromaticity upon reacting.^{22c} Díaz-Ortiz and coworkers overcame this obstacle with the application of microwave energy, becoming the first to successfully perform such reactions. The reaction gives only products **42** when Ar = 2-thienyl; in other instances small amounts of nitro-free product (8-9%) are observed (Scheme 9).

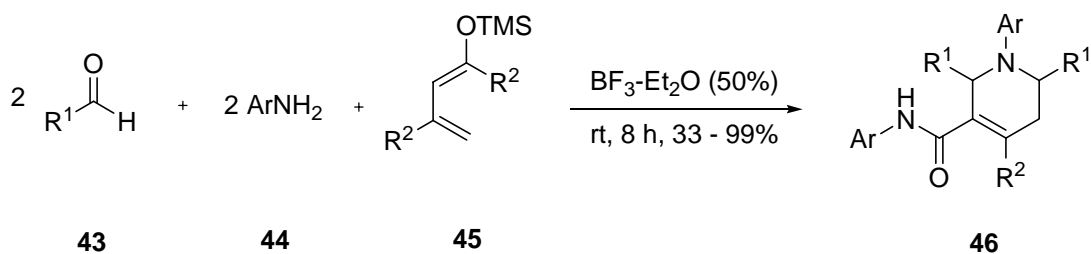


Scheme 8



Scheme 9

For their roles in active natural products and pharmaceuticals,²³ tetrahydropyridines are also of interest to the synthetic chemist, and like their unsaturated counterparts these systems are available via Diels-Alder cycloadditions. One green route towards tetrahydropyridines involves a three-component process and was performed by Xiao and coworkers.²⁴ The process is simple, as aromatic aldehydes **43**, anilines **44**, and Brassard's type dienes **45** are mixed together for 8 hours (Scheme **10**). Aldehydes with electron donating substituents give the highest yields for this reaction. The process is catalyzed by BF₃-Et₂O and is not solely a [4 + 2] cycloaddition, but rather an aldol condensation followed by an aza Diels-Alder reaction. In addition, it can be performed on gram scale while still maintaining a respectable yield (62% with benzaldehyde). In light of the green philosophy, such readily scalable processes are of great value.

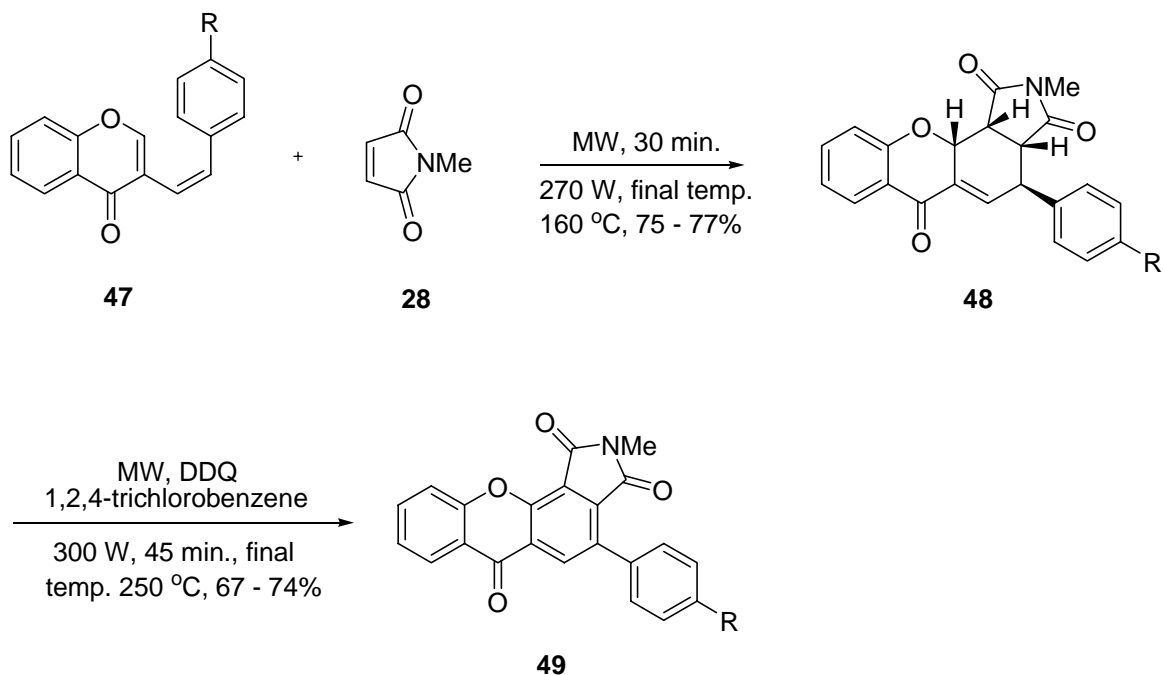


Scheme 10

2.1.2 Synthesis of Xanthenes

Silva and coworkers have studied microwave assisted Diels-Alder reactions of 3-styrylchromones, an important family of naturally occurring compounds, as a means of preparing

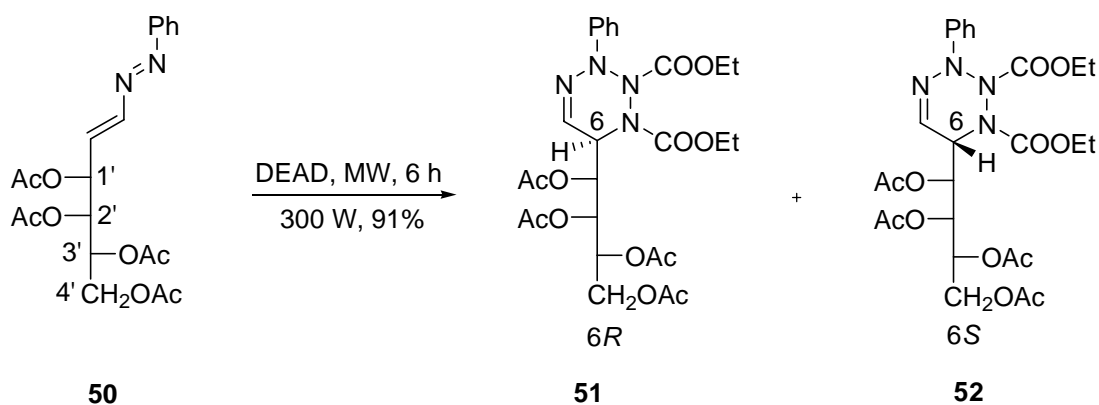
xanthone-type compounds (Scheme 11).²⁵ 3-Styrylchromones **47** react with *N*-methylmaleimide with complete stereoselectivity, giving *endo* cycloadducts **48** when (*Z*)-3-styrylchromones are used and *exo* cycloadducts when the *E* isomers are used. To oxidize the cycloadducts to the requisite xanthenes **49** DDQ must be added, unless 2-(2-nitrovinyl)thiophene is used as the dienophile, in which case oxidation takes place *in situ*, directly after the cycloaddition. At temperatures of 160 °C or more (*Z*)-3-styrylchromones can isomerize to the *E* isomers, and as a result selectivities break down; for instance, cycloadditions with the less reactive *N*-phenylmaleimide take place at high temperatures (200 °C) and always lead to mixtures of *endo* and *exo* isomers.



Scheme 11

2.1.3 Synthesis of Tetrazines

Avalos and coworkers have shown that enantiopure 1,2,3,6-tetrahydro-1,2,3,4-tetrazines are available via microwave induced aza Diels-Alder reactions of sugar derived, chiral 1-aryl-1,2-diaza-1,3-butadienes (Scheme 12).²⁶ The dienes are reacted with DEAD to give the corresponding hetero-Diels-Alder cycloadducts in good to excellent yields (87 – 96%) and good diastereoselectivities.

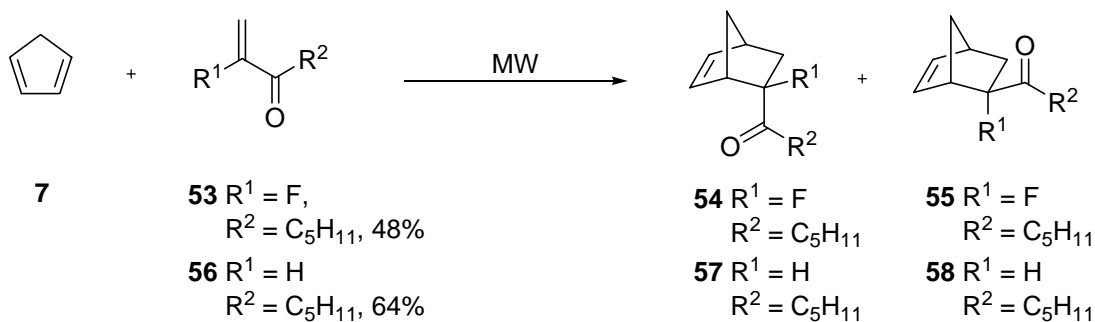


Scheme 12

Butadienes with a *threo* configuration at C-1'2' give diastereoselectivities in the range of 5.25:1 to 7.3:1 (*6R*:*6S*). Diastereomeric ratios are lower, however, when butadienes with an *erythro* configuration at C-1'2' are used, as shown in the formation of **51** and **52** (2:1, respectively).

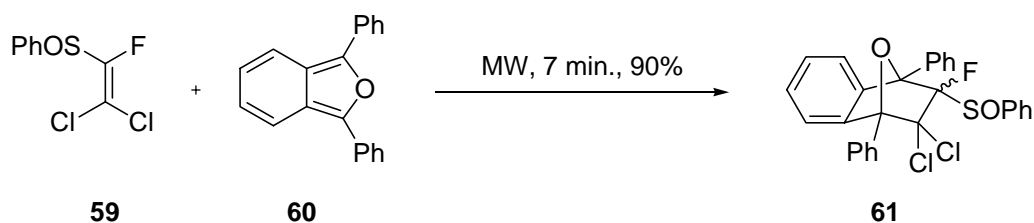
2.1.4 Diels-Alder Reactions of Fluorinated Compounds

Essers and coworkers have shown that Fluorine can have an influential effect on the course of a Diels-Alder reaction, especially in terms of stereoselectivity.²⁷ The authors reacted CPD with various α -fluorinated α,β -unsaturated carbonyl compounds, resulting in stereoselectivities that were governed by the presence of fluorine (Scheme 13). The reaction of CPD with **53** gave products that favored *exo* isomer **55** (**55:54**, 3.5:1), and for the reaction of dienophile **56** the *endo* cycloadduct **57** predominated (**57:58**, 3.8:1). Calculations (B3LYP/6-31G, R² = CH₃) showed both the acetyl and halogen groups to thermodynamically favor *exo* orientation; the stereoselectivity is thus attributed to kinetic effects resulting from fluorine substitution.



Scheme 13

Mono-fluorinated vinyl sulfoxides are also good dienophiles for solvent-free, Diels-Alder reactions (Scheme 14).²⁸ When vinyl sulfoxide **59** is reacted with 1,3-diphenylisobenzofuran (**60**), the resulting Diels-Alder adduct **61** is afforded in 90% yield. 1,2-difluoro vinyl sulfoxides work equally well under the same conditions.



Scheme 14

2.2 HETEROGENEOUS CATALYSIS AND DIELS-ALDER REACTIONS

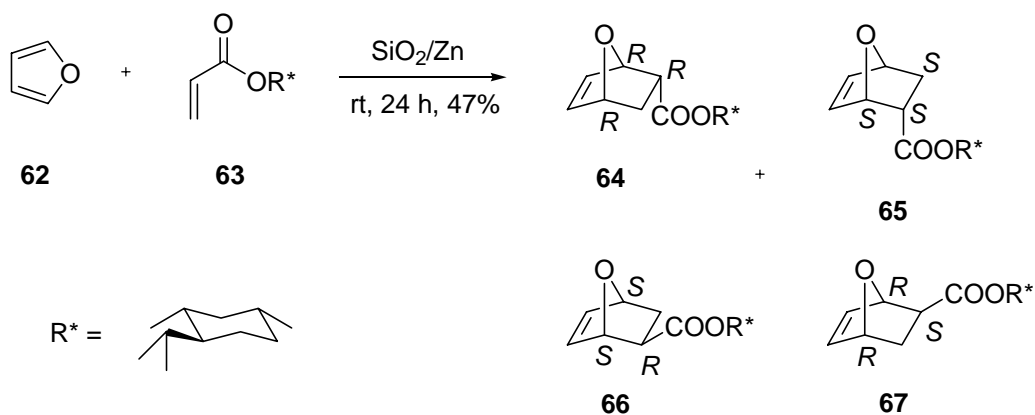
It is widely known that acids catalyze the Diels-Alder reaction. We can group such catalysts into two major categories: homogeneous and heterogeneous systems. Of the two, the latter are more environmentally friendly. The catalysts are in a separate phase, so that their separation from the product is easier and doesn't require the hazardous-waste producing water quench typical of

homogeneous systems. The catalysts are also often milder, more selective, and reusable so that atom economy is high.²⁹ Silica gel, alumina, and clay are popular catalysts for solvent-free systems. These will be discussed below.

2.2.1 Diels-Alder Reactions of Furan, Cyclopentadiene, and Other Simple Substrates

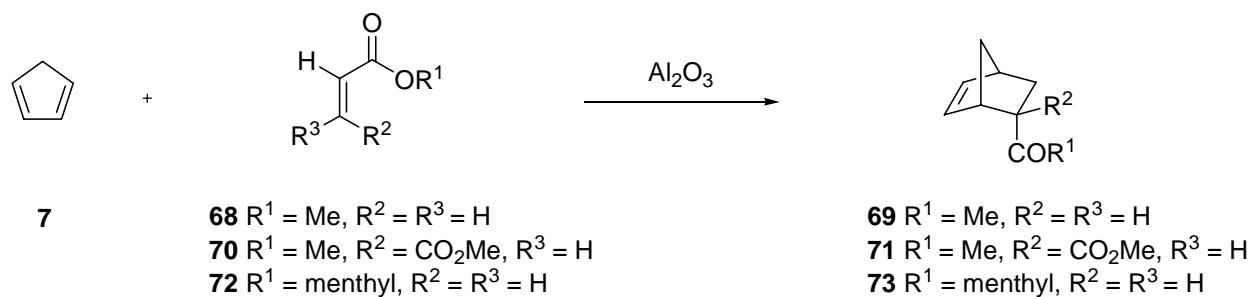
Caple and coworkers were the first to perform solvent-free Diels-Alder reactions adsorbed onto silica gel.³⁰ The starting materials were simple (e.g. butadiene and acrolein), and by applying the reactants to the solid support they prepared a variety of adducts in good to excellent yields. Reactions of CPD with methylvinyl ketone, acrolein, or methacrolein at -20 °C afforded 90% yields of the corresponding bicycles.

Lewis acids can be immobilized onto silica gel and subsequently used to catalyze a variety of Diels-Alder reactions. The catalysts are prepared by treating silica gel with an aqueous solution of the desired Lewis acid, followed by drying and activation. Such solid catalysts have been used successfully with the Diels-Alder reactions of furan (**62**) and various chiral acrylates, as shown by Fraile and coworkers (Scheme **15**).³¹ SiO₂/Zn is the best catalyst for the reaction between furan and (1*R*,2*S*,5*R*)-menthyl acrylate (**63**). Unfortunately the reaction is slow, requiring 24 hours until completion, and the stereoselectivity is low, affording a 1:1 mixture of *endo* (26% de in favor of **64**) and *exo* (8% de in favor of **66**) isomers in 47% yield. The yield of this reaction can be increased to 82% by using SiO₂/Ti, but only if 10 equivalents of furan are used. Thus, the greenness of the reaction is decreased considerably as furan is a waste by-product that is not recovered.



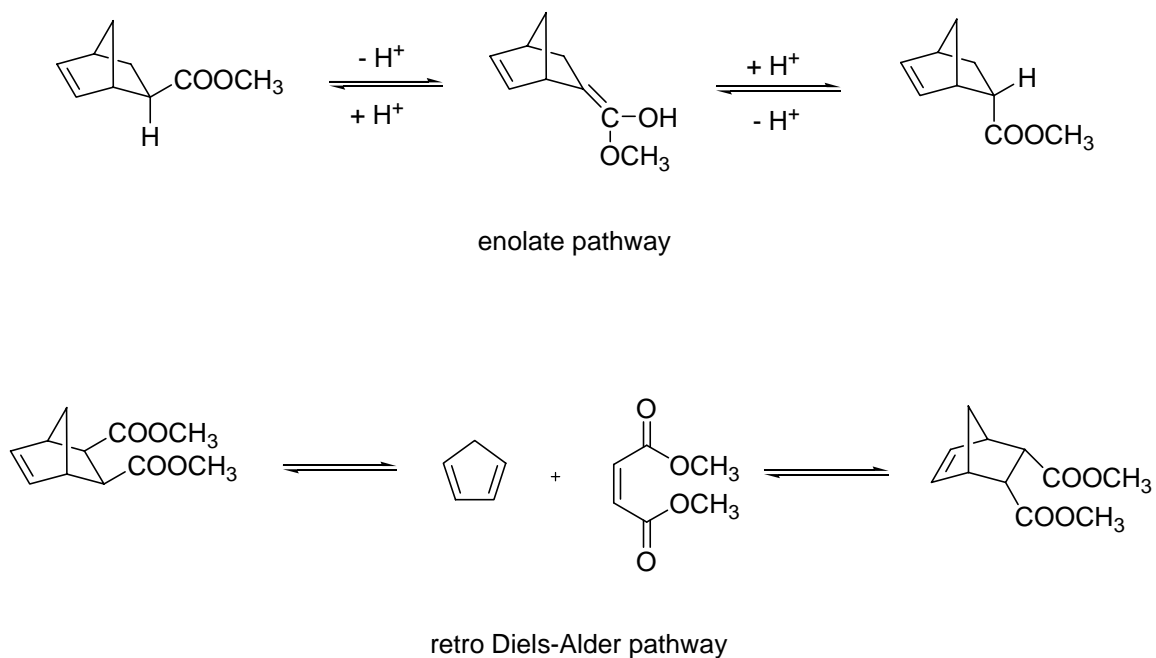
Scheme 15

A great deal of time has been spent on studying the Diels-Alder reactions between CPD, methyl acrylate **68**, and dimethyl maleate/dimethyl fumarate **70**, as well as Diels-Alder reactions between CPD and optically active menthyl acrylate **72**, dimethyl fumarate, and menthyl methyl fumarate, all on alumina and under solvent-free conditions (Scheme **16**).³²



Scheme 16

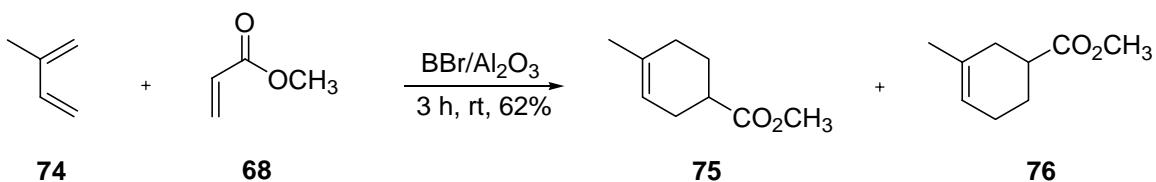
For the aforementioned reactions, *endo* selectivities are dependent upon the activation of the alumina. Activating alumina is a simple process involving the application of heat to remove water and expose Al^{3+} cations. In the cases of methyl acrylate **68** and menthyl acrylate **72**, activating the alumina at successively higher temperatures leads to increased *endo* selectivity. The trend is not completely linear, though; while alumina activated at 400 °C leads to good selectivity for the conversion of **72** to **73** (*endo:exo*, 9.0:1), alumina activated at 800 °C leads to a large decrease in selectivity for the same reaction (*endo:exo*, 3.2:1).^{32b} The more activated alumina causes epimerization of the adducts in two ways: via a retro-Diels-Alder pathway, in which CPD and the dienophile are reformed and then react to give the *exo* isomer, and enolate chemistry, which occurs for dimethyl maleate/fumarate **70** on alumina activated at 700 °C (Scheme 17).^{32e}



Scheme 17

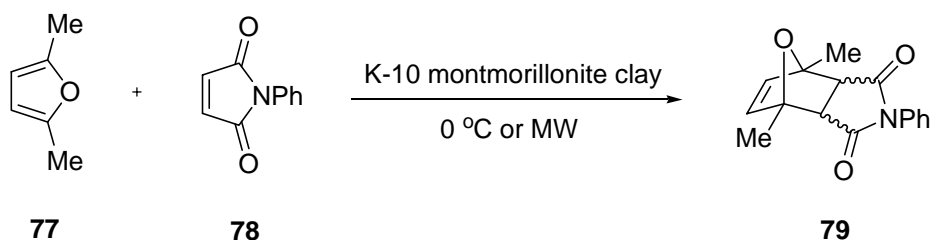
The observed *endo:exo* distribution is also effected by the weight ratio of alumina to reactants. For example, at ratios of less than or equal to 0.4:1 (unactivated alumina:reactants), adduct **69** is formed as a 2.9:1 ratio of *endo* and *exo* isomers, respectively.^{32e} Lower reactant loadings (5:1 – 10:1) lead to successively higher diastereoselectivities (*endo:exo*, 4.2:1 – 5.8:1) because more of the reactant is exposed to the catalyst.

The reaction between isoprene (**74**) and methyl acrylate has been studied by McGinnis and coworkers using a boronated alumina as the heterogeneous catalyst (Scheme **18**).³³ The authors achieved a 56:1 mixture of **75** and **76**, respectively, in 62% yield. The uncatalyzed, neat reaction gave a drastically reduced selectivity (**75:76**, 2.5:1).



Scheme 18

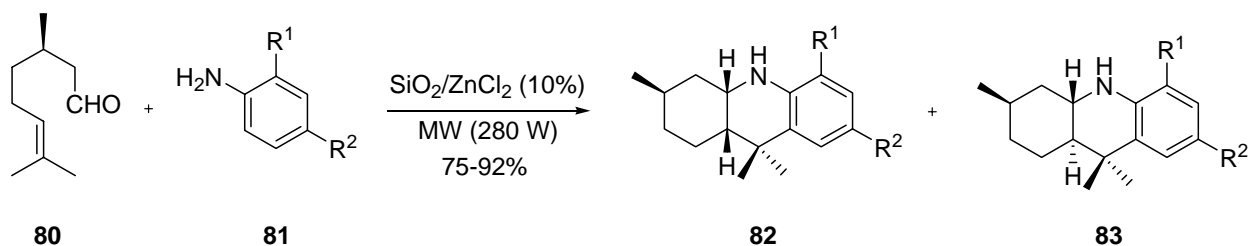
Avalos and coworkers have looked at the reaction between 2,5-dimethylfuran (**77**) and *N*-phenylmaleimide **78** on K-10 montmorillonite clay (Scheme **19**).³⁴ Reacting for 1.5 hours at 0 °C affords **79** as a 2.3:1 mixture of *endo* and *exo* isomers, respectively, in 77% yield. Microwave irradiation (300 W) for 10 minutes affords a quantitative yield of *endo* and *exo* isomers in the same ratio.



Scheme 19

2.2.2 Synthesis of Octahydroacridines

SiO_2/Zn catalyzes a green route to the class of gastric acid secretion inhibitors known as octahydroacridines (Scheme 20).³⁵ Jacob and coworkers have reacted citronellal (**80**) with several aromatic amines **81** via an *N*-arylimino-Diels-Alder reaction to furnish the respective octahydroacridines **82** and **83** in good to excellent yields. Most selectivities were in the range of 1:1 to 3:1 (**82**:**83**) and in one instance the selectivity was reversed to favor the *trans* product (2:1, $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$); the use of microwave irradiation provided extremely short reaction times

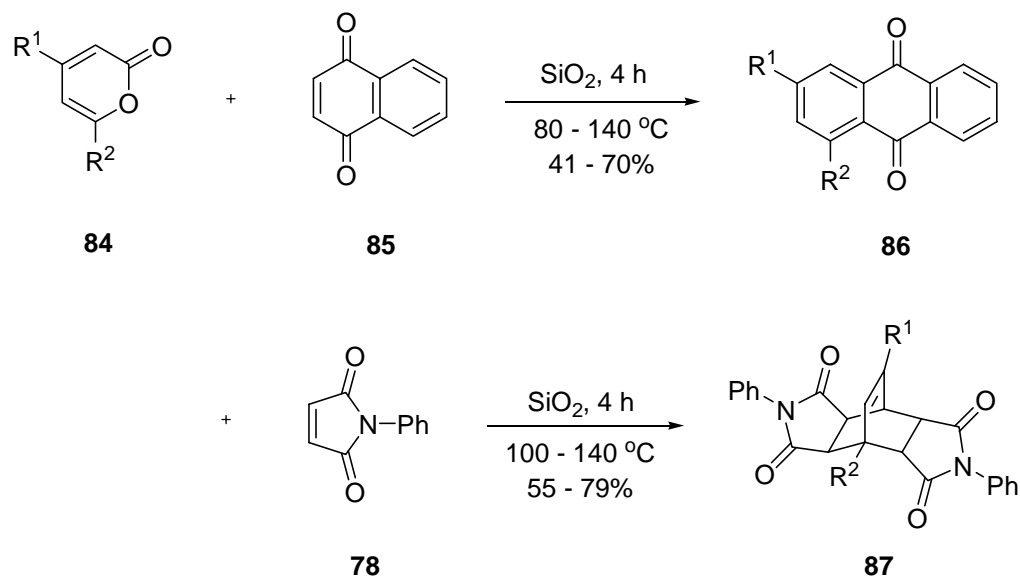


Scheme 20

(1 to 5 minutes). Moreover, the authors extended the greenness of this route by replacing pure citronellal with the essential oil of citronella, a renewable raw material feedstock that contains 40 – 51% (+)-*R*-citronellal. In this case the reaction worked just as well.

2.2.3 Diels-Alder Reactions of Quinones

Prabhu and Samant have used silica gel as a solid support for the Diels-Alder reactions of 4,6-disubstituted-2*H*-pyran-2-ones **84** with naphthoquinone (**85**) and *N*-phenylmaleimide (Scheme 21).³⁶

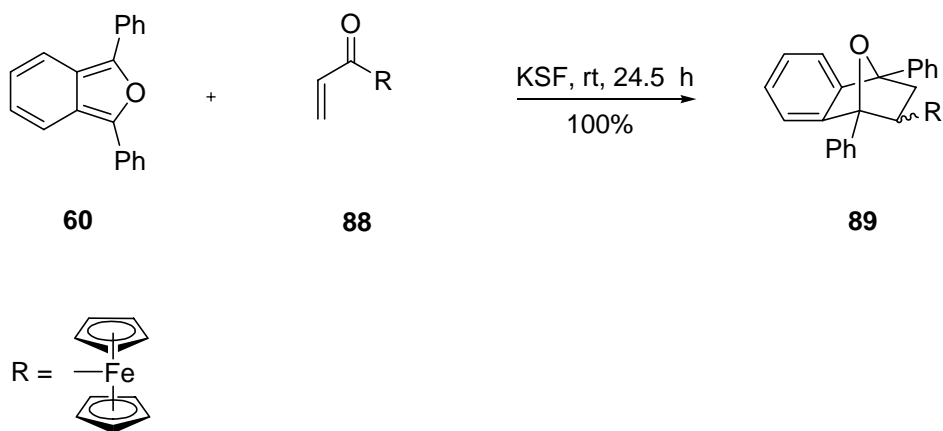


Scheme 21

At 120 °C the authors achieved good yields of products **86** and **87** (60 – 79%). They also performed these reactions on K-10 bentonite clay, but the resulting yields were lower (20 – 71%).

2.2.4 Diels-Alder Reactions of Ferrocenyl Compounds

Prokešová and coworkers have studied the Diels-Alder chemistry of ferrocenyl chalcone analogues on both silica and KSF (a montmorillonite clay, Scheme **22**).³⁷ 1,3-diphenylisobenzofuran reacted with chalcone **88** on KSF to give a 1:1 mixture of *endo* and *exo* products **89** quantitatively. All other cases (both SiO₂ and clay) gave poor to moderate yields of the various adducts (5.7 – 78%). On the whole, silica gel functioned as a better solid support.



Scheme 22

3.0 DIELS-ALDER REACTIONS IN WATER

For reactions performed in solvent there is no doubt that water is the most environmentally sound choice. Since life as we know it is aqueous in nature, there is no reason in expounding upon the benefits of using water as a medium for chemical reactions, but we must realize that aqueous systems also have drawbacks. Specifically, these drawbacks include difficulties in removing small organics from aqueous phases.³⁸ For some reactions, then, energy must be expended in purifying water before it is released back into the environment.

The reasons for using water as a reaction medium go beyond matters of environmental awareness. As it turns out, what was once thought detrimental to the success of many organic reactions is now known as potentially beneficial.³⁹ Breslow and Rideout were the first chemists to fully realize the potential of water as a solvent for the Diels-Alder reaction.⁴⁰ They found more than a 700-fold increase in the rate of reaction between CPD and methylvinyl ketone in water when compared to isooctane. These authors were not the first to use water as a medium for the Diels-Alder reaction. The fathers of the reaction, Diels and Alder, had already used water as a solvent in 1931.⁴¹ Yet it was after Breslow and Rideout published their results that interest in this

'new' solvent was sparked; not long after it was recognized that water also enhances *endo* selectivity in the Diels-Alder reaction.⁴² These effects are currently thought to arise from hydrophobic interactions between the diene and dienophile, hydrogen bonding to the dienophile, and the high polarity of water.⁴³

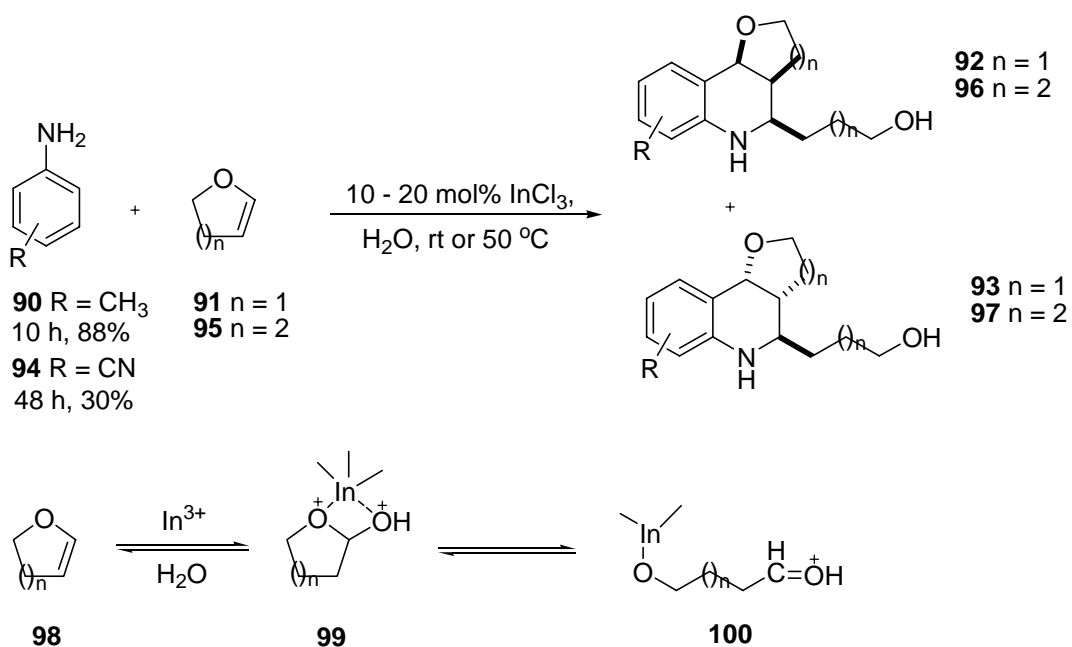
The number and variety of organic transformations performed in water over the years is staggering. These reactions have recently been collected in a very thorough review, in which Diels-Alder processes are well represented.⁴⁴ As a result, this review will only cover the more recent advances in the field of aqueous Diels-Alder chemistry.

3.1 HETERO DIELS-ALDER REACTIONS

3.1.1 Synthesis of Tetrahydroquinolines

Hetero-Diels-Alder reactions between aromatic amines and cyclic enol ethers yield quinolines, a class of products with biological activities that include antiallergic, anti-inflammatory, and estrogenic effects.⁴⁵ Li and Zhang have focused on the preparation of these molecules in aqueous media. The authors have accessed these systems by an indium catalyzed reaction between aromatic amines and cyclic enol ethers (Scheme **23**).⁴⁶ This domino reaction is thought to involve hydration and ring opening of the enol ethers to give compounds **100**, which then react with the amines to form imines and subsequently undergo aza Diels-Alder reactions with enol ethers to give the final products. Yields for this reaction range from poor to excellent (30 – 90%)

and aromatic amines bearing electron-donating groups are the most reactive. For example, reaction of **90** with **95** takes 10 h and gives an 88% yield, compared to the reaction of **94** with **95**, which takes 48 h and gives a 30% yield. Furthermore, 2,3-dihydrofuran (**91**) gives better yields and higher *cis* selectivities (**92:93**, 2.2:1 – 24:1) than 3,4-dihydro-2*H*-pyran (**95**) (**96:97**, 0.52:1 – 2.9:1). This reaction also works with cyclic hemiacetals in place of the enol ethers.⁴⁷



Scheme 23

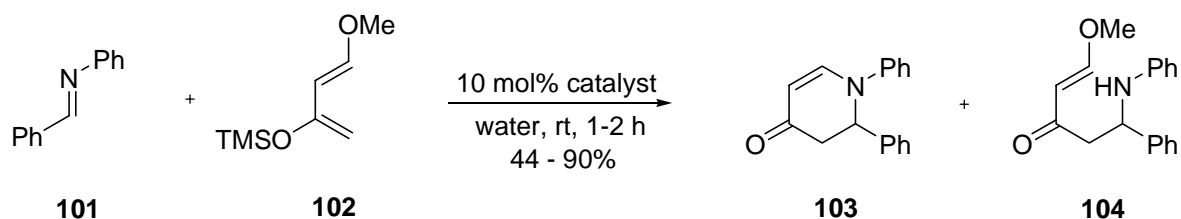
The aromatic amine in the aforementioned reaction can be replaced with an aromatic nitro compound, but in doing so InCl_3 no longer works as a catalyst.⁴⁸ Instead, the reactions are performed in acidic mediums (0.1M HCl, 0.2M HCl, or 0.1MHCl/sat. NH_4Cl) and with In powder. Indium is proposed to reduce the nitro substituent to an amine, being oxidized to In^{3+} in return. After this initial redox reaction the rest of the mechanism is the same as the one discussed previously. Also, just as before, substrates bearing electron donating groups are the most reactive (R = CN, 20 h/36% yield vs. R = OCH_3 , 4 h/44% yield).

Li and Chen have designed a greener version of the reaction between 3,4-dihydro-2H-pyran and aromatic amines by replacing the indium catalyst with various ion exchange resins.⁴⁹ AG[®]50W-X2 hydrogen form resin works the best, supposedly due to its small size (and hence large surface area) when compared to other resins. The conditions for these reactions call for high temperature (80 °C), and while the authors note that microwaves are sufficient to heat these reaction they lead to poorer yields. Again, electronics play a role. Aromatic amines with strongly electron withdrawing groups give higher *trans* selectivities (*trans:cis*, 1.9:1 – 2.9:1) than neutral aromatic amines or those with electron donating groups (*trans:cis*, 0.82:1 – 1.8:1).

3.1.2 Synthesis of Pyridones

The Aza-Diels-Alder reaction of an imine with Danishefsky's diene is a good way to access the 2,3-dihydro-4-pyridone skeleton, a key player in the syntheses of heterocyclic natural products.⁵⁰ Loncaric and coworkers have developed a route to these compounds that involves the reaction of Danishefsky's diene (**102**) with an aldimine.⁵¹ A representative example with aldimine **101** is shown in Scheme **24**. The formation of Mannich-type product **104** is easily subdued by choosing

the right catalyst. Catalysts include sodium alkanesulfonates, alkaline triflates, and other water soluble salts, as well as sodium iodide. Alkaline triflates give product **103** in good to excellent yields and excellent selectivities (**103:104**, >99:1). A variety of aromatic and heteroaromatic aldimines are catalyzed by NaOTf under these conditions.



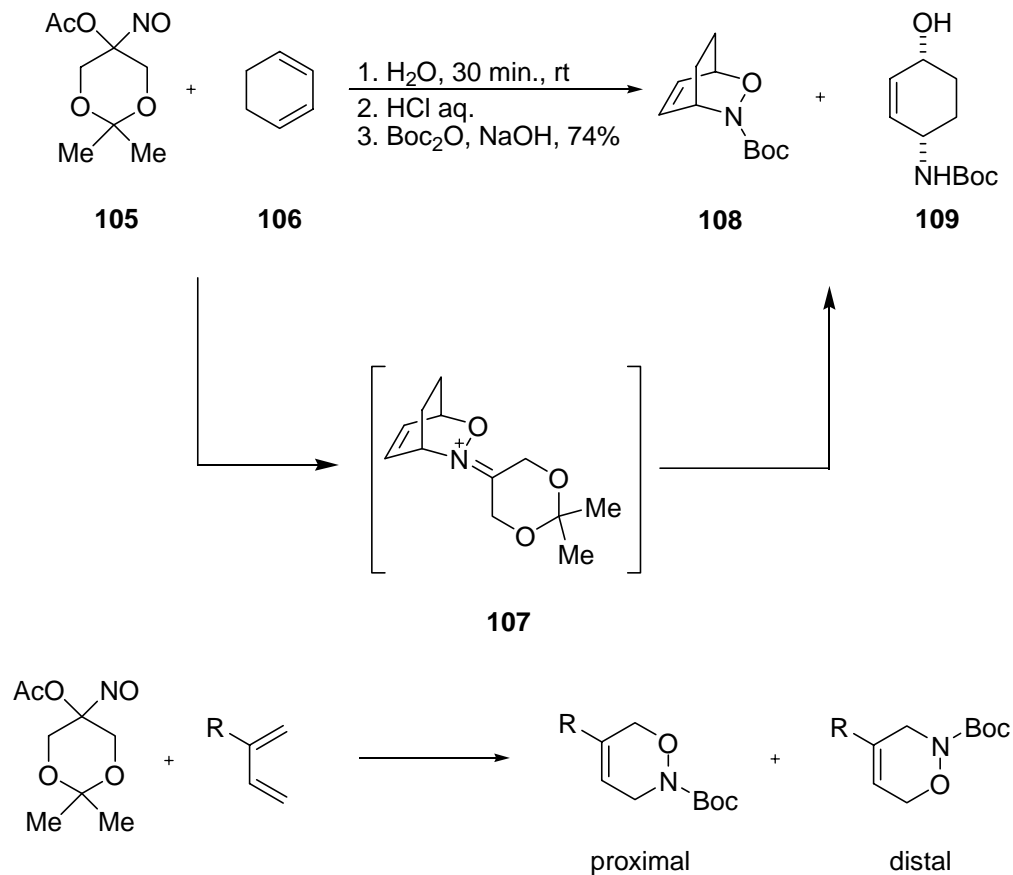
Scheme 24

Moreover, in some instances the aldimines can be generated *in situ* from the corresponding aldehydes and amines; for these one pot procedures the product yields are also good (72 – 96%). A greener version of this one pot procedure has been developed by Akiyama and coworkers, who have used the more environmentally benign K10 Montmorillonite clay as a catalyst.⁵² Products are afforded in good yields (78 – 86%).

3.1.3 Synthesis of 3,6-dihydro-1,2-oxazines

The reaction of α -acetoxynitroso derivative **105** with cyclic and acyclic dienophiles in water leads to 3,6-dihydro-1,2-oxazines, as shown by Calvet and coworkers.⁵³ When reacted with 1,3-

cyclohexadiene (**106**) in pure water, a greater than 49:1 mixture of products in favor of the Diels-Alder adduct **108** is obtained (Scheme 25); the minor product **109** is proposed to result from N-O bond cleavage of the intermediate imine **107**.



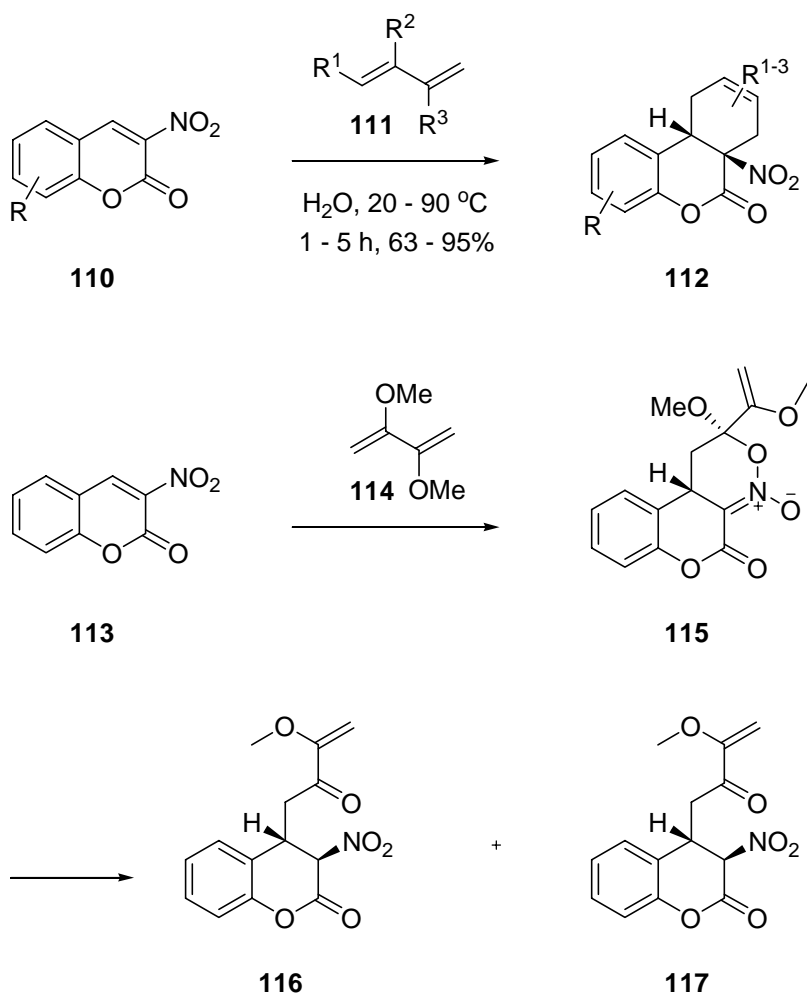
Scheme 25

Under anhydrous conditions (CH₂Cl₂) this cleavage predominates, but under aqueous conditions interception of intermediate **107** by water accounts for the observed oxazine. Asymmetric,

acyclic dienophiles react to give either ‘proximal’ (R is *meta* to oxygen) or ‘distal’ products (R is *para* to oxygen), as shown in scheme **25**. In most cases the ‘proximal’ product predominates (‘proximal’:‘distal’, 1.7:1 – 4:1).

3.1.4 Synthesis of Nitrotetrahydrobenzo[*c*]chromenones

Nitrotetrahydrobenzo[*c*]chromenones can be converted into the interesting and relatively unexplored class of molecules known as 1,4-dihydrodibenzo[*b,d*]furans. To access the former compounds Amantini and coworkers have explored the Diels-Alder reactions of 3-nitrocoumarins (Scheme **26**).⁵⁴ 3-Nitrocoumarins are an interesting class of molecules, since they can function as either dienophiles or dienes;⁵⁵ in the work described herein they serve mainly as dienophiles, giving good to excellent yields of nitrotetrahydrobenzo[*c*]chromenones **112** when reacted with simple dienes **111**. Coumarin **113** reacted as a diene, however, with 2,3-dimethoxy-1,3-butadiene (**114**) to give nitronate **115**, which then hydrolyzed to provide adducts **116** and **117**. To further explore this anomalous result the authors performed the same reaction in CH₂Cl₂ and found that, under anhydrous conditions, coumarin **113** reacted once again as a dienophile. Supposedly, solvation of the diene methoxy groups in water prevents it from adopting the necessary *s-cisoid* conformation, causing it to act as the dienophile instead.

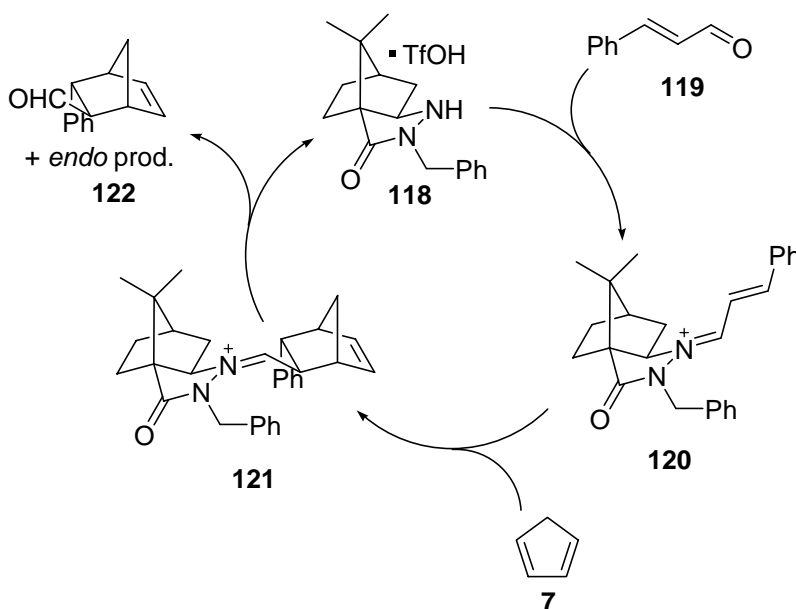


Scheme 26

3.2 ENANTIOSELECTIVE DIELS-ALDER REACTIONS

The ability to control the stereochemistry of a reaction is quite vital in light of the green philosophy, as good stereocontrol ensures products that don't require as much purification. As a

result both material resources and energy are conserved. Chiral catalysts are one way of controlling stereochemistry. A green catalyst has recently been developed by Lemay and Ogilvie and is based on a camphor derived hydrazide framework (Scheme 27).⁵⁶ It is an organocatalyst, which means that it does not incorporate a metal, and this is a vast improvement over potentially toxic metal based catalysts.

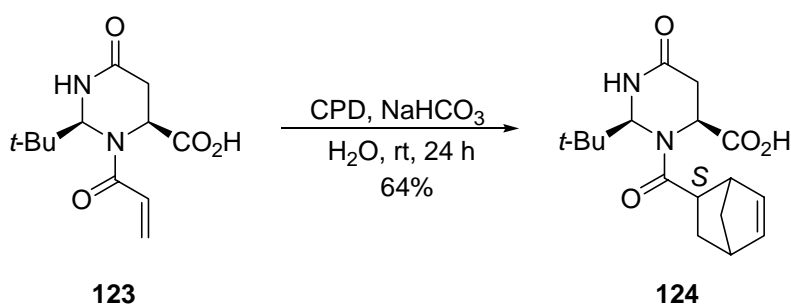


Scheme 27

The catalyst **118** forms an iminium ion upon reaction with the dienophile (thus increasing the electron-deficiency of the system) before directing the approach of the diene. There are three features critical to its success. The most important of these is the alkyl group on the nitrogen, which if removed results in deactivation of the catalyst. The corresponding acid is also

important, since the activity of the catalyst decreases as this co-catalyst becomes less acidic. For example, the reaction between CPD and cinnamaldehyde (**119**), using 20 mol% of catalyst **118** and TfOH as the co-catalyst (10 mol% - 40 mol%) affords the Diels-Alder adduct **122** as a 96% mixture of *exo* and *endo* isomers (1.9:1 respectively, with respect to CHO, *exo* ee = 90%). With the less strong AcOH as a co-catalyst the yield is 7%. Finally, the tertiary nitrogen is thought to play a role in making the hydrazide more nucleophilic by means of the α -heteroatom effect.⁵⁷ The catalyst is relatively general in that it works just as well with a variety of dienes bearing aromatic and aliphatic substitution. Yields were good to excellent and favored the *exo* isomers (*exo:endo*, 1.2:1 – 2.6:1). *Exo* enantioselectivities were also very good (81 – 92% ee).

Chiral catalysts represent just one approach to the area of asymmetric chemistry. Another approach is to attach a chiral moiety to one of the reacting molecules. Of course, the moiety must be removed afterwards, and from a green perspective should be recyclable. Lakner and Negrete have designed a chiral acrylamide auxiliary and have successfully applied this strategy to the Diels-Alder reaction (Scheme 28).⁵⁸



Scheme 28

Synthesis of the auxiliary is straightforward and performed in water. Removal of the auxiliary is also easily accomplished by simply boiling the product in water for several hours. A one-pot procedure, including the synthesis and attachment of the auxiliary followed by a Diels-Alder reaction and removal of the auxiliary, was attempted but with less than desirable results (< 47% ee). The reactions worked better when the dienophiles were prepared beforehand. Reaction of compound **123** with CPD gave product **124** with an *endo:exo* ratio of 4.6:1 and an enantiomeric excess of 64% (2*S*) for the *endo* isomer.

Mahindaratne and coworkers have further explored the roles of salts in the reaction between dienophile **123** and CPD.⁵⁹ To account for selectivity they postulate a chelate model as shown in Figure 4.

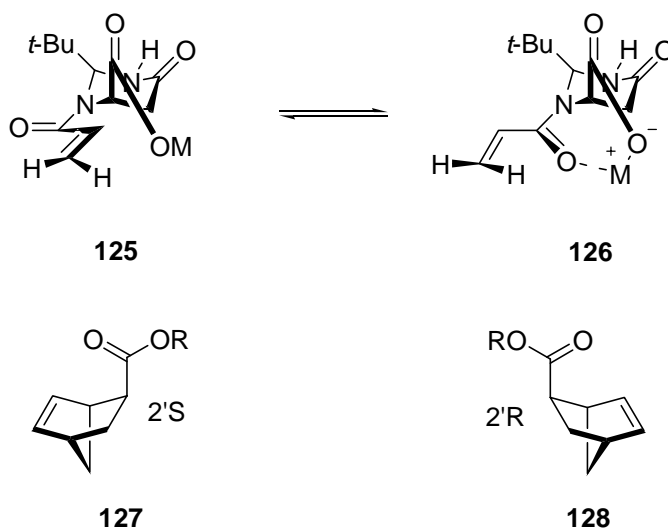
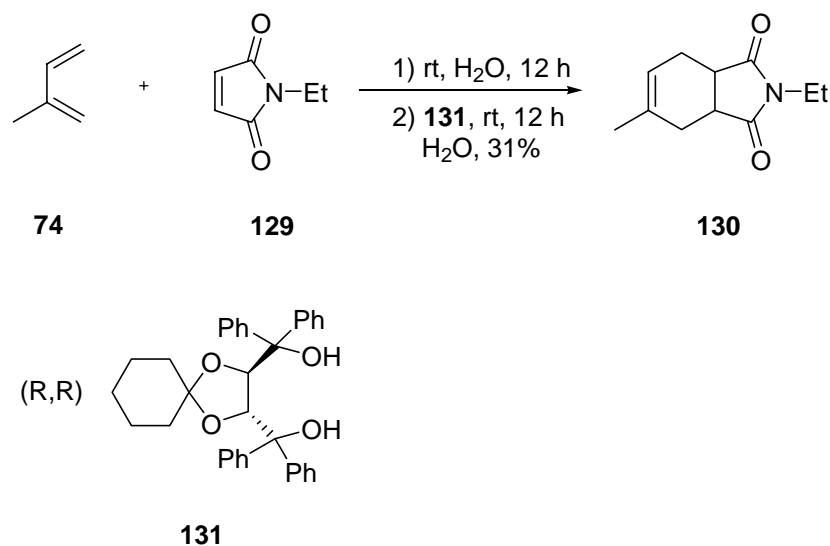


Figure 4. Mahindaratne's chelate model.

The major product of the reaction, the 2'S *endo* product **127**, results from rotamer **125** where the salt's cation binds to the carboxyl group and the amide takes an anti conformation. The minor 2'R product **128** results from the other rotamer **126**, in which the cation binds to the carboxyl group and chelates to the amide carbonyl group as well, forcing the amide into a syn conformation. By experimenting with cations of differing chelating ability the authors provide sufficient support for this model; moreover, salt anions have an even greater effect on this reaction than cations, with weakly basic salts giving poor stereoselectivity (NaCl, 2.0% ee) and strongly basic salts giving better selectivity (NaHCO₃, 70.7% ee).

Another interesting approach to the issue of enantioselectivity has been taken by Miyamoto and coworkers (Scheme **29**).⁶⁰



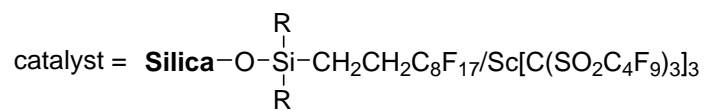
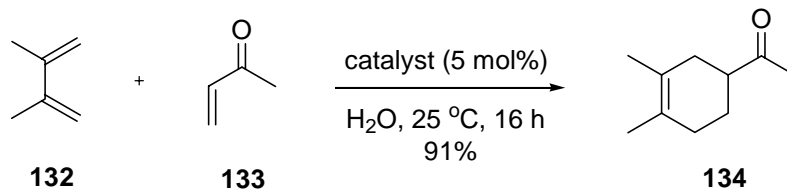
Scheme 29

So far we have seen methods that determine stereoselectivity during the course of a reaction. These authors have opted for after the fact stereocontrol; a reaction is first performed in water, which in this case is the reaction between isoprene and *N*-alkylmaleimides. After completion of the reaction a chiral compound is added to the mixture to form a chiral inclusion complex with the Diels-Alder adduct. After continued stirring the inclusion crystals are separated to yield an enantioenriched product. For the case with *N*-ethylmaleimide (**129**) and chiral host **131**, the (+)-Diels-Alder adduct **130** can be obtained in 31% yield and 94% enantiomeric purity.

3.3 OTHER DIELS-ALDER REACTIONS

Chen and coworkers have recently developed a tungsten based Lewis acid catalyst, $[O=P(2\text{-py})_3W(CO)(NO)_2](BF_4)_2$, that is readily available via a simple and expedient microwave assisted synthesis.⁶¹ The catalyst is recyclable, air stable, and useful for simple Diels-Alder reactions in water. It gives good to excellent yields (80 – 99%) and *endo* selectivities between 3.7:1 and 100:0 under both classical conditions (rt and 50 °C) and microwave irradiation. This is one of the few examples of microwave assisted Diels-Alder chemistry in pure water.

A recyclable Lewis acid catalyst has also been developed by Yamazaki and coworkers, who have attached $Sc[C(SO_2C_4F_9)_3]_3$ to fluorous reverse phase silica gel and have catalyzed the reaction between 2,3-dimethyl-1,3-butadiene (**132**) and methylvinyl ketone (**133**) to give adduct **134** (Scheme 30).⁶²



Scheme 30

As stated previously, increases in rate and selectivity of Diels-Alder reactions in water are due partly to hydrogen bonding interactions.⁴³ Wittkopp and Schreiner have used hydrogen bonding effects in their design of catalysts for aqueous Diels-Alder systems.⁶³ The catalysts are 1,3-disubstituted alkyl, cycloalkyl, and phenyl thioureas as shown in Figure 5.

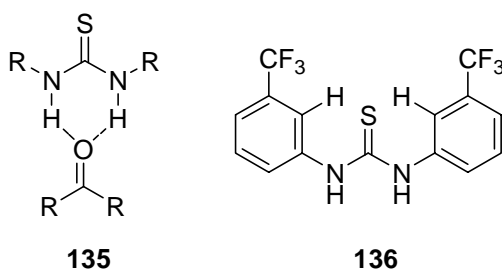


Figure 5. Thiourea catalysts.

The amine hydrogens coordinate to dienophile carbonyls in a bidentate manner. In doing so, their action is thought to be analogous to that of a Lewis acid, with the hydrogen bonds lowering $LUMO_{\text{dienophile}}$ energies, thereby bringing HOMOs and LUMOs closer together to accelerate reactions. These catalysts work in organic solvents (cyclohexane, chloroform), but have very high activity in aqueous systems (water with 10% *t*-BuOH). At only 1 mol% of catalyst **136** the reaction between CPD and methylvinyl ketone yields 85% of product, compared to 74% yield without the catalyst. In general, alkyl, cycloalkyl, and phenyl thiourea catalysts work poorly in comparison to phenyl thioureas substituted with electron withdrawing groups. It is proposed that to allow effective hydrogen bonding with their substrates, the former catalysts must arrange their substituents away from the dienophile carbonyl. Such order is entropically disfavored, but is not a problem with the electron deficient catalysts. The aryl hydrogens of these catalysts are thought to be activated by the electron withdrawing groups, coordinating to sulfur as a result and contributing to a rigid system that is easily accessible for the dienophile.

4.0 DIELS-ALDER REACTIONS IN IONIC LIQUIDS

Loosely defined, an ionic liquid is a salt. Typically these salts are liquid at room temperature, though not necessarily so. Some ionic liquids currently in use are solid at room temperature (we will see a few examples of these later), and must be heated anywhere between 60 and 80 °C to liquefy. Actually, these are more appropriately classified as low temperature molten salts, though in the literature the terms ‘ionic liquid’ and ‘molten salt’, along with a few others, are sometimes ambiguously used.⁶⁴ Regardless of what they are called, both room temperature ionic liquids and those that melt at higher temperatures are being praised as green alternatives to traditional organic solvents.

Since the idea of using ionic liquids as solvents in organic chemistry is a relatively new idea, the reader might be tempted to believe that ionic liquids themselves are also new. This is most certainly not the case. Reports of salts that are liquid at room temperature date back to the 19th century, and U.S. Air Force initiatives to develop low melting salts, precursors to modern day ionic liquids, began in the 1960s.⁶⁴ At that time these salts were developed for applications in batteries and other electrochemical systems. For a well written and concise history of ionic

liquids the reader is encouraged to reference *Ionic Liquids in Synthesis*.⁶⁴ A very thorough review encompassing chemical and biochemical reactions performed in ionic liquids has also recently been written.⁶⁵

Most modern ionic liquids are composed of large, nitrogen based organic cations coupled with polyatomic anions. Their structures can range from simple to complex, as shown in Figure 6, which includes the simple ethylammonium nitrate (EAN) and the common imidazolium based ionic liquid [bmim][BF₄]. Anion and cation structures of the other ionic liquids mentioned below are given in Figure 7. The pool of anions and cations capable of forming ionic liquids is really quite extensive, and the physical properties of ionic liquids such as viscosity and melting point are largely dependent on the anions and cations chosen.⁶⁵

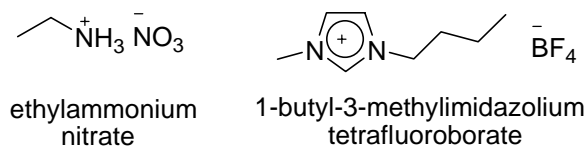


Figure 6. Examples of ionic liquid structures.

The physical properties of ionic liquids are what make them such promising reaction media. As opposed to traditional organic solvents, which are volatile and hence environmentally unsound, ionic liquids are held together entirely by ionic forces and exhibit virtually no vapor pressure.⁶⁴ They have other valuable properties as well,⁶⁵ they are stable over wide temperature ranges, are able to dissolve a great variety of synthetically useful organic compounds, are

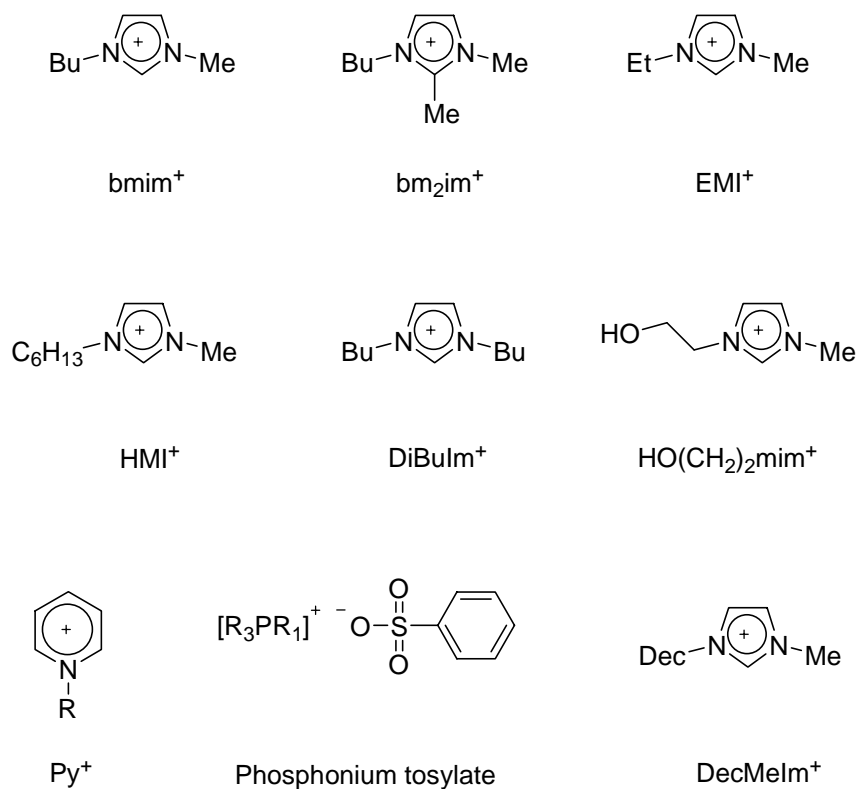


Figure 7. Other ionic liquid structures.

generally not flammable or explosive, and are generally recyclable and easy to reuse. Due to their ionic character these solvents are also very polar, and as such are found to increase both the rates and selectivities of various reactions.⁶⁵

While these properties are certainly in line with the green philosophy, whether or not ionic liquids are green is really another question, and one that should be addressed here. They are an improvement over traditional organic solvents in many ways, but they also possess their own hazards. Chloroaluminate ionic liquids, for example, contain AlCl₃ and are corrosive.⁶⁶ Under sonochemical conditions imidazolium based ionic liquids such as [bmim][Cl] and

[DecMeIm][BPh₄] (Figure 7) decompose to give volatiles such as chloromethane and benzene, respectively,⁶⁷ and even more worrisome is the potential for imidazolium based, fluorosulfate ionic liquids such as [bmim][PF₆] to hydrolyze and produce the very toxic hydrofluoric acid.⁶⁸

In addition to these concerns are those of replacing a well characterized agent such as benzene or dichloromethane with an agent of which much less is known. A vivid example of this type of danger was the use of chlorofluorocarbons in the 1970s. These solvents were thought to be environmentally friendly at the time, but were discovered in 1974 to cause depletion of the ozone layer.^{69,70} Until chemists gather enough information to elucidate the potential dangers of ionic liquids we cannot predict what harmful effects might, in the future, manifest themselves as a result of their use. Indeed, it has already been stated that sound judgment concerning the use of ionic liquids is called for.⁶⁸

Yet as indicated before ionic liquids adhere to several green principles, and with respect to their negligible vapor pressure they are certainly less harmful to the environment than traditional organic solvents; this reasoning is most likely behind the acceptance of ionic liquids as green. Also for this reason, as well as those previously mentioned, ionic liquids are presented here as green media for the Diels-Alder reaction.

4.1 DIELS-ALDER REACTIONS OF CYCLOPENTADIENE WITH METHYL ACRYLATE

A large number of Diels-Alder reactions performed in ionic liquids have concerned reacting CPD with methyl acrylate. The low-melting fused salt EAN was used by Jaeger and Tucker as a solvent for this reaction and with great success (98% yield of products).⁷¹ The ratio of *endo* to *exo* isomers was 6.7:1 and could be increased to 7.4:1 with the addition of lithium iodide; this salt also had an effect on the reaction rate, increasing it from $1.7 \times 10^4 \text{M}^{-1}\text{sec}^{-1}$ to $5.4 \times 10^4 \text{M}^{-1}\text{sec}^{-1}$.

Much better rates and *endo* selectivities for the reaction of CPD with methyl acrylate have been achieved by using chloroaluminate ionic liquids as solvents. Lee has demonstrated this fact nicely with [EMIC][AlCl₃], a chloroaluminate melt with Lewis acidic character that can be tuned by varying the percentage of AlCl₃.⁷² With 48% AlCl₃, the solvent is slightly basic and the reaction is 7 times faster than that of the reaction performed in EAN (without LI). At 51% AlCl₃ the solvent is slightly acidic, and in this case the reaction is 175 times faster than in EAN! For the acidic melt the *endo:exo* ratios are also raised to 19:1. For the basic melt *endo:exo* ratios are lower (5.3:1).

A substantial setback to the use chloroaluminate melts as solvents is their sensitivity to water. Dry conditions are a must with these liquids; water will react with them to give HCl and hydrated aluminium(III) ionic species, thus rendering the liquids unusable in situations that require aqueous conditions (i.e. an aqueous quench). Moreover, these liquids can form adducts with heteroatomic functional groups such as ketones.⁶⁴

Fortunately air and water stable ionic liquids are available. Fischer and coworkers have surveyed a number of such ionic liquids from the bmim^+ and emim^+ families in their studies of the reaction between CPD and methyl acrylate.⁷³ In $[\text{bmim}][\text{BF}_4]$ at room temperature, a product yield of 91% (*endo:exo*, 4.3:1) is possible after 72 hours.

The previous examples serve to illustrate the sensitive nature of *endo* selectivity in the Diels-Alder reaction. Just as with Diels-Alder reactions in water, selectivity in ionic liquids is presumed to depend, in part, on hydrogen bonding. Aggarwal and coworkers have looked at the reaction of CPD with methyl acrylate in a number of imidazolium based ionic liquids.⁷⁴ Switching from $[\text{bm}_2\text{im}][\text{BF}_4]$ to $[\text{bmim}][\text{BF}_4]$ leads to an increase in *endo* selectivity (from 3.3:1 to 4.6:1, respectively). A further increase in selectivity to 6.7:1 is brought about by switching to $[\text{HO}(\text{CH}_2)_2\text{mim}][\text{N}(\text{Tf})_2]$ as a solvent. Each of these liquids is a successively better hydrogen bond donor, so it appears that greater donating ability on the part of the ionic liquid's cation leads to greater *endo* selectivity in the reaction. This effect results from hydrogen bond donation to the carbonyl of the methyl acrylate molecule, yet in theory the associated anion should also be capable of accepting this hydrogen bond. Competition between methyl acrylate and the anion for hydrogen bonding should thus result in lower *endo* selectivity (Figure 8).⁷⁴

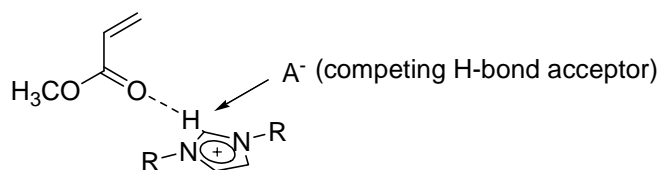


Figure 8. Competition with methyl acrylate for hydrogen bonding.

Such a result is observed when CPD and methyl acrylate are reacted in [bmim][BF₄]/[bmim][Cl]; selectivity is lowered from 4.6:1 to 3.7:1. Presumably, the chloride ion, a better hydrogen bond acceptor, interferes with the hydrogen bonding to the ketone and lowers *endo* selectivity.

Yet Vidiš and coworkers have performed the reaction in a variety of ionic liquids and have shown that reactions in 1-alkyl-2,3-dimethylimidazolium ionic liquids *can* lead to better *endo* selectivity than reactions in 1-alkyl-3-methylimidazolium liquids, even though the latter solvents are better hydrogen bond donors.⁷⁵ When the hydrogen bond donor is separated from the center of positive charge, such as with *N*-alkyl-*N*-(2-hydroxyethyl)-*N,N*-dimethylammonium ionic liquids, *endo* selectivity is generally higher in comparison to 1-alkyl-2,3-dimethylimidazolium systems. The authors sought to study these hydrogen bonding effects more thoroughly; they ran the reaction in several bmim⁺ based ionic liquids and used IR to determine the wavenumbers of the C_{im}-H · · · A⁻ stretches. This experiment tests the same ideas as Agarwaal's work. A strong hydrogen bond accepting anion should lower the CH wavenumber and also interfere with hydrogen bonding to methyl acrylate, resulting in lower *endo* selectivity. This trend is observed for [PF₆]⁻ ($\nu_{\text{CH}} = 3126 \text{ cm}^{-1}$, *endo:exo* = 5.0:1), [BF₄]⁻ ($\nu_{\text{CH}} = 3123 \text{ cm}^{-1}$, *endo:exo* = 4.9:1), and [Tf₂N]⁻ ($\nu_{\text{CH}} = 3121 \text{ cm}^{-1}$, *endo:exo* = 4.3:1), but not for [CF₃COO]⁻ ($\nu_{\text{CH}} = 3087 \text{ cm}^{-1}$, *endo:exo* = 4.4:1). The last ion is a much stronger hydrogen bond acceptor than [Tf₂N]⁻, yet it allows for slightly greater *endo* selectivity. Clearly, more work is needed to clarify the situation.

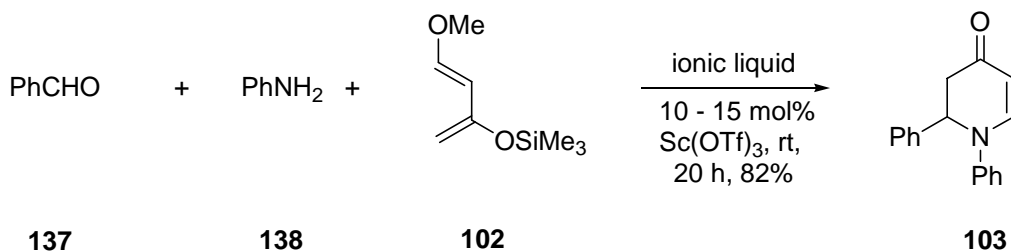
In moving away from classic melt compositions such as the ones discussed up until this point, Imperato and coworkers have taken an interesting step by designing ionic liquids from mixtures of sugars, ureas, and salts.⁷⁶ Because the melts are composed of essentially non-toxic, readily available compounds they are very green. Furthermore, they have little vapor pressure

and are thermally stable and reusable. The best results for the reaction of CPD with methyl acrylate took place in a mixture of sorbitol, DMU, and NH₄Cl (70:20:10, respectively, melting point = 67 °C). The products were obtained quantitatively with an *endo* selectivity of 5.0:1. A selectivity of 6.0:1 was achieved upon addition of 10 mol% Sc(OTf)₃.

4.2 HETERO DIELS-ALDER REACTIONS

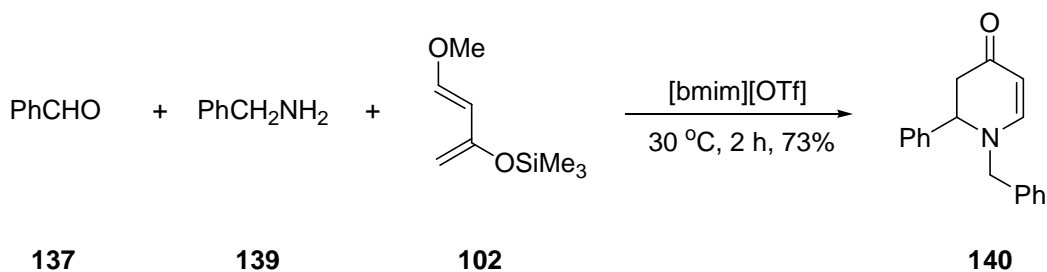
4.2.1 Synthesis of Pyridones

Zulfiqar and Kitazume have developed a one-pot procedure in which aromatic imines are formed *in situ* and then allowed to react with Danishefsky's diene to produce the corresponding pyridones (Scheme **31**).⁷⁷ The authors used two ionic liquids with equal success: 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate and [emim][OTf]. Each gave adducts in good to excellent yields with a variety of aldehydes and amines (75 – 99%). Reaction of benzaldehyde (**137**) with aniline (**138**) in the former ionic liquid gave product **103** in 82% yield, similar in magnitude to yields observed for this reaction in water (Scheme **24**).⁵¹ Compared to those aqueous reactions, however, this process requires a much longer time (20 h versus 1 – 2 h). After a reaction is complete, the ionic liquid and scandium catalyst are nearly fully recovered (92 – 98%) and capable of use two more times while maintaining similar yields.



Scheme 31

Pégot and Vo-Thanh have recently improved upon the greenness of this process by switching the medium to [bmim][OTf] and circumventing the need for a catalyst.⁷⁸ The reaction times are much shorter (1 – 6 h versus 20 h for the former reactions). However, the imines are prepared separately in these conditions, meaning the reactions are not one-pot as in the previous example. The authors attempted a one-pot, three component procedure for the preparation of pyridine **140** (Scheme 32).

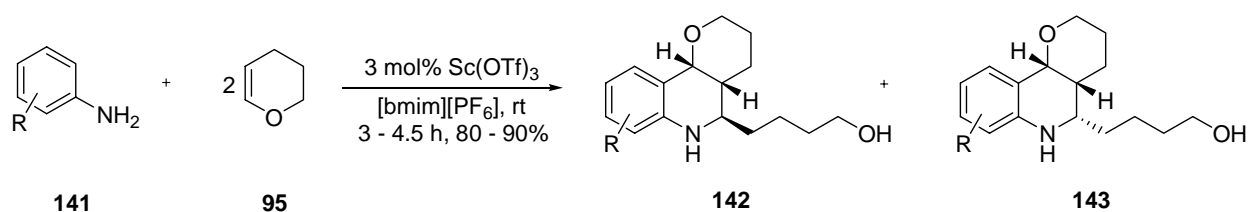


Scheme 32

However, the yield (73%) falls below the good yields they typically obtained for their two component procedure (69 – 90%). The ionic liquid can be reused up to three times while maintaining good yields.

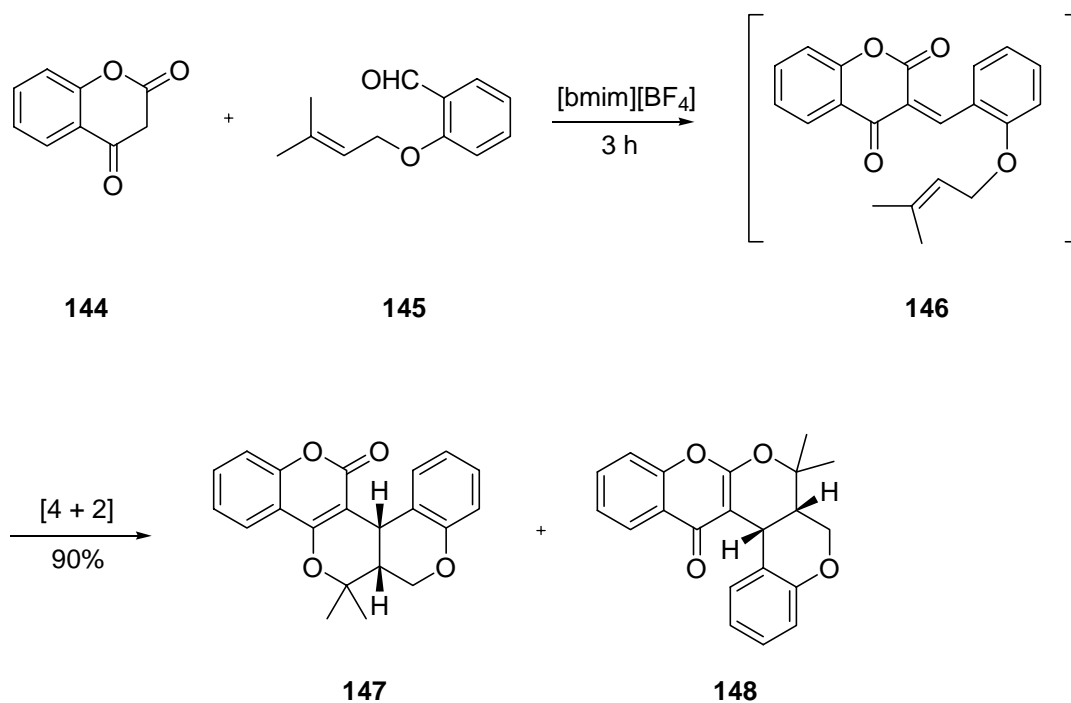
4.2.2 Synthesis of Tetrahydroquinolines and Pyranocoumarins

Yadav and coworkers have provided a green route to tetrahydroquinolines using [bmim][PF₆] as a reaction medium and Sc(OTf)₃ as a catalyst.⁷⁹ Both 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran give products in very good to excellent yields, with *endo:exo* ratios often greater than or equal to 11.5:1 (**142:143**, Scheme 33). When compared to the previously mentioned aqueous synthesis of these compounds (Scheme 23)⁴⁶ the present route gives products in generally higher yields and shorter reaction times (3 – 4.5 h versus 2 – 72 h). The ionic liquid/catalyst phase is recoverable and reusable.



Scheme 33

Due to their roles as anticoagulants, insecticides, antifungals, and HIV protease inhibitors coumarins are also of considerable interest in the world of heterocyclic molecules.⁸⁰ A procedure involving a domino Knoevenagel and Hetero-Diels-Alder reaction, also developed by Yadav and coworkers, works well for the synthesis of pyrano[3,2-*c*]coumarins (Scheme 34).⁸¹



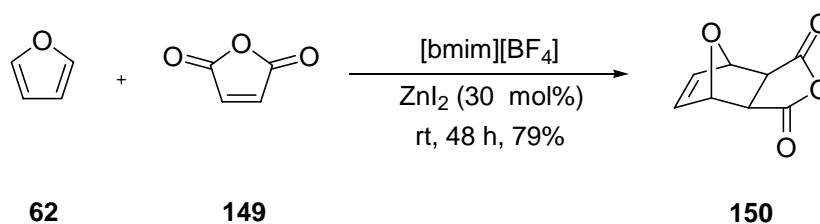
Scheme 34

The reaction of 1,3-dione **144** with *O*-prenylated aromatic aldehyde **145** results in a Knoevenagel condensation, the product of which (**146**) undergoes an intramolecular Diels-Alder reaction to give *cis* coumarin **147** along with chromone byproduct **148** (**147**:**148**, 9:1). For a

variety of aromatic 1,3-diones and aldehydes, yields ranged from 78 to 91% and the ratios of coumarin to chromone ranged from 4:1 to 9:1. The reaction works in [bmim][PF₆] and [bmim][BF₄], though the yields of products are much lower in the hydrophobic [bmim][PF₆] (25 – 40%). Also, the reaction is limited to 4-hydroxy-1,3-diones and *O*-prenylated aldehydes.

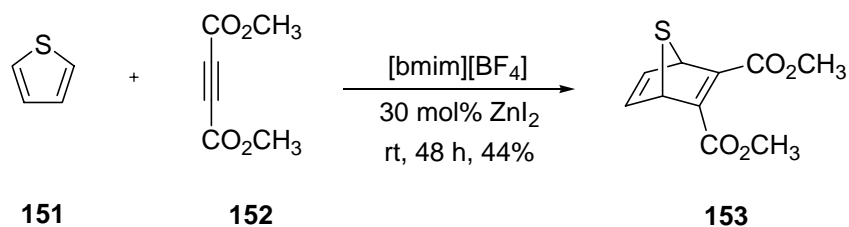
4.2.3 Diels-Alder Reactions of Furan and Thiophene

Hemeon and coworkers have successfully reacted furan with methyl acrylate and maleic anhydride in [bmim][BF₄] and [bmim][PF₆].⁸² Owing to the greater ease of product isolation from [bmim][BF₄], this solvent was found to be the ideal medium. At a catalyst loading of 30 mol% the *endo* selectivity for reaction with methyl acrylate (*endo:exo*, 2.3:1 in either ionic liquid) is better than at 100 mol% (*endo:exo*, 1.4:1/[bmim][PF₆], 1.8:1/[bmim][BF₄]). Note that solvent-free conditions give *exo* favored products.⁸³ Reaction with maleic anhydride (**149**) gives solely *exo* product **150**, irregardless of catalyst loading (Scheme 35).



Scheme 35

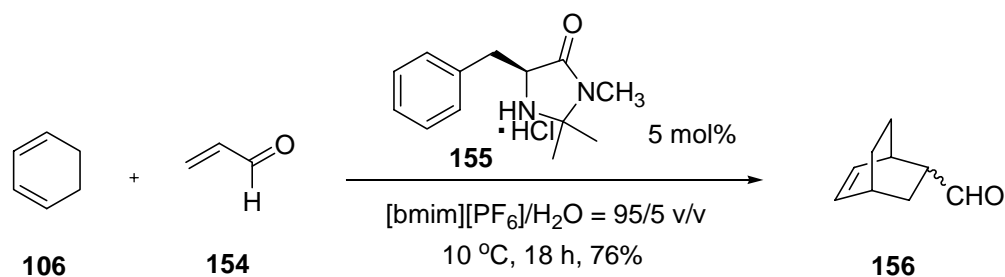
The benefit of stoichiometric ZnI_2 is that the yields are generally higher. The authors have also reacted thiophene (**151**) with DMAD (**152**), resulting in a moderate yield of adduct **153** (44%, Scheme 36).⁸²



Scheme 36

4.3 ENANTIOSELECTIVE DIELS-ALDER REACTIONS

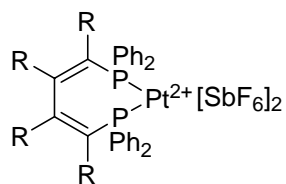
The chiral amine catalyst **155**⁸⁴ has tremendous green potential. It is not based on a toxic metal, but is rather a simple amine salt, and furthermore it is usable in ionic liquid systems; Park and coworkers have successfully shown this by using it to catalyze the reaction between cyclohexadiene and acrolein (**154**) (Scheme 37).⁸⁵



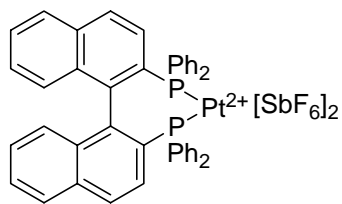
Scheme 37

Without water the amine salt cannot function as a catalyst,⁸⁴ so it is essential that the ionic medium be hydrophobic and not hydrophilic. For example, performing the reaction in hydrophobic [bmim][PF₆] gives a 76% yield of product **156** (*endo:exo*, 17:1) with an *endo* ee of 93%. In the hydrophilic [bmim][BF₄] only 5% of the product is obtained. The ionic liquid/catalyst phase is recoverable, though the ee drops from 93% to 87% with the third reuse.

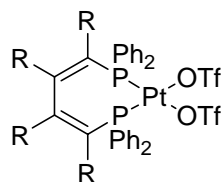
Using more traditional, metal based Lewis acid catalysts, Doherty and coworkers have carried out reactions between acryloyl-*N*-oxazolidinones and CPD in a variety of imidazolium based ionic liquids.⁸⁶ Two types of platinum catalysts were used, one type based on the R₄-NUPHOS diphosphine system (**157** and **159**), and the other type based on the BINAP system (**158** and **160**, Figure 9).



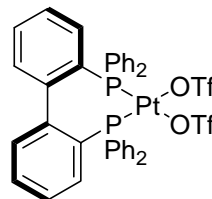
157



158



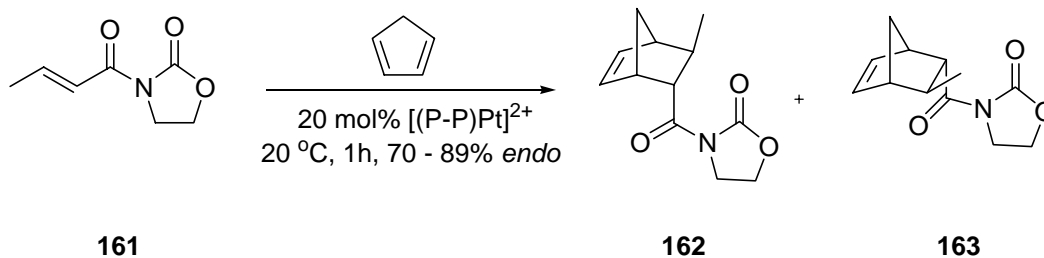
159



160

Figure 9. Flexible and rigid catalysts for asymmetric Diels-Alder reactions.

For the reaction of oxazolidinone **161** all of the catalysts worked well, often giving enantioselectivities of around 90% (**162** or **163**), and in only 1 hour at 20 °C (Scheme 38).



161

162

163

Scheme 38

This was a dramatic improvement over reactions performed in dichloromethane, which were run for extended times (20 h or more) at -20 °C because the catalysts would form inactive $[\eta^5\text{-Cp}^+]$ species at room temperature. The ionic liquid/catalyst phase is reusable, yet the use of 7.5 equivalents of CPD means that it is also wasteful, a fact that must be taken into account when determining the greenness of this process.

The reaction of oxazolidinone **161** with CPD was studied by Meracz and Oh as well. Using the copper bisoxazoline-based chiral Lewis acid **164** (Figure 10) they achieved an *endo* selectivity of 13.3:1 and a selectivity for **162** of 24:1 in $[\text{DiBuIm}][\text{BF}_4]$.⁸⁷

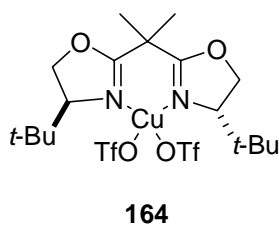
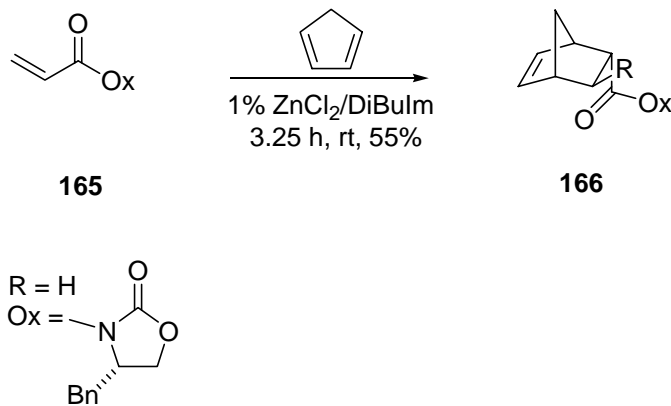


Figure 10. Copper bisoxazoline-based chiral Lewis acid.

The authors also demonstrated excellent stereocontrol in the same solvent by using a chiral oxazolidinone instead (**165**, Scheme 39). The reaction included 1% ZnCl_2 and in just over 3 hours yielded 55% of product **166**.

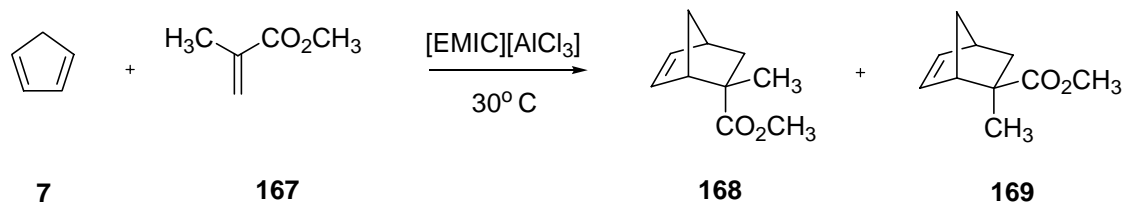


Scheme 39

4.4 OTHER DIELS-ALDER REACTIONS

CPD has been reacted with dimethyl maleate, ethyl acrylate, and acrylonitrile in a variety of bmim^+ based ionic liquids, with very good to excellent yields of products (80 – 99%) and moderate *endo* selectivities (1.6:1 – 6.0:1).⁸⁸

The reaction between CPD and methyl methacrylate (**167**) shows a reversal in selectivity when performed in the chloroaluminate ionic liquid $[\text{EMIC}][\text{AlCl}_3]$ (Scheme 40).⁸⁹ This is another good example of how Lewis acids can affect the outcome of a Diels-Alder reaction. As the mol% of AlCl_3 in the liquid increases, so does the stereoselectivity; it reaches a maximum at 60 mol% AlCl_3 , so that the typical selectivity of 1:2 in favor of the *exo* isomer **169** is reversed to 4.6:1 in favor of the *endo* isomer **168**.



Scheme 40

Silvero and coworkers have used the reaction between CPD and methylvinyl ketone as a model to study the effects of Lewis acid catalysis in [HMI][BF₄].⁹⁰ TfOH and Tf₂NH work well as Lewis acids, giving greater than 99% conversion and *endo* selectivities of 13.3:1 and 15.7:1, respectively. Ce(OTf)₄·5H₂O, Y(OTf)₃, and Sc(OTf)₃ work even better, achieving similar yields (95 – 99%) and the same selectivities in much shorter reaction times (5 min as opposed to 1h with TfOH and Tf₂NH). Catalyst loading is also important. At 0.5 mol%, Ce(OTf)₄·5H₂O gives greater than 99% conversion in 5 min, and at 0.2 mol% it takes 1 h to achieve the same yield. The *endo* selectivity (*endo:exo*, 15.7:1) is the same for both loadings.

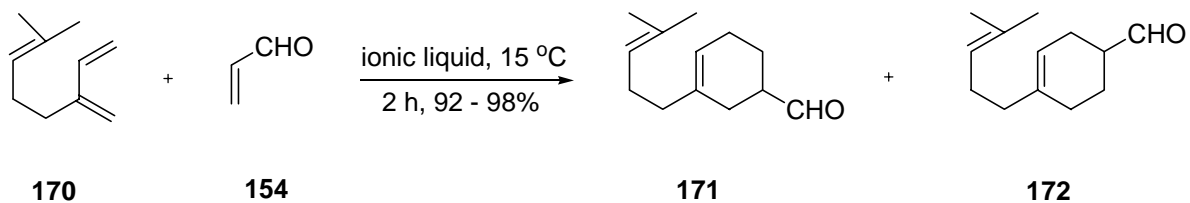
In the presence of Sc(OTf)₃, 2,3-dimethylbutadiene and cyclohexadiene react well with methylvinyl ketone, maleic anhydride, and 1,4-naphthoquinone in various bmim⁺ based ionic liquids, as shown by Song and coworkers.⁹¹ The optimal catalyst loading is 0.2 mol%. At 10 mol% catalyst the reactions are difficult to control, as the authors report heat generation and a color change to dark brown in a matter of seconds. Yields of products range from good to excellent (71% - > 99%). In cases where *endo:exo* selectivity is an issue the reactions are virtually completely *endo* selective (*endo:exo*, >99:1). The ionic liquid/catalyst phase is recoverable and can be reused up to 11 times without any loss in activity.

Reactions of 2,3-dimethylbutadiene and cyclohexadiene with simple dienophiles such as acrolein, methylvinyl ketone, and methyl acrylate were studied by Abbott and coworkers, but in the more Lewis acidic choline chloride-MCl₂ ionic liquids (M = Zn or Sn).⁶⁶ Yields are very good to excellent for all cases (85 – 94%), as are *endo* selectivities (4.9:1 – 32:1), though the Zn containing ionic liquids allow for faster reaction rates (8 min – 5 h) than their Sn counterparts (20 – 24 h). The reaction between isoprene and acrolein was also studied and the selectivity for the 1,4-product is excellent (1,4-product:1,3-product, 19:1). For both the Zn and Sn containing ionic liquids, neither the reaction rates nor selectivities are influenced by the presence of water in the system, which makes these conditions very easy to work with.

Ludley and Karodia have looked at the reactions between isoprene and methyl acrylate, methylvinyl ketone, and acrylonitrile in phosphonium tosylates, ionic liquids that are solid at room temperature.⁹² The yields and selectivities for these reactions are dependent upon both the substrates involved and the ionic liquid used, with methyl acrylate and methylvinyl ketone generally showing excellent selectivity for 1,4-products (1,4:1,3, >99:1). As a dienophile, acrylonitrile leads to poorer selectivity (1,4:1,3, 2.2:1 – 3.2:1).

There are some instances in which 1,4-selectivity is crucial, and for an example we can look at the synthesis of myrac aldehyde, available via the Diels-Alder reaction of myrcene (**170**) with acrolein (Scheme **41**). Of the two compounds produced in this reaction, '*para*'-myrac aldehyde (**172**) (the 1,4-product) is the desired one, with uses in perfumes and cosmetics that aldehyde **171** does not have.⁹³ The '*para*' product, as it turns out, is readily available when the reaction is performed in ionic liquid, as Yin and coworkers have recently shown.⁹³ Bmim⁺, emim⁺, and Py⁺ based salts, coupled with ZnCl₂ (ZnCl₂:salt, 2:1 – 3:1) make ionic liquids that are great mediums for this reaction, giving yields of 92% to 98% and regioselectivities of 15.7:1

and 19:1 in favor of **172**. For the reactions of myrcene with other dienophiles, regioselectivity is very much dependent on temperature. Higher reaction temperatures give higher yields but at the expense of producing more '*meta*' product **171**.



Scheme 41

5.0 DIELS-ALDER REACTIONS IN SUPERCRITICAL CARBON DIOXIDE

The chemical and material industries have been developing numerous applications for CO₂.⁷⁰ Among these applications are the decaffeination of coffee beans with supercritical CO₂ (an extraction process) and the production of polymethylmethacrylate and polystyrene using supercritical CO₂ as a reaction medium.⁹⁴ CO₂ is also used in microelectronics processing and textile dyeing.⁷⁰ Below we will consider Diels-Alder reactions performed in supercritical CO₂.

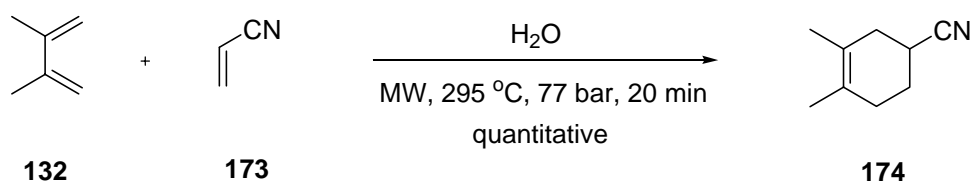
Here, 'supercritical' refers to placing a substance under pressures greater than its critical pressure (P_C) and under temperatures greater than its critical temperature (T_C). At this point the substance takes on properties between those of a liquid and a gas.⁹⁴ For example, in its supercritical state CO₂ ($P_C = 73.8$ bar and $T_C = 31.1$ °C) has densities above that of gaseous CO₂ but below the density of liquid CO₂. These densities vary depending upon the temperatures and pressures applied to the system.⁹⁴

The varying density of supercritical fluids is a useful characteristic, as in theory hard to dissolve substances can be made to dissolve in supercritical CO₂ by increasing the fluid's density. Moreover, gases are completely soluble in supercritical CO₂, so the possibility arises to create systems that can dissolve solids, liquids, and gases all at the same time.⁹⁴ In practice this

type of control is not always easy to obtain, for the phase properties of supercritical fluids are very sensitive to solute content and structure and are not yet fully understood.⁷⁰

CO₂ is not the only substance that provides a reaction medium in its supercritical state. Fluoroform ($P_C = 48.2$ bar and $T_C = 25.9$ °C) and water ($P_C = 220.6$ bar and $T_C = 374.0$ °C) also find use as supercritical fluids.⁹⁵ Recently, Kreamer and Kappe have reported that the Diels-Alder reaction of 2,3-dimethylbutadiene and acrylonitrile in near critical water (295 °C, 77 bar) under focused microwave irradiation gives a quantitative yield of product **174** (Scheme 42).⁹⁶ A few other examples of Diels-Alder reactions in near critical water have also been reported.⁹⁷

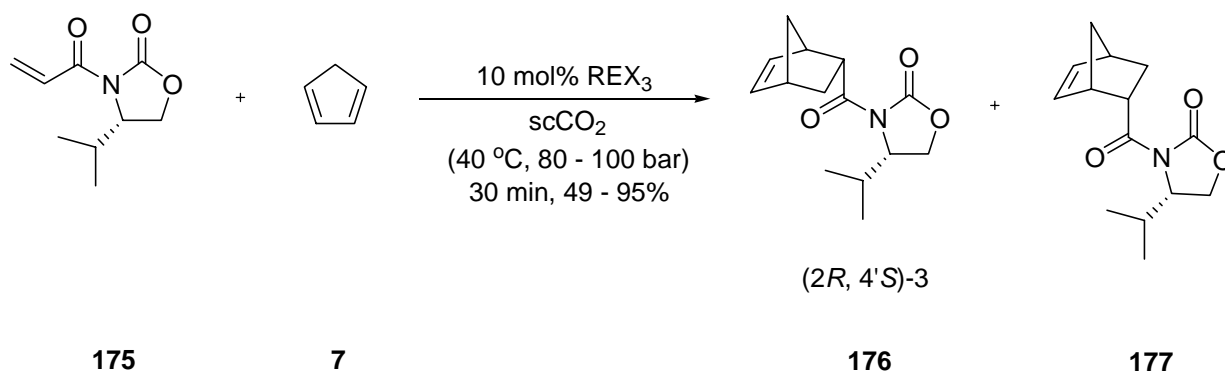
Supercritical CO₂ is considered green for a number of reasons.⁹⁴ It is non-toxic, non flammable, and relatively inert. Aside from this, removal of the solvent is simple, for it need only evaporate upon completion of a reaction. CO₂ is also cheap and abundant. Diels-Alder reactions in supercritical CO₂ up until the year 2000 have been previously reviewed,⁹⁴ so we will consider only the most recent advances in the field.



Scheme 42

5.1 ENANTIOSELECTIVE DIELS-ALDER REACTIONS

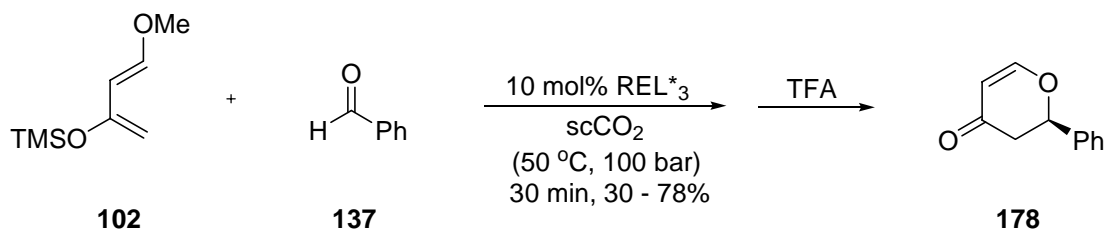
Fukuzawa and coworkers have studied rare earth metal catalyzed reactions between 3-acryloyl-(4*S*)-isopropylloxazolidin-2-one (**175**) and CPD, both in supercritical CO₂ and traditional organic solvents (Scheme 43).⁹⁸



Scheme 43

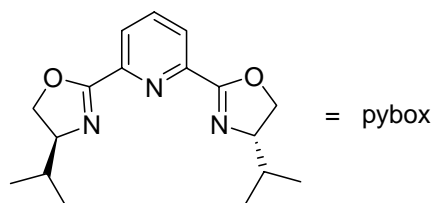
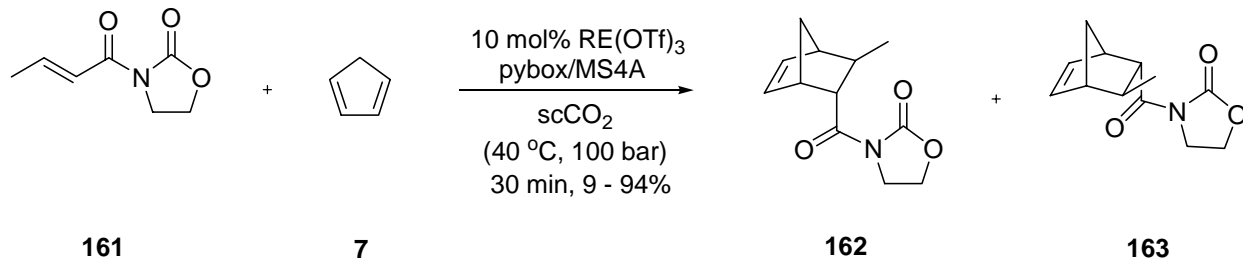
Reactions in supercritical CO₂ gave *endo* selectivities in the range of 2.3:1 to 11.5:1 and generally moderate *endo* diastereoselectivities of 49 – 69% de in favor of diastereomer **176**. An *endo* diastereoselectivity of 77% was achieved with the use of Yb(ClO₄)₃·8H₂O as a catalyst. Diastereoselectivities were always higher in supercritical CO₂ than in CH₂Cl₂ (49 – 69% versus 32 – 42%, respectively), and showed no correlation with the densities of the CO₂ systems. For

some chiral rare earth catalysts, the reaction between Danishefsky's diene and benzaldehyde gave poor to good yields (78% with (+)-Yb(hfc)₃ as catalyst) but no catalysts gave enantioselectivities exceeding 38% *R* for product **178** (Scheme 44).



Scheme 44

The authors also had success in catalyzing the reaction between 3-crotonoyl-2-oxazolidinone **161** and CPD (Scheme 45). The use of Sc(OTf)₃ as a catalyst, coupled with pybox afforded a 71% yield of products (*endo:exo*, 13.3:1) with an *endo* ee of 83% in favor of product **162**. 4Å molecular sieves were necessary for the high enantioselectivity, as it dropped to 63% in their absence. As before, there was no correlation between enantioselectivity and density.

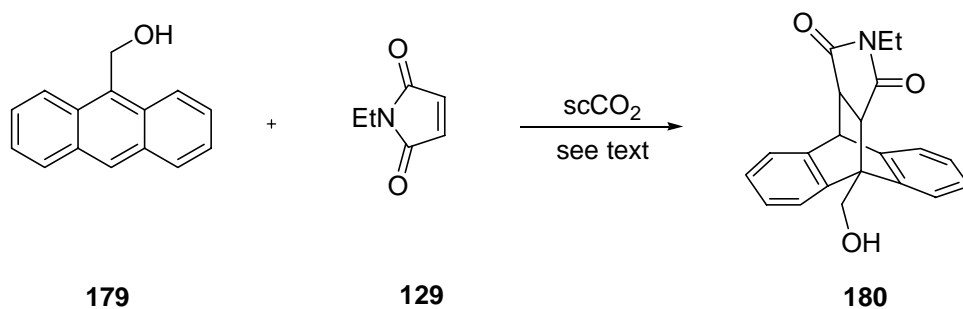


Scheme 45

5.2 OTHER DIELS-ALDER REACTIONS

Several studies over the years have found that reaction rates can increase with increasing pressure/density in supercritical CO₂ systems.⁹⁹ To further explore this issue Qian and coworkers have studied the Diels-Alder reaction between 9-hydroxymethylantracene (**179**) and *N*-ethylmaleimide (Scheme **46**).¹⁰⁰ The authors measured rate constants for the reaction over a range of pressures (90 – 190 bar) and temperatures (45, 60, and 75 °C). At 45 °C and 90 bar the reaction rate in supercritical CO₂ was 25 times faster than in acetonitrile; furthermore, rate constants *decreased* linearly with increasing pressure/density.

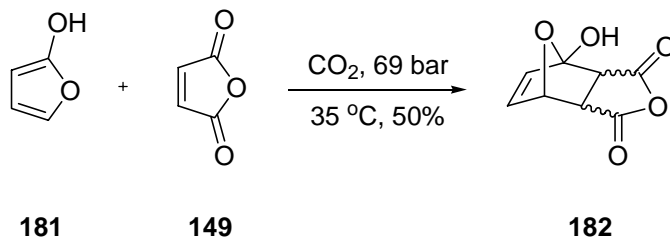
The difference in trends between this and the aforementioned studies can be explained by referring to reactant solubility. 9-hydroxymethylantracene belongs to a class of substrates that are not very soluble in supercritical CO₂ (solubilities $\leq 1 \times 10^{-3}$ mol% at 60 °C/90 bar); the previously mentioned dienes (i.e. cyclopentadiene) are substantially soluble (solubilities ≥ 0.2 mol%). Increasing the pressure/density of supercritical CO₂ does little to improve the solubility of compounds that are already significantly soluble. It does, however, improve the solubilities of the corresponding transition states, decreasing their energies relative to the reactants and thus accelerating reaction rates.



Scheme 46

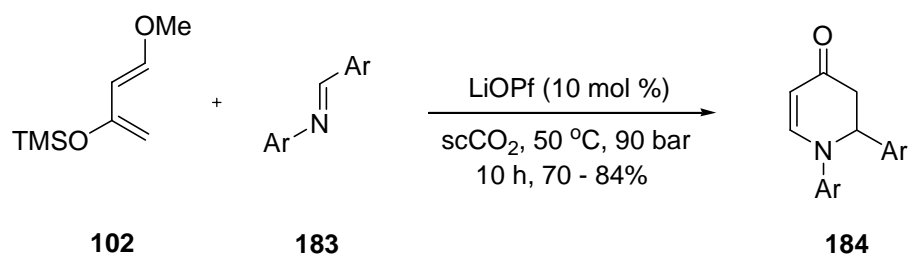
For less soluble substrates such as 9-hydroxymethylantracene, increases in pressure/density lead to better reactant solubilities relative to the transition states; the concomitant lowering of reactant energies relative to the transition state energies decreases reaction rates.

Kinetic studies have also been performed by Cott and coworkers (Scheme 47).¹⁰¹ This group has studied the reaction of furfuryl alcohol (**181**) with maleic anhydride. At 69 bar a 50% yield of product is obtained (*exo:endo*, 3.2:1). The kinetics of this system are second order.



Scheme 47

Shi and coworkers have explored the synthesis of nitrogen containing heterocycles via LiOPf catalyzed aza-Diels-Alder reactions of Danishefsky's diene with imines **183** (Scheme 48).¹⁰² These conditions give good yields of pyridones **184**. A catalyst is essential for these reactions to occur.



Scheme 48

6.0 CONCLUDING REMARKS

The objectives of this review have been twofold: to introduce the premises of green chemistry and to discuss the Diels-Alder reaction within the context of these premises. We have focused on benign solvent systems and have seen exciting advancements in the areas of aqueous chemistry, ionic liquids, supercritical carbon dioxide, and solvent-free chemistry.

Solvent-free Diels-Alder chemistry, while being the most atom economical, also benefits from the use of energy efficient microwave technology. Diels-Alder reactions performed in water are very benign and benefit from dramatically increased rates and increased stereoselectivities. Increased rates and selectivity are also true of Diels-Alder reactions performed in ionic liquids, and, moreover, these mediums have no vapor pressure and are generally recyclable and reusable. Supercritical carbon dioxide holds tremendous potential for industrial application. The physical properties of reactions performed in this medium vary with density and pressure, and this may prove to be extremely useful. All of these systems are environmentally benign alternatives to those of traditional synthetic chemistry; this is perhaps more apparent with aqueous and solvent-free chemistry, as well as chemistry performed in supercritical carbon dioxide. The use of ionic liquids warrants more caution, although they also embody many of the principles of the green philosophy. Clearly each area discussed herein has room for growth and contributes to a cleaner chemical future.

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