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# Environmentally Benign Solvent Systems: Toward a Greener [4+2] Cycloaddition Process

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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.

**Keywords:** Diels-Alder chemistry, green chemistry, benign solvents.

## I. INTRODUCTION

With technological advancement comes cost, and with respect to the chemical sciences the most important cost to be dealt with is the impact of chemical technologies on our environment [1]. Dealing with these issues can be expensive, especially for industries. For example, U. S. industries spend about 100 to 150 billion dollars a year to adhere to environmental regulations [2]. In order to efficiently minimize financial burdens, and more importantly detrimental effects to the environment, improvements to chemical processes should take place at the design stage. Green chemistry does exactly this. It offers technologies that are more benign than traditional chemical systems. The philosophy of green chemistry is often summed up in twelve principles as shown in Fig. (**1**) [1,3]. These guidelines aid in the design of processes that are efficient, non-wasteful, and non-hazardous; most importantly, for green chemistry to have an impact, the assimilation of these principles needs to happen in both academia and industry [3].

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 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)

**Fig. (1).** The 12 principles of green chemistry.

The Diels-Alder reaction, a concerted [4+2] cycloaddition of a diene and dienophile, is a good example of a green reaction as it is theoretically 100% atom economical [4] and furnishes products of high complexity from simple starting materials [5]. However, there are several ways to make the Diels-Alder reaction more environmentally friendly. Recent work in our group showcases the benefits of using transition metal catalysts (Scheme **1**) [6]. In a one pot, three step procedure substrate **1** is treated with $[Rh(CO)_2Cl]_2$ to give cross conjugated triene **2**. The subsequent addition of $[Rh(dppe)Cl]_2$ and $AgSbF_6$ then catalyzes an intramolecular Diels-Alder reaction. The addition of *N*-methylmaleimide (**4**) affects an intermolecular cycloaddition to give the products **5** and **6**. 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.

There are numerous other examples of green Diels-Alder processes. It is the aim of this paper to review some of these reactions. For the present application green principle 5 will be adopted as the base definition of a green process, with a focus on Diels-Alder reactions that eliminate solvents when possible or otherwise use benign solvents. Developments in microwave (MW) assisted, solvent-free Diels-Alder chemistry, as well as Diels-Alder chemistry performed in

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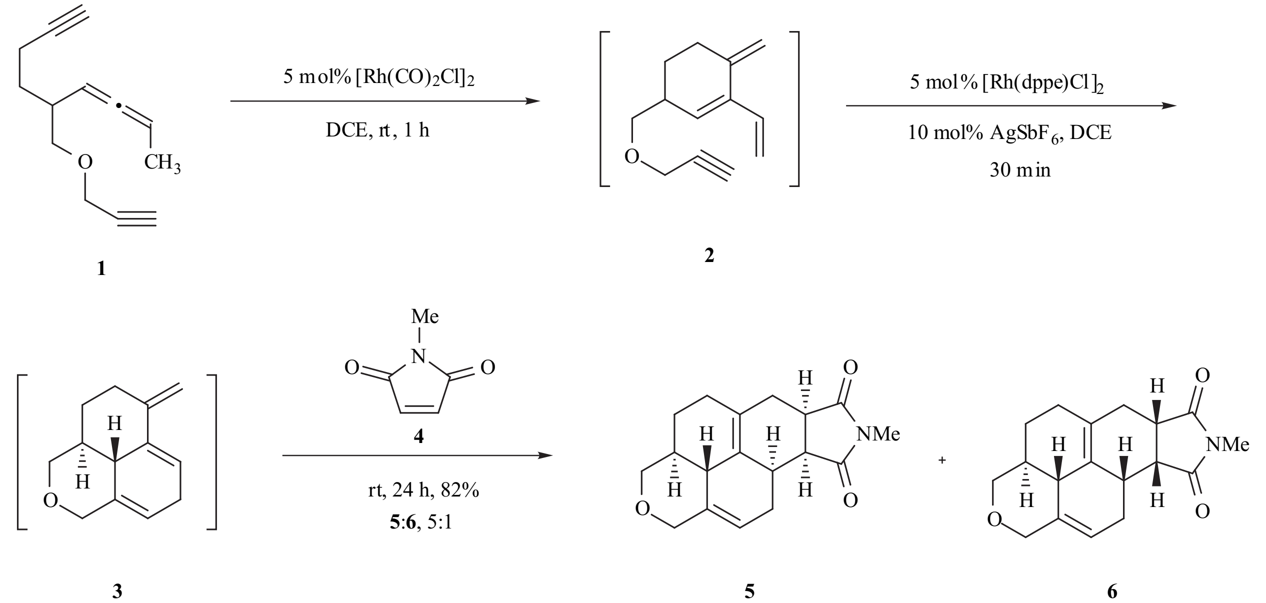


**Scheme 1.**

ionic liquids, water, and in supercritical $CO_2$ will be discussed. These solvent categories will be further divided into classes of compounds.

## II. MW ASSISTED, SOLVENT-FREE DIELS-ALDER REACTIONS

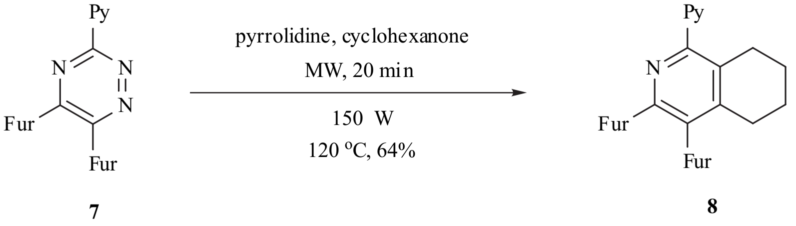
While common organic solvents provide an excellent media for the majority of organic reactions, they are nevertheless toxic and harmful to the environment. Performing reactions without the use of solvent is optimal as two principles of the green chemistry philosophy are addressed: harmful materials are 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 [7]. After the realization in 1986 that microwaves are a viable energy source for synthetic chemistry [8], chemists realized that solvent-free Diels-Alder reactions could benefit from this technology.

### II.1. Synthesis of Pyridines

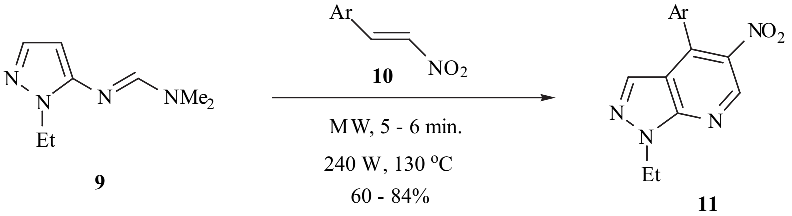
Pyridines have been of interest to synthetic chemists for over 100 years [9]. Díaz-Ortiz and coworkers have performed the Diels-Alder reactions of 4,6-dimethyl-1,2,3-triazine with a variety of enamines under microwave irradiation to give the corresponding pyridines [10]. The yields of products ranged from 21 – 71% and were an improvement over classical conditions, which gave much lower yields (0 – 27%) [11]. 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.

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-triazines (Scheme **2**) [9]. Pyrrolidine was used because it was found that cyclic amines work better than acyclic amines. Again the benefits of microwave irradiation are evident; considering cyclohexanone as a substrate, prolonged heating with pyrrolidine and triazine **7** under classical conditions (96 h) afforded only 25% yield of the desired product **8**. However, microwave irradiation afforded this cycloadduct in 64% yield in only 20 minutes. Unsymmetrical dienophiles reacted with triazines with moderate to high regioselectivity.

Pyrazolo[3,4-*b*]pyridines (**11**) have been prepared in 60 – 84% yield from the Diels-Alder reactions of pyrazolyl imine **9** and aromatic nitroalkenes **10** (Scheme **3**) [12]. Pyrazolyl imines are poor dienes because the molecules lose aromaticity upon reacting [12c]. Díaz-Ortiz and coworkers overcame this obstacle with the application of microwave energy, becoming the first to successfully perform such reactions. The reaction gave only products **11** when Ar = 2-thienyl; in other instances small amounts of nitro-free product (8-9%) were observed.



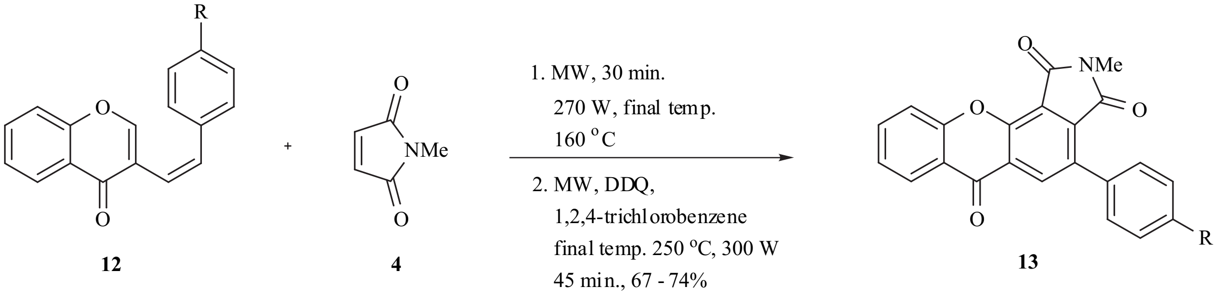
**Scheme 2.**



**Scheme 3.**

## II.2. Synthesis of Xanthones

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 **4**) [13]. 3-Styrylchromones reacted with *N*-methylmaleimide with complete stereoselectivity, giving *endo* cycloadducts with (Z)-3-styrylchromones and *exo* cycloadducts with the E isomers. To oxidize the cycloadducts to the requisite xanthones **13**, the addition of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) was necessary, unless 2-(2-nitrovinyl)thiophene was used as the dienophile, in which case oxidation took place *in situ*, immediately upon cycloaddition. At temperatures of 160 °C or more (Z)-3-styrylchromones isomerized to the E isomers. As a result, selectivities decreased; for example, cycloadditions with the less reactive *N*-phenylmaleimide took place at 200 °C and always led to mixtures of *endo* and *exo* isomers.



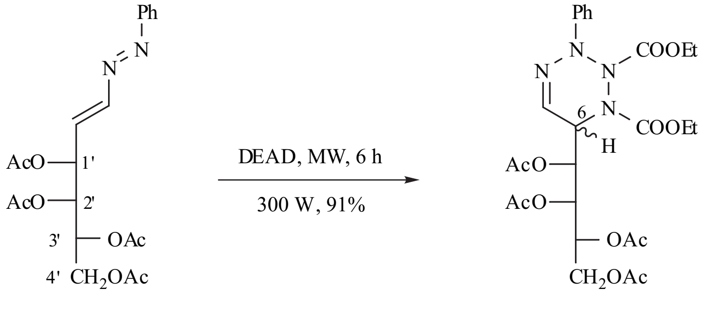
**Scheme 4.**

## II.3. Synthesis of Tetrazines

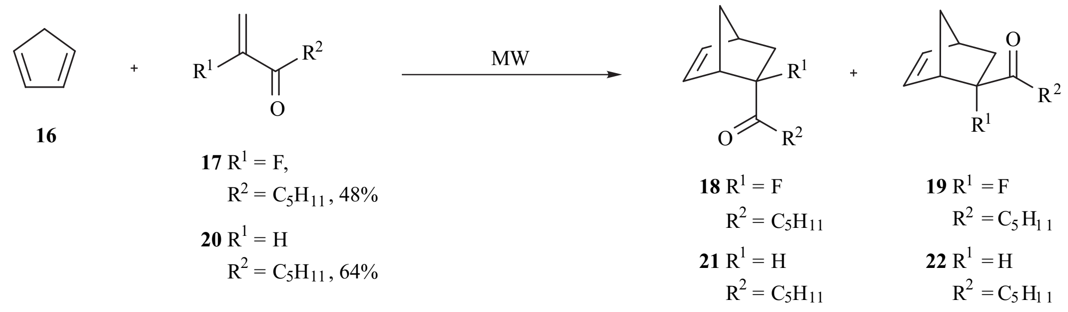
Avalos and coworkers have shown that chiral 1,2,3,6-tetrahydro-1,2,3,4-tetrazines **15** are available via microwave induced aza Diels-Alder reactions of sugar derived, chiral 1-aryl-1,2-diaza-1,3-butadienes **14** (Scheme **5**) [14]. The dienes were reacted with diethyl azodicarboxylate (DEAD) to give the corresponding hetero-Diels-Alder cycloadducts in 87 – 96% yield. Butadienes with a *threo* configuration at C-1'2' gave diastereoselectivities of 84:16 – 88:12 (6R:6S). Diastereomeric ratios were lower when butadienes with an *erythro* configuration at C-1'2' were used (6R:6S, 66:33).

## II.4. Diels-Alder Reactions to Produce Fluorinated Compounds

Fluorine can have an influential effect on the course of a Diels-Alder reaction, as shown by Essers and coworkers [15]. For example, the authors reacted cyclopentadiene (CPD, **16**) with various α-fluorinated α,β-unsaturated carbonyl compounds to find that the stereoselectivities were governed by the presence of fluorine (Scheme **6**). The reaction of CPD with **17** gave products that favored *exo* isomer **19** (**19**:**18**, 78:22), and for the reaction of dienophile **20**, the *endo* cycloadduct **21** predominated (**21**:**22**, 79:21). Calculations were done at the B3LYP/6-31G level on cycloadducts with $R^2 = CH_3$. Both the acetyl and halogen groups thermo-dynamically favor *exo* orientation when compared to their *endo* counterparts; thus, the stereoselectivity is attributed to kinetic effects resulting from fluorine substitution.



**Scheme 5.**



**Scheme 6.**

Monofluorinated vinyl sulfoxides are also good dienophiles for solvent-free Diels-Alder reactions, as shown by Sridhar and coworkers [16]. When the vinyl sulfoxide (2,2-dichloro-1-fluoroethenyl)sulfinyl benzene was reacted with 1,3-diphenylisobenzofuran, the resulting Diels-Alder adduct was afforded in 90% yield. 1,2-Difluoro vinyl sulfoxides worked equally well under the same conditions.

### II.5. Heterogeneous Catalysts and Diels-Alder Reactions

Avalos and coworkers have looked at the reaction between 2,5-dimethylfuran and *N*-phenylmaleimide on K-10 montmorillonite clay [17]. The cycloadduct was afforded as a diastereomeric mixture in 77% yield (*endo*:*exo*, 2.3:1) after 1.5 h at 0 °C. Alternatively, microwave irradiation (300 W) for 10 minutes afforded a quantitative yield of the product with the same *endo*:*exo* ratio.

Lewis acids immobilized onto silica gel can be used to catalyze a variety of Diels-Alder reactions. $SiO_2$/Zn catalyzes a green route to the class of gastric acid secretion inhibitors known as octahydroacridins (Scheme **7**) [18]. Jacob and coworkers reacted citronellal (**23**) with several aromatic amines **24** via an *N*-arylimino-Diels-Alder reaction to furnish the respective octahydroacridins **25** in 75 – 92% yield (*cis*:*trans*, 1 – 3:1). Microwave irradiation provided extremely short reaction times, typically on the order of 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 containing 40 – 51% (+)-*R*-citronellal.

## III. DIELS-ALDER REACTIONS IN WATER

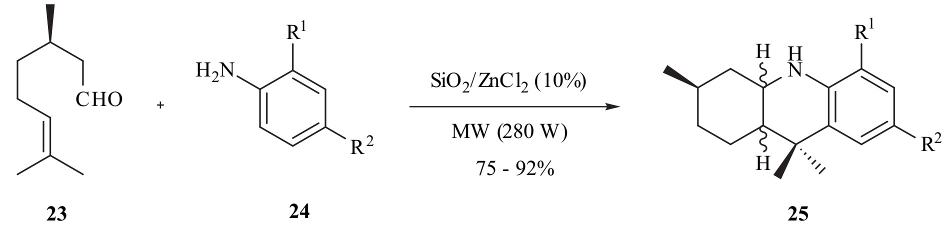
Breslow and Rideout were the first chemists to fully realize the potential of water as a solvent for the Diels-Alder reaction [19]. They found more than a 700-fold increase in the rate of reaction between CPD and methyl vinyl ketone in water when compared to isooctane, and also recognized that water enhances *endo* selectivity in the Diels-Alder reaction [20]. These effects are thought to arise from hydrophobic interactions between the diene, dienophile, and water, the high polarity of water, and hydrogen bonding of water and dienophile [21]. The number and variety of organic transformations performed in water over the years is staggering, and these reactions have recently been collected in a very thorough review in which Diels-Alder processes are well represented [22]. As a result, this review will only cover the more recent advances in the field of aqueous Diels-Alder chemistry.

### III.1. Hetero-Diels-Alder Reactions

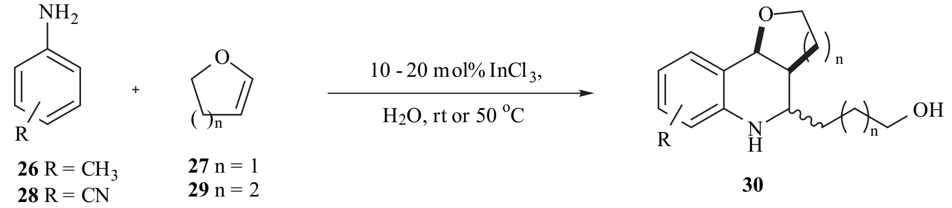
### *III.1.1. Synthesis of Tetrahydroquinolines*

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 [23]. Li and Zhang have focused on the preparation of these molecules in aqueous media using an indium catalyst (Scheme **8**) [24]. This domino reaction is thought to involve hydration and ring opening of the enol ethers to give compounds that 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 ranged from 30 – 90%, and aromatic amines bearing electron-donating groups were the most reactive. For example, reaction of **26** with **29** required 10 h and gave an 88% yield, compared to the reaction of **28** with **29**, which took 48 h and gave a 30% yield of the corresponding cycloadducts. Furthermore, 2,3-dihydrofuran (**27**) gave better yields and higher *cis* selectivities (46 – 85%, *cis*:*trans*, 69:31 – 96:4) than 3,4-dihydro-2*H*-pyran (**29**) (30 – 90%, *cis*:*trans*, 34:66 – 74:26). This reaction also worked with cyclic hemiacetals in place of the enol ethers [25].

Li and Chen have designed a greener version of the reaction between 3,4-dihydro-2*H*-pyran and aromatic amines



**Scheme 7.**



**26** R = $CH_3$
**28** R = CN
**27** n = 1
**29** n = 2
**30**

**Scheme 8.**

by replacing the indium catalyst with various ion exchange resins [26]. AG®50W-X2 hydrogen form resin worked the best due to its large surface area. These reactions required high temperature (80 °C), and the authors also noted that microwave irradiation led to *lower* yields. Aromatic amines with strongly electron-withdrawing groups gave slightly higher *trans* selectivities (*trans*:*cis*, 64:36 – 74:26) than neutral aromatic amines or those with electron donating groups (*trans*:*cis*, 45:55 – 64:36).

### *III.1.2. Synthesis of Pyridones*

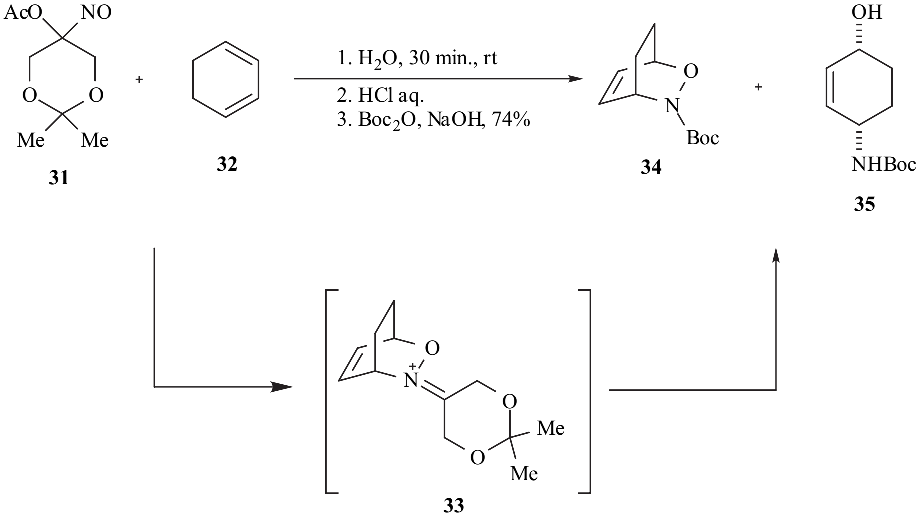
The aza-Diels-Alder reaction of an imine with Danishefsky's diene is a good way to access the 2,3-dihydro-4-pyridone skeleton, a key player in the syntheses of heterocyclic natural products [27]. A representative example was carried out by Loncaric and coworkers, who reacted Danishefsky's diene with an aldimine [28]. The formation of the Mannich by-product was subdued by using sodium alkanesulfonates, alkaline triflates, and other water soluble salts, as well as sodium iodide as catalysts. For example, alkaline triflates gave the pyridone in 65 – 90% and with excellent selectivity (pyridone:byproduct, >99:1). A variety of aromatic and heteroaromatic aldimines afforded pyridones when catalyzed by NaOTf. Moreover, in some instances the aldimine was generated *in situ* from the corresponding aldehydes and amines; for these one pot procedures the product yields were 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 [29]. The pyridones were afforded in 78 – 86% yields.

### *III.1.3. Synthesis of 3,6-Dihydro-1,2-oxazines*

The reaction of α-acetoxynitroso derivative **31** with cyclic and acyclic dienophiles in water leads to 3,6-dihydro-1,2-oxazines, as shown by Calvet and coworkers (Scheme **9**) [30]. When reacted with 1,3-cyclohexadiene (**32**) in pure water, a 49:1 mixture of products in favor of the Diels-Alder adduct **34** was obtained. The minor product **35** is proposed to result from N-O bond cleavage of the intermediate imine **33**. Under anhydrous conditions ($CH_2Cl_2$) intermediate **33** predominates, but under aqueous conditions interception of the intermediate by water accounts for the formation of **35**. Asymmetric, acyclic dienophiles reacted to give regioisomers where R is *meta* or *para* to oxygen (63:37 – 80:20, respectively).

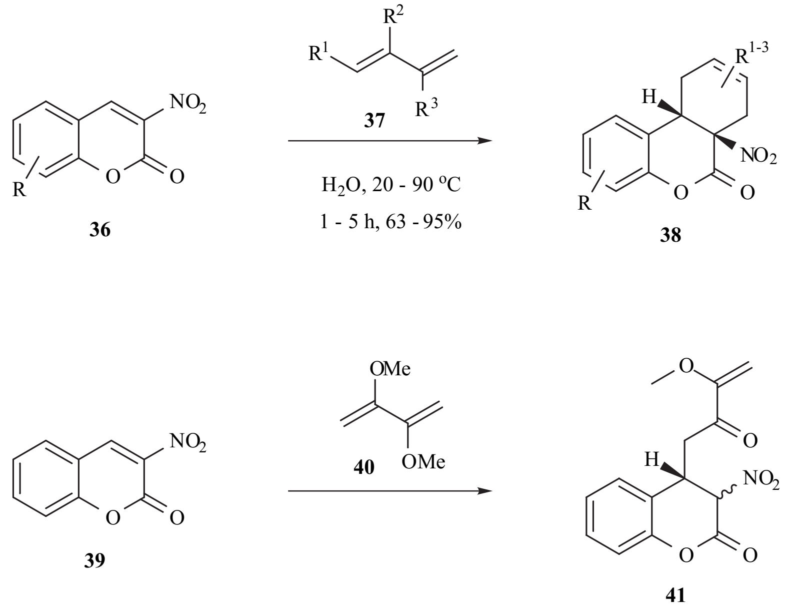
### *III.1.4. Synthesis of Nitrotetrahydrobenzo[*c*]chromenones*

Nitrotetrahydrobenzo[*c*]chromenones can be converted to 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 **10**) [31]. 3-Nitrocoumarins are an interesting class of molecules, since they can function as either dienophiles or dienes [32]; in the work described herein, they served mainly as dienophiles, giving 63 – 95% yields of nitrotetrahydrobenzo [*c*]chromenones **38** when reacted with simple dienes. Coumarin **39** reacted as a diene, however, with 2,3-dimethoxy-1,3-butadiene (**40**) to give a nitronate, which then hydrolyzed to provide adduct **41**. To further explore this anomalous result, the authors performed the same reaction in $CH_2Cl_2$ and found that, under anhydrous conditions,



**31** **32** **34** **35** **33**

**Scheme 9.**

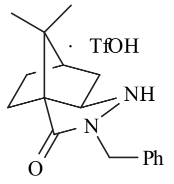


**Scheme 10.**

coumarin **39** reacted once again as a dienophile. It is postulated that 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.

## III.2. Enantioselective Diels-Alder Reactions

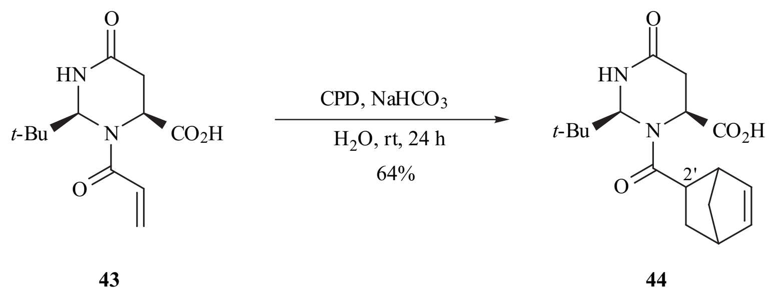
A green chiral catalyst has recently been developed by Lemay and Ogilvie and is based on a camphor derived hydrazide framework (Fig. **2**) [33]. It is an organocatalyst which means that it does not incorporate a metal, an improvement over potentially toxic metal based catalysts. Organocatalyst **42** forms an iminium ion upon reaction with the dienophile and directs the approach of the diene. There are three features critical to its success. The most important of these is the benzyl group on the nitrogen, which if removed results in deactivation of the catalyst. The acid additive 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, using 20 mol% of catalyst **42** and trifluoromethanesulfonic acid (TfOH) as the co-catalyst (10 mol% - 40 mol%), afforded the Diels-Alder adduct in 96% yield and as a mixture of *exo* and *endo* isomers (1.9:1, respectively, with respect to CHO, *exo* ee = 90%). Acetic acid as a co-catalyst gave a 7% yield. Finally, the tertiary nitrogen is thought to increase the nucleophilicity of the hydrazide by means of the α-heteroatom effect [34]. The catalyst worked well with dienes bearing aromatic and aliphatic substitution. Yields were good to excellent and favored the *exo* isomer in most cases (*exo*:*endo*, 1.2 – 2.6:1). *Exo* enantioselectivities were 81 – 92%.



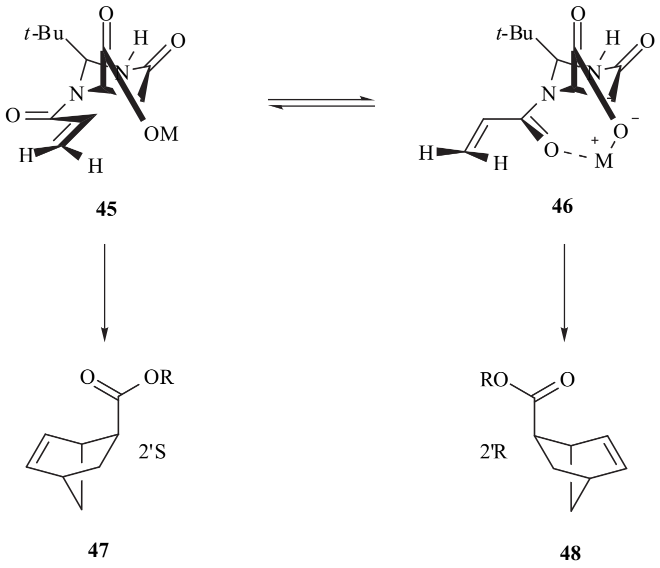
**42**

**Fig. (2).** Hydrazide catalyst.

Lakner and Negrete have designed a chiral acrylamide auxiliary and have successfully applied it to the Diels-Alder reaction (Scheme **11**) [35]. Attachment of the auxiliary to give **43** was performed in water and removal of the auxiliary was accomplished by 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 resulted in low enantioselectivities. The reactions gave higher enantioselectivities when the dienophile **43** was prepared beforehand. For example, reaction of compound **43** with



**Scheme 11.**

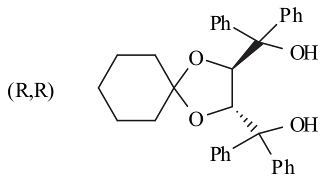


**Scheme 12.**

CPD gave cycloadduct **44** with an *endo*:*exo* ratio of 82:18 in 64% enantiomeric excess.

Mahindaratne and coworkers have further explored the role of carboxylate salts in the reaction between dienophile **43** and CPD [36]. To account for selectivity they postulate a chelate model (Scheme **12**). The major product of the reaction, the 2'S *endo* product **47**, results from **43** reacting via rotamer **45**, where the amide takes an anti conformation. The minor 2'R *endo* product **48** results from **43** reacting via rotamer **46** in which the cation chelates to the amide carbonyl group as well, forcing the amide into a syn conformation. In both cases, CPD comes in from the bottom face. By experimenting with cations of differing chelating ability, the authors provided sufficient support for this model.

Miyamoto and coworkers have utilized inclusion chemistry in their efforts at stereocontrol [37]. A reaction was first performed in water, which in this case was the reaction between isoprene and *N*-alkylmaleimides. A chiral compound was then added to the racemic mixture, forming a chiral inclusion complex. The inclusion crystals were then separated to yield an enantioenriched product. For the case of *N*-ethylmaleimide and chiral host **49** (Fig. **3**), the (+)-Diels-Alder adduct was obtained in 31% yield and 94% enantiomeric purity.



**49**

**Fig. (3).** Chiral host.

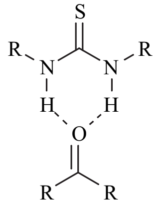
### III.3. Other Diels-Alder Reactions

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 [38]. The catalyst can be recycled, is air stable, and is useful for simple Diels-Alder reactions in water. It gave 80 – 99% yields and *endo* selectivities ranging from 3.5:1 to 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.

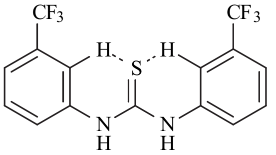
A recyclable Lewis acid catalyst was also been developed by Yamazaki and coworkers. They have attached $Sc[C(SO_2C_4F_9)_3]_3$ to fluorous reverse phase silica gel and have catalyzed the reaction between 2,3-dimethyl-1,3-butadiene and methyl vinyl ketone [39]. The catalyst was recovered by filtration and reused with no loss in yield or selectivity after four cycles.

Wittkopp and Schreiner have used 1,3-disubstituted alkyl, cycloalkyl, and phenyl thioureas as catalysts for aqueous Diels-Alder systems [40]. It is postulated that the amine hydrogens bond to the dienophile carbonyls (Fig. **4**). In doing so, their action is thought to be analogous to that of a Lewis acid. These thiourea catalysts worked in organic solvents (cyclohexane, chloroform), but had very high activity in aqueous systems (90:10, $H_2O$:*t*-BuOH). For example, when 1 mol% of catalyst **51** was used, the reaction between CPD and methyl vinyl ketone yielded 85% of product, compared to 42% yield in cyclohexane and 52% yield in chloroform. In general, alkyl, cycloalkyl, and phenyl thiourea catalysts worked poorly in comparison to phenyl thioureas substituted with electron withdrawing groups. It is proposed that for effective hydrogen bonding, the catalysts arrange their substituents away from the dienophile carbonyl. Such order is entropically disfavored, but the electron deficient catalysts do not suffer from this problem, since the aryl hydrogens are thought to be activated by the electron withdrawing groups. Resulting coordination to the sulfur contributes to a rigid system that is easily accessible for the dienophile.

Yanai and coworkers have effected intramolecular Diels-Alder reactions of 1,7,9-decatrienoates in $H_2O$-$^i$PrOH

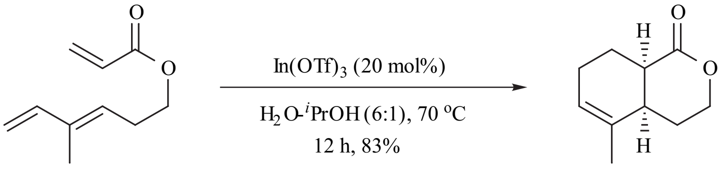


**50**



**51**

**Fig. (4).** Thiourea catalysts.



**52** **53**

**Scheme 13.**

mixtures (6:1) via In(OTf)$_3$ catalysis [41]. For example, compound **52** reacted to give adduct **53** in 83% yield (Scheme **13**). The aqueous/catalyst phase was recovered and used two more times with no loss in yield.

## IV. DIELS-ALDER REACTIONS IN IONIC LIQUIDS

Loosely defined, an ionic liquid is a salt that is liquid at room temperature, though some ionic liquids currently in use are solid at room temperature [42a]. Ionic liquids have several properties that make them greener alternatives to traditional solvents [43]: they 1) have virtually no vapor pressure, 2) are stable over wide temperature ranges, 3) are able to dissolve a variety of synthetically useful organic compounds, 4) are generally not flammable or explosive, and 5) are recyclable. 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. A very thorough review encompassing chemical and biochemical reactions performed in ionic liquids has recently been written [43].

### IV.1. Diels-Alder Reactions of Cyclopentadiene with Methyl Acrylate

A large number of Diels-Alder studies performed in ionic liquids have used CPD and methyl acrylate. The low-melting fused salt EAN was used by Jaeger and Tucker as a solvent for this reaction to give a 98% yield of product [44]. 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 $1.7 \times 10^4$ $M^{-1}$ $sec^{-1}$ to $5.4 \times 10^4$ $M^{-1}$ $sec^{-1}$.

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 that the Lewis acidic character of [EMIC][AlCl$_3$], a chloroaluminate melt, can be tuned by varying the percentage of AlCl$_3$ [45]. With 48% AlCl$_3$ the media is slightly basic and the reaction is 7 times faster than the reaction performed in pure EAN. At 51% AlCl$_3$ the media is slightly acidic, and the reaction is 175 times faster than in pure EAN. For the acidic melt the *endo*:*exo* ratios were higher than for the basic melt (19:1 and 5.3:1, respectively).

One limitation of the chloroaluminate melts is their sensitivity to water, since they react with it to give HCl and hydrated aluminium(III) ionic species. Moreover, these liquids can form adducts with heteroatomic functional groups such as ketones [42b].

Fortunately, air and water stable ionic liquids are available. For example, Fischer and coworkers surveyed a number of such ionic liquids from the bmim$^+$ and emim$^+$ families and found that the reaction between CPD and methyl acrylate in [bmim][BF$_4$] gives the Diels-Alder cycloadduct in 91% yield (*endo*:*exo*, 4.3:1) at rt after 72 hours [46].

Aggarwal and coworkers have looked at the reaction of CPD with methyl acrylate in a number of imidazolium based ionic liquids [47]. Switching from [bm$_2$im][BF$_4$] to [bmim][BF$_4$] led to an increase in *endo* selectivity (from 3.3:1 to 4.6:1, respectively). A further increase in selectivity to 6.7:1 was brought about by switching to [HO(CH$_2$)$_2$mim] [N(Tf)$_2$] as a solvent. These ratios are thought to reflect the hydrogen bond donating ability of the respective ionic liquid cations to methyl acrylate, because [HO(CH$_2$)$_2$mim][N(Tf)$_2$] is the strongest hydrogen bond donor and gives the highest *endo* selectivity and [bm$_2$im][BF$_4$] is the weakest hydrogen bond donor and gives the lowest *endo* selectivity.

Vidiš and coworkers sought to study these hydrogen bonding effects more thoroughly [48]; they ran the reaction in several bmim$^+$ based ionic liquids and used IR to determine the wavenumbers of the $C_{im}$-H · · · $A^-$ stretches. 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 was observed for [PF$_6$]$^-$ ($\nu_{CH}$ = 3126 cm$^{-1}$, *endo*:*exo* = 5.0:1), [BF$_4$]$^-$ ($\nu_{CH}$ = 3123 cm$^{-1}$, *endo*:*exo* = 4.9:1), and [Tf$_2$N]$^-$ ($\nu_{CH}$ = 3121 cm$^{-1}$, *endo*:*exo* = 4.3:1), but not for [CF$_3$COO]$^-$ ($\nu_{CH}$ = 3087 cm$^{-1}$, *endo*:*exo* = 4.4:1). The last ion is a much stronger hydrogen bond acceptor than $[Tf_2N]^-$, yet it allows for slightly greater *endo* selectivity. Clearly, selectivity is dependent upon other factors.

As opposed to Aggarwal's results, the authors 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. When the hydrogen bond donor was separated from the center of positive charge, such as with *N*-alkyl-*N*-(2-hydroxyethyl)-*N,N*-dimethylammonium ionic liquids, *endo* selectivity was generally higher in comparison to 1-alkyl-2,3-dimethylimidazolium systems.

Imperato and coworkers have taken an interesting step by moving away from classic melt compositions and designing ionic liquids from mixtures of sugars, ureas, and salts [49]. Because these melts are composed of essentially non-toxic and readily available compounds, they are considered to be greener. The best results were obtained for the reaction of CPD with methyl acrylate in a mixture of sorbitol, dimethylurea (DMU), and ammonium chloride (70:20:10, respectively, melting point = 67 °C). The product was obtained quantitatively with an *endo* selectivity of 5.0:1. The addition of 10 mol% $Sc(OTf)_3$ resulted in a marginal increase in the *endo* selectivity (5.0:1 to 6.0:1).

## IV.2. Hetero-Diels-Alder Reactions

### *IV.2.1. Synthesis of Pyridones*

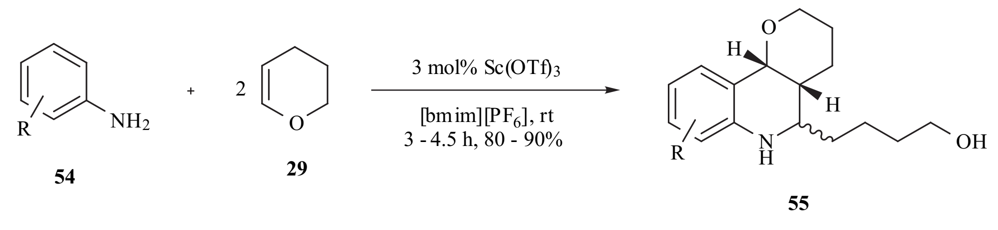
Zulfiqar and Kitazume have developed a one-pot procedure in which aromatic imines are formed *in situ* from aldehydes and amines and then allowed to react with Danishefsky's diene to produce the corresponding pyridones in 75 – 99% yield [50]. The authors used two ionic liquids with equal success: 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate, and [emim][OTf]. For example, reaction of benzaldehyde, aniline, and Danishefsky's diene gave the product in 82% yield in the former ionic liquid, and in 80% yield in the latter ionic liquid. A direct comparison can be made between this reaction performed in ionic liquid and the same reaction performed in water [28]. The yields are similar in magnitude, but this process requires a much longer time. After a reaction was completed, the ionic liquid and scandium catalyst were nearly fully recovered (92 – 98%) and could be used two more times without a decrease in yield.

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 [51]. The reaction times were much shorter (1 – 6 h versus 20 h for the former reactions). However, the imines were pre-prepared. Pégot and Vo-Thanh attempted a one-pot, three component procedure in which benzaldehyde, benzylamine, and Danishefsky's diene are reacted, but the yield fell below the good yields they typically obtained for the former two component procedure (69 – 90%). The ionic liquid was reused up to three times.

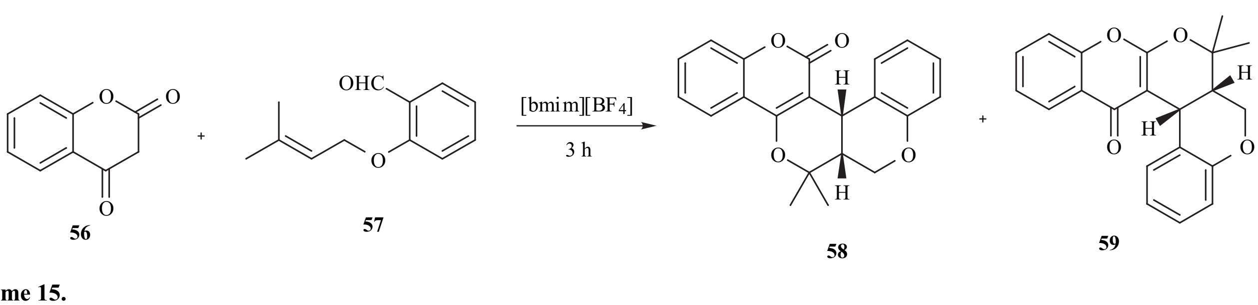
### *IV.2.2. Synthesis of Tetrahydroquinolines and Pyranocoumarins*

Yadav and coworkers have provided a green route to tetrahydroquinolines using $[bmim][PF_6]$ as a reaction medium and $Sc(OTf)_3$ as a catalyst [52]. Both 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran gave product **55** in 80 – 90% yield and with *endo*:*exo* ratios often greater than or equal to 92:8 (Scheme **14**). This reaction can be compared to the same reaction performed in water (compare Scheme **14** to Scheme **8**). The present route gives products in slightly higher yields and shorter reaction times (3 – 4.5 h versus 2 – 72 h). The ionic liquid/catalyst phase was recovered and reused.

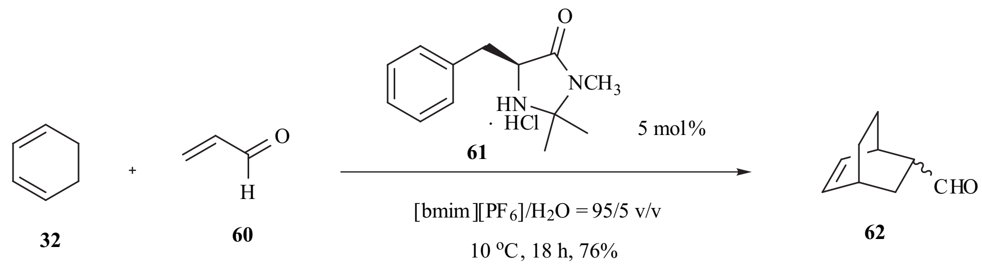
Due to their roles as anticoagulants, insecticides, antifungals, and HIV protease inhibitors, coumarins are also of considerable interest in the world of heterocyclic molecules [53]. A procedure involving a domino Knoevenagel and Hetero-Diels-Alder reaction, also developed by Yadav and coworkers, works well for the synthesis of pyrano[3,2-*c*]coumarins (Scheme **15**) [54]. The reaction of 1,3-dione **56** with *O*-prenylated aromatic aldehyde **57** results in a Knoevenagel condensation, the product of which undergoes an intramolecular Diels-Alder reaction to give *cis* coumarin **58** along with chromone byproduct **59** (**58**:**59**,



**Scheme 14.**



**Scheme 15.**



**Scheme 16.**

90:10). For a variety of aromatic 1,3-diones and aldehydes, yields ranged from 78 to 91% and the ratios of coumarin to chromone range from 80:20 to 90:10. The reactions worked in [bmim][$PF_6$] and [bmim][$BF_4$], though the yields of products were much lower in the hydrophobic [bmim][$PF_6$] (25 – 40%). Also, the reaction was limited to 4-hydroxy-1,3-diones and *O*-prenylated aldehydes.

### *IV.2.3. Diels-Alder Reactions of Furan and Thiophene*

Hemeon and coworkers have successfully reacted furan with methyl acrylate and maleic anhydride in [bmim][$BF_4$] and [bmim][$PF_6$] [55]. The former served as an ideal medium due to greater ease of product isolation. At a catalyst loading of 30 mol%, the *endo* selectivity for reaction with methyl acrylate (*endo*:*exo*, 2.3:1 in either ionic liquid) was better than at 100 mol% (*endo*:*exo*, 1.4:1/[bmim][$PF_6$], 1.8:1/[bmim][$BF_4$]). Note that solvent-free conditions give *exo* favored products [56]. Reaction with maleic anhydride gave solely *exo* product, irregardless of catalyst loading. The benefit of stoichiometric $ZnI_2$ is that the yields were generally higher. The authors have also reacted thiophene with DMAD, resulting in 44% yield of product.

## IV.3. Enantioselective Diels-Alder Reactions

The chiral amine catalyst **61** [57] has tremendous green potential. Its reactivity is not based on a potentially toxic metal, and furthermore it can be used in ionic liquid systems; Park and coworkers have successfully shown this by catalyzing the reaction between cyclohexadiene and acrolein (**60**, Scheme **16**) [58]. Without water, the amine salt cannot function as a catalyst [57], so it is essential that the ionic medium be hydrophobic and not hydrophilic. For example, performing the reaction in hydrophobic [bmim][$PF_6$] gave a 76% yield of product **62** (*endo*:*exo*, 17:1) with 93% enantioselectivity (*R*) for the *endo* product. In the hydrophilic [bmim][$BF_4$], only 5% of the product was obtained. The ionic liquid/catalyst phase was recovered, though the enantioselectivity dropped 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 [59]. Two types of platinum catalysts were used, one type based on the $R_4$-NUPHOS diphosphine system (**63** and **65**) and the other type based on the BINAP system (**64** and **66**, Fig. **5**).

For the reaction of oxazolidinone **67**, all of the catalysts worked well, giving enantioselectivities of 78 – 95% (*R* or *S*) in 1 hour at room temperature (Scheme **17**). This was a dramatic improvement over reactions performed in dichloromethane, which required extended times (20 h or more) at -20 °C because the catalysts formed inactive [$\eta^5$-$Cp^+$] species at room temperature.

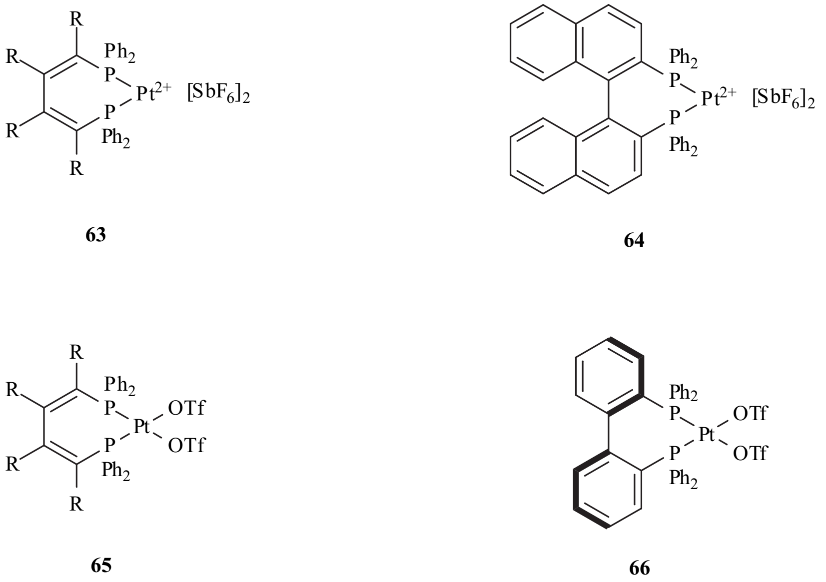
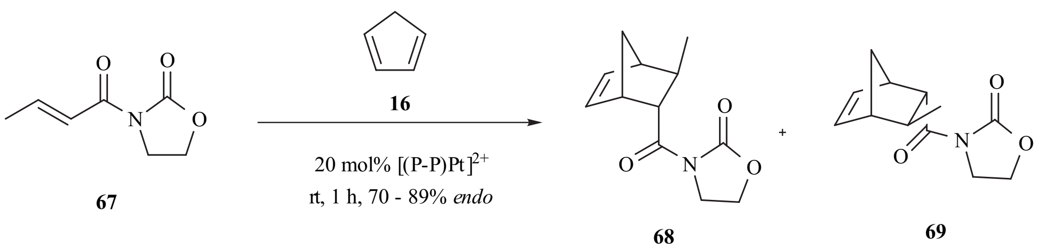
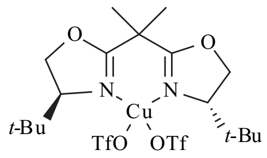


**Fig. (5).** Flexible and rigid catalysts for asymmetric Diels-Alder reactions.



**Scheme 17.**

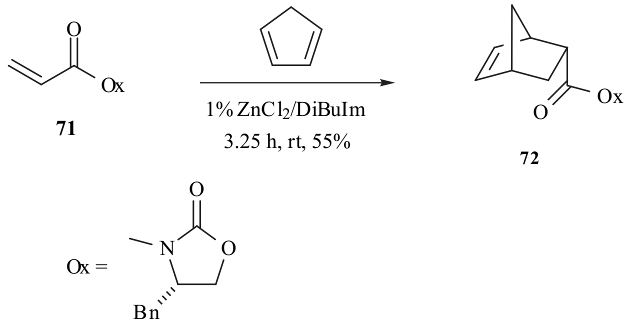
The reaction of oxazolidinone **67** with CPD was studied by Meracz and Oh as well. Using the copper bisoxazoline-based chiral Lewis acid **70** (Fig. **6**) in [DiBuIm][BF$_4$], they prepared the adducts in 65% yield with an *endo* selectivity of 93:7 and a selectivity for **68** of 96:4 [60]. In CH$_2$Cl$_2$, only a 4% yield of product was obtained.



**70**

**Fig. (6).** Copper bisoxazoline-based chiral Lewis acid.

The authors also demonstrated excellent stereocontrol in the same solvent by using a chiral oxazolidinone (**71**, Scheme **18**). The reaction included 1% ZnCl$_2$ and in just over 3 hours yielded 55% of product **72**.



**Scheme 18.**

### IV.4. Other Diels-Alder Reactions

Earle and coworkers have reacted CPD with dimethyl maleate, ethyl acrylate, and acrylonitrile in a variety of bmim$^+$ based ionic liquids, achieving 80 – 99% yields of products with moderate *endo*:*exo* selectivities (1.6 – 6.0:1) [61].

In addition to catalyzing aqueous Diels-Alder reactions, the tungsten based Lewis acid catalyst developed by Chen and coworkers, [O=P(2-py)$_3$W(CO)(NO)$_2$](BF$_4$)$_2$, also works in [bmim][PF$_6$] [38]. Like their aqueous counterparts, these reactions worked at room temperature and 50 °C, as well as under microwave irradiation, and gave yields (65 – 99%) and *endo*:*exo* selectivities (3.5:1 – 100:0) that were generally comparable to the aqueous systems.

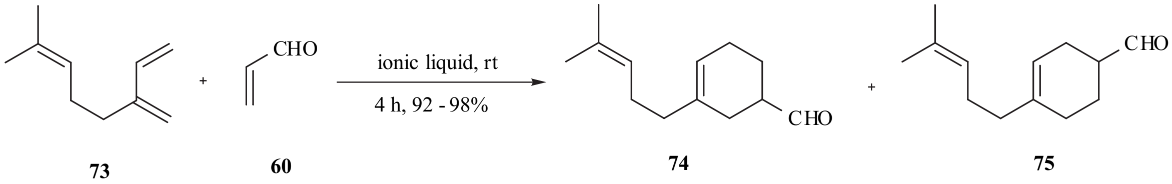
Kumar and Pawar have shown that the reaction between CPD and methyl methacrylate gives a reversal in selectivity when performed in the chloroaluminate ionic liquid [EMIC][AlCl$_3$] [62]. As the mol% of AlCl$_3$ increased so did the stereoselectivity; at 60 mol%, the typical selectivity for the *exo* isomer (*endo*:*exo*, 1:2) was reversed to favor of the *endo* isomer (*endo*:*exo*, 4.55:1).

Nobuoka and coworkers have used mixtures of imidazolium based ionic liquids as mediums for the reaction between ethyl acrylate and CPD [63]. In a mixture of [bmim][BF$_4$] and [bmim][CS] (6.7:1, respectively) the authors isolated a 66% yield of product with an *endo* selectivity of 10.3:1, almost twice the selectivity in pure [bmim][BF$_4$] (6.1:1). In their studies, the authors found that the counter anion of [bmim][CS], camphorsulfonate, binds very loosely to the imidazolium cation. This weak affiliation is thought to allow for greater hydrogen bonding between bmim$^+$ and ethyl acrylate, accounting for the high stereoselectivity of the reaction.

Silvero and coworkers have used the reaction between CPD and methyl vinyl ketone as a model to study the effects of Lewis acid catalysis in [HMI][BF$_4$] [64]. Lewis acids such as TfOH and bis(trifluoromethanesulfonate)imide (Tf$_2$NH) gave greater than 99% conversions and *endo*:*exo* selectivities of 93:7 and 94:6, respectively. Ce(OTf)$_4$·5H$_2$O, Y(OTf)$_3$, and Sc(OTf)$_3$ gave similar yields (95 – > 99%) and the same selectivities in much shorter reaction times (5 min compared to 1h for TfOH and Tf$_2$NH). Catalyst loading was also important. At 0.5 mol%, Ce(OTf)$_4$·5H$_2$O gave quantitative conversion to the product in 5 min. 0.2 mol% of catalyst required 1 h to achieve the same result. The *endo*:*exo* selectivity (*endo*:*exo*, 94:6) was the same for both catalyst loadings.

In the presence of Sc(OTf)$_3$, 2,3-dimethylbutadiene and cyclohexadiene reacted well with methyl vinyl ketone, maleic anhydride, and 1,4-naphthoquinone in various bmim$^+$ based ionic liquids, as shown by Song and coworkers [65]. The optimal catalyst loading was 0.2 mol%. At 10 mol% catalyst, the reactions were difficult to control, as the authors reported heat generation and a color change to dark brown in a matter of seconds. Yields of products ranged from 71% to greater than 99%. In cases where *endo*:*exo* selectivity was an issue, the reactions were virtually completely *endo* selective (*endo*:*exo*, >99:1). The ionic liquid/catalyst phase is recoverable, and was reused up to 11 times without any loss in activity.

Reactions of 2,3-dimethylbutadiene and cyclohexadiene with simple dienophiles such as acrolein, methyl vinyl ketone, and methyl acrylate were studied by Abbott and coworkers in the Lewis acidic choline chloride-MCl$_2$ ionic liquids (M = Zn or Sn) [66]. Yields were very good to excellent for all cases (85 – 94%), as were *endo* selectivities



**Scheme 19.**

(*endo*:*exo*, 83:17 – 97:3). The Zn containing ionic liquids allowed for faster reaction rates (8 min – 5 h) than their Sn counterparts (20 - 24 h). The reaction between isoprene and acrolein was also studied. The selectivity for the 1,4-product was excellent (1,4-product:1,3-product, 95:5). For both the Zn and Sn containing ionic liquids neither the reaction rates nor selectivities were influenced by the presence of water in the system.

Ludley and Karodia have looked at the reactions between isoprene and methyl acrylate, methyl vinyl ketone, and acrylonitrile in phosphonium tosylates, ionic liquids that are solid at room temperature [67]. The yields and selectivities for these reactions were dependent upon both the substrates involved and the ionic liquid used. Methyl acrylate and methyl vinyl ketone generally showed excellent selectivity for 1,4-products (1,4:1,3, >99:1). As a dienophile, acrylonitrile led to poorer selectivity (1,4:1,3, 69:31 – 76:24).

There are some instances in which 1,4-selectivity is crucial. An example is the synthesis of myrac aldehyde, available via the Diels-Alder reaction of myrcene (**73**) with acrolein (Scheme **19**). Of the two compounds produced in this reaction *'para'*-myrac aldehyde **75** (the 1,4-product) is the desired one due to its uses in perfumes and cosmetics. The *'para'* product is readily available when the reaction is performed in ionic liquid, as Yin and coworkers have recently shown [68]. Bmim$^+$, emim$^+$, and Py$^+$ based salts, coupled with $ZnCl_2$ ($ZnCl_2$:salt, 2 – 3:1), made ionic liquids that were good mediums for this reaction. Yields and regioselectivities were in the range of 15.7 – 19:1 in favor of **75**. For the reactions of myrcene with other dienophiles, regioselectivity was dependent on temperature. Higher reaction temperatures gave higher yields but at the expense of producing more *'meta'* product **74**.

## V. DIELS-ALDER REACTIONS IN SUPERCRITICAL CARBON DIOXIDE

The chemical and material industries have been developing numerous applications for $CO_2$ [69]. Among these applications are the decaffeination of coffee beans with supercritical $CO_2$, and the production of polymethylmethacrylate and polystyrene using supercritical $CO_2$ as a reaction medium [70]. $CO_2$ is also used in microelectronics processing and textile dyeing [69]. Below we will consider Diels-Alder reactions performed in supercritical $CO_2$.

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 [70]. For example, in its supercritical state $CO_2$ ($P_C$ = 73.8 bar and $T_C$ = 31.1 °C) has densities above that of gaseous $CO_2$ but below the density of liquid $CO_2$. These densities vary depending upon the temperatures and pressures applied to the system [70]. The varying density of supercritical fluids is a useful characteristic; substances which are poorly soluble in supercritical $CO_2$, for instance, exhibit increased solubility with increases in fluid density [70]. Moreover, gases are completely soluble in supercritical $CO_2$, so the possibility arises to create systems that can dissolve solids, liquids, and gases all at the same time [70]. 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 [69].

Supercritical $CO_2$ is considered green for a number of reasons [70]. It is non-toxic, non-flammable, and relatively inert. Aside from this, removal of the solvent is simple, just evaporation upon completion of a reaction. $CO_2$ is also cheap and abundant. Diels-Alder reactions in supercritical $CO_2$ up until the year 2000 have been previously reviewed [70], so only the most recent advances in this field will be discussed below.

### V.1. Enantioselective Diels-Alder Reactions

Fukuzawa and coworkers have studied rare earth metal catalyzed reactions between 4*S*-3-acryloyl-4-isopropyl-oxazolidin-2-one (**76**) and CPD (Scheme **20**) [71]. Reactions in supercritical $CO_2$ gave *endo* selectivities in the range of 70:30 to 92:8, and generally moderate *endo* diastereoselectivities of 46 – 69% de in favor of diastereomer **77**. An *endo* diastereoselectivity of 77% was achieved with the use of $Yb(ClO_4)_3 \cdot 8H_2O$ as a catalyst. Diastereoselectivities were always higher in supercritical $CO_2$ than in $CH_2Cl_2$ (46 – 69% versus 32 – 42%). For some chiral rare earth catalysts, the reaction between Danishefsky's diene and benzaldehyde gave poor to good yields of product (78%, with (+)-Yb(hfc)$_3$ as catalyst), but no catalysts gave enantioselectivities exceeding 38% *R*.

The authors also had success in catalyzing the reaction between 3-crotonoyl-2-oxazolidinone and CPD. The use of $Sc(OTf)_3$ as a catalyst, coupled with pybox (**79**, Fig. **7**) afforded a 71% yield of products (*endo*:*exo*, 93:7) with an

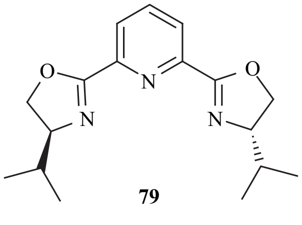


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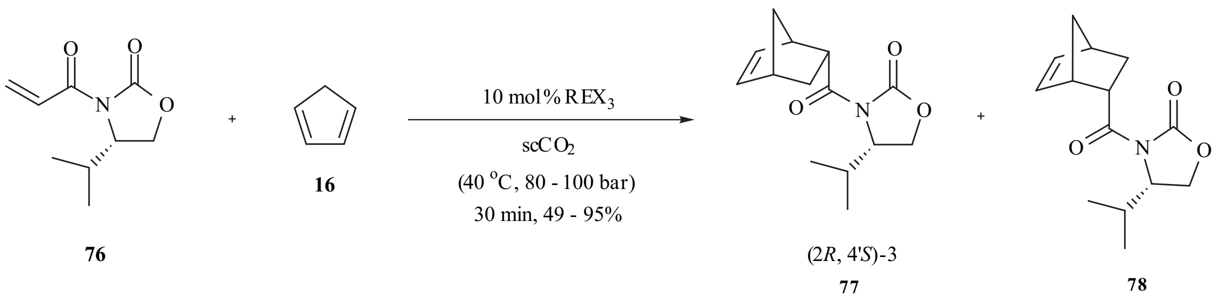
**Fig. (7).** Pybox.



**Scheme 20.**

*endo* ee of 83%. 4Å molecular sieves were necessary for the high enantioselectivity as it dropped to 63% in their absence. There was no correlation between enantioselectivity and $CO_2$ density.

### V.2. Other Diels-Alder Reactions

Several studies over the years have found that reaction rates can increase with increasing pressure/density in supercritical $CO_2$ systems [72]. To further explore this issue, Qian and coworkers have studied the Diels-Alder reaction between 9-hydroxymethylanthracene and *N*-ethylmaleimide [73]. 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 $CO_2$ 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 solubilities. 9-Hydroxymethylanthracene belongs to a class of substrates that are not very soluble in supercritical $CO_2$ (solubilities $\leq 1 \times 10^{-3}$ mol % at 60 °C/90 bar); the previously mentioned dienes (i.e. cyclopentadiene) are substantially soluble (solubilities $\geq 0.2$ mol %). The authors postulate that increasing the pressure/density of supercritical $CO_2$ 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. For less soluble substrates such as 9-hydroxymethylanthracene, increases in pressure/density lead to better reactant solubilities relative to the transition states, concomitantly lowering reactant energies and decreases reaction rates.

Kinetic studies have also been performed by Holmes and coworkers [74]. This group has studied the reaction of furfuryl alcohol with maleic anhydride. At 69 bar the product was obtained in 50% yield (*exo*:*endo*, 0.76:0.24). The kinetics of this system are second order.

Shi and coworkers have explored the synthesis of nitrogen containing heterocycles via LiOPf catalyzed aza-Diels-Alder reactions of Danishefsky's diene with diaryl imines [75]. These conditions gave good yields of pyridones and in shorter reaction times when compared to ionic liquid systems [50]. Reaction times were longer than in aqueous systems [28]. A catalyst was essential for these reactions to occur.

## VI. CONCLUDING REMARKS

The last several years have seen advancements in the design of benign solvent systems for the Diels-Alder reaction. In the area of solvent-free Diels-Alder chemistry, as Díaz-Ortiz and Sainz have shown, microwave technology allows for the efficient synthesis of compounds that are traditionally difficult to access. Moreover, one can synthesize biologically relevant targets such as the octahydroacridines in an environmentally benign manner, as shown by Jacob. Aqueous systems allow for the synthesis of biologically active molecules such as the tetrahydroquinolines and are also effective environments for catalytic and enantioselective chemistry; the development of a chiral organocatalyst by Lemay and Ogilvie, and well as catalytic systems from Chen, Schreiner, and Wittkopp are good examples. Catalytic and enantioselective chemistry is not limited to aqueous systems, however. Ionic liquids have also proven to be excellent mediums for these types of processes, as illustrated by the use of a chiral amine catalyst by Park and the use of a chiral Lewis acid by Meracz and Oh. In addition, ionic liquids show a number of green properties. Negligible vapor pressure and recyclability are two of these. There is, however, plenty of incentive for the development of ionic liquids with even more benign characteristics. The sugar/urea/salt compositions developed by Imperato are a significant step in this direction. While all of the systems mentioned so far exemplify the green philosophy in one way or another, the issue of industrial application must not be forgotten. To this end, supercritical $CO_2$ shows great potential. This medium is also suitable for enantioselective chemistry and the synthesis of heterocycles as shown by Fukuzawa and Shi, respectively. Variations of density in supercritical $CO_2$ are often correlated with reaction rates and this characteristic offers the possibility of tuning the outcomes of Diels-Alder reactions. In this field, as in the others discussed herein, there is potential for growth and for contribution to a cleaner chemical future.

## ACKNOWLEDGEMENTS

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## ABBREVIATIONS

$Boc_2O$ = Di-*tert*-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][CS] = 1-Butyl-3-methylimidazolium camphorsulfonate
[bmim][OTf] = 1-Butyl-3-methylimidazolium triflate
[bmim][PF$_6$] = 1-Butyl-3-methylimidazolium hexafluorophosphate
CPD = Cyclopentadiene
DDQ = 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DEAD = Diethyl azodicarboxylate
[DiBuIm][BF$_4$] = 1,3-Dibutylimidazolium tetrafluoroborate
DMU = Dimethylurea
EAN = Ethylammonium nitrate
[EMIC]AlCl$_3$ = 1-Ethyl-3-methyl-1*H*-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
TfOH = Trifluoromethanesulfonic acid
Tf$_2$NH = *Bis*(trifluoromethanesulfonyl)imide
sc = Supercritical

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