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# "Green" Pericyclic Reactions Assisted by Ionic Liquids

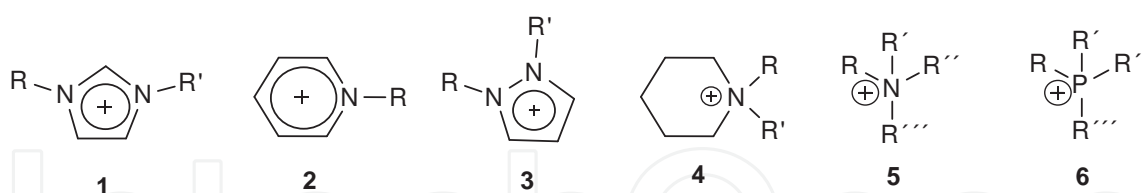
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Additional information is available at the end of the chapter

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## 1. Introduction

Ionic liquids (ILs) are compounds that consist exclusively of ions. These compounds, which can be considered as salts, feature low melting temperatures (generally below 100°C), at which other salts are solids. The cations in these compounds are of organic type and some of the most common structures are heterocyclic such as imidazolium (1), pyridinium (2), pyrazolium (3) and piperidinium (4), or may also be formed by non-cyclic, heteroatom-containing cations such as ammonium (5) and phosphonium (6) (Figure 1) [1].



**Figure 1.** Typical cations in ILs.

Where R, R', R'', R''' are generally alkyl or alkyl functionalized chains.

As for the anions, they can be either inorganic ( $\text{Cl}^-$ ,  $\text{Br}^-$  and  $\text{I}^-$ , which are known to have been part of the first generation ILs, and others such as  $[\text{BF}_4]^-$ ,  $[\text{PF}_6]^-$ ,  $[\text{SbF}_6]^-$ ,  $[\text{AlCl}_4]^-$ ,  $[\text{AuCl}_4]^-$ ,  $[\text{NO}_3]^-$ ,  $[\text{NO}_2]^-$ ,  $[\text{SO}_4]^-$ ) or in other cases the anion is organic ( $[\text{AcO}]^-$ ,  $\text{Tf}^-$ ,  $[\text{N}(\text{OTf})_2]^-$ ,  $[\text{CF}_3\text{CO}_2]^-$ ,  $[\text{CF}_3\text{SO}_3]^-$ ,  $[\text{PhCOO}]^-$ ,  $[\text{C}(\text{CN})_2]^-$ ,  $[\text{RSO}_4]^-$ ,  $[\text{OTs}]^-$ , and  $[\text{SCN}]^-$ ).

Nowadays, ILs are gaining wide recognition as potential environmental solvents due to their unique properties [2]. Physicochemical properties such as low vapor pressure (evaporation losses are minimized), thermal and chemical stability, catalytic activity, non-flammability and

non-corrosive properties, which decrease the risk of worker exposure and solvent loss to the atmosphere, make ILs powerful candidates to replace the so-called "volatile organic compounds" (VOCs) in the development of more environmentally friendly technologies and specially for the petroleum industry [3, 4].

Pericyclic reactions belong to a very important group of organic reactions, including some of the most powerful synthetically useful reactions like the Diels-Alder reaction, 1,3-dipolar cycloadditions, the Alder-ene reaction, Cope and Claisen rearrangements, the 2,3-Wittig rearrangement, diimide reduction, sulfoxide elimination, Fisher indole synthesis and many others.

In the last years, ILs have been employed as reaction media and/or catalysts and co-catalysts to facilitate the course of many pericyclic reactions. Due to the nature and properties of this kind of compounds, the application of ILs in these reactions has contributed to the development of more efficient and environmentally friendly methodologies. In this chapter, the principles of pericyclic reactions are presented and an overview of the applications of ILs in assisted pericyclic reactions is discussed.

## 2. Pericyclic reactions

The term Pericyclic reactions refers to a set of reactions that are characterized by concerted processes that proceed via cyclic transition states, which can be interpreted according to the Molecular Orbital Theory. Pericyclic reactions are reactions, where a cyclic, conjugated system of electrons is created in the transition state, having highly predictable stereochemical features [5].

The stereochemistry of the pericyclic reactions can be predicted based on the principle of conservation of orbital symmetry, employing the rules proposed by Robert Burns Woodward and Ronald Hoffmann in 1965 (Woodward-Hoffmann rules) [6]. This principle applies only to the concerted pericyclic reactions, and in this case, it serves as a powerful predictive tool.

The Woodward-Hoffmann rules were established by the authors as:

1. In an open chain system containing a  $4n$  electron orbital symmetry of the highest occupied molecular orbital of the ground state is such that a bonding interaction between the ends must engage the overlapping between orbital regions in opposite sides of the system, and this can only be achieved through a conrotatory process.
2. In open systems containing  $4n+2$  electrons, the terminal binding interaction between molecules in the ground state requires the overlapping regions of the orbitals of the same side of the system, and this is attainable only by disrotatory displacements.
3. In a photochemical reaction, an electron in the HOMO of the reactant is promoted to an excited state, leading to the reversal of terminal symmetry relations (stereospecificity).

It is said that the organic reactions that obey these rules are allowed by symmetry. Reactions that take the opposite course are forbidden by symmetry and require much more energy if they happen to take place.

The pericyclic reactions are classified according to the number of electrons that are directly involved in the transition state. Processes with 2- and 6-electron (Huckel,  $4n+2$ ) are allowed suprafacially, and 4-electron processes must occur antarafacially (Möbius,  $4n$ ). The main pericyclic reactions are classified as follows:

- Cycloaddition (two new  $\sigma$  and two less  $\pi$  bonds)
- Electrocyclic (one new  $\sigma$  and one less  $\pi$  bonds)
- Sigmatropic (one is changed to another  $\sigma$ -bond)
- Group Transfer (one new  $\sigma$  and one less  $\pi$  bonds)

### 3. Cycloaddition reactions

Cycloaddition reactions are the most studied pericyclic reactions, where two or more unsaturated systems react to give a cycle with one less unsaturation. This reaction allows simultaneous construction of two new carbon-carbon bonds and the formation of cyclic compounds which gave high versatility and applicability in organic synthesis [7]. A typical cycloaddition reaction is the Diels-Alder reaction.

The Diels-Alder (D-A) reaction was discovered and published for the first time in 1928 by Otto Diels and Kurt Alder [8]. This is a thermal, concerted, suprafacial,  $[4+2]$  cycloaddition.

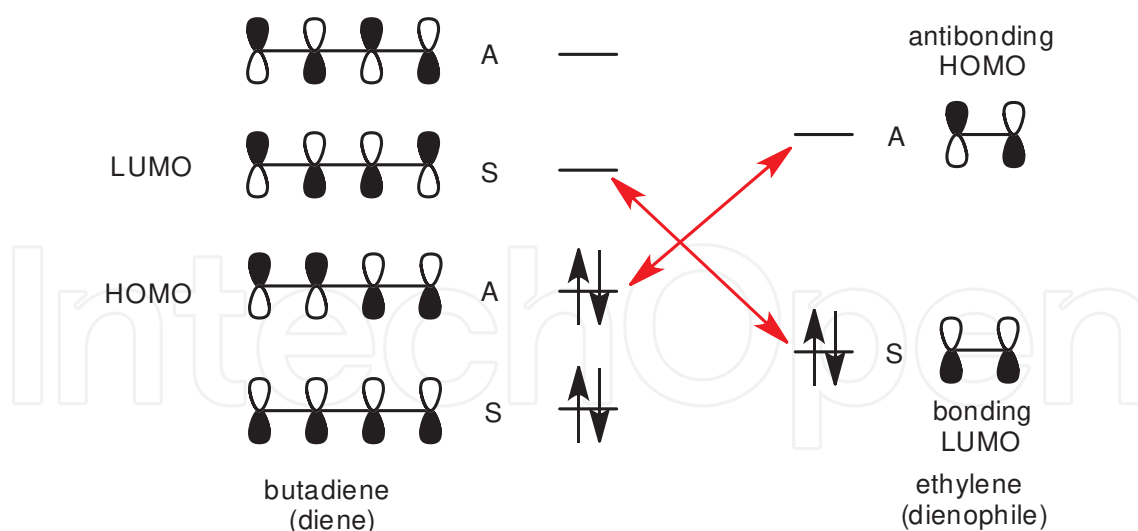
In this reaction 1,3-butadiene (diene) reacts with ethylene (dienophile) to give an adduct cyclic product as described in Figure 2. In this kind of reactions, both  $\sigma$ -bonds are formed at the same time, not by steps.



**Figure 2.** An example of cycloaddition reaction.

These reactions proceed according to the following selection rules:

The suprafacial-suprafacial (S-S) reaction geometry is thermally permitted when  $m+n=4k+2$ , for example, the Diels-Alder reaction between butadiene and ethylene, where  $m$  and  $n$  are the number of  $\pi$  electrons (Figure 3).



**Figure 3.** Molecular orbital interaction in a cycloaddition reaction.

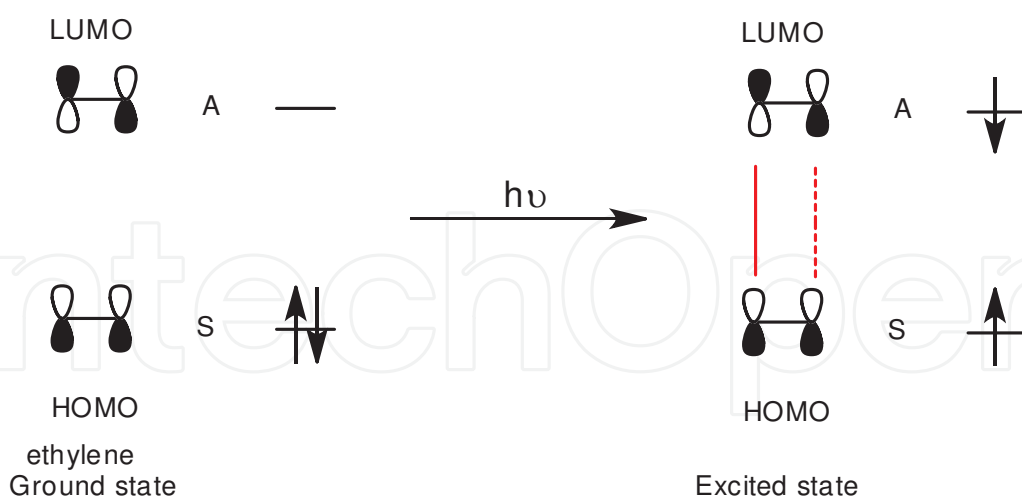
Suprafacial (S) means that new bonds are formed on the same face of each reagent, the diene and dienophile. The opposite to suprafacial is antarafacial (A). The term [4+2] refers to a conjugated system of electrons, where a 4- reacts with a 2-electron system.

Figure 3 shows the molecular orbitals (MOs) of 1,3-butadiene and ethylene, and their respective relative energies. As noted earlier, the HOMO-LUMO energy gap is greater in ethylene than in butadiene. For the two compounds to react, the HOMO of one must react with the LUMO of the other one with conservation of orbital symmetry. There are two seemingly isoenergetic possibilities, the SS and AA reactions (red arrows), which conserve symmetry. Both energy gaps are equal and too large for a reaction to occur readily.

1. One way to reduce the HOMO-LUMO energy gap is by lowering the LUMO of one reactant. This is accomplished by using an "ethylene" that has an electron-withdrawing group attached to it.
2. The supra-antara reaction geometry is allowed thermally when  $m+n=4k$ , for example, cycloaddition [2+2]. The formation of cyclobutane from two ethylenes cannot be concerted by thermal reaction; the HOMO-LUMO gap requires light (photochemical reaction) for the excitation of ethylene (Figure 4).

In the S-S mode, the concerted [4+2] cycloaddition is ground state (thermal) allowed and excited state ( $h\nu$ ) forbidden, while the [2+2] cycloaddition is just the opposite, ground state forbidden and excited state allowed.

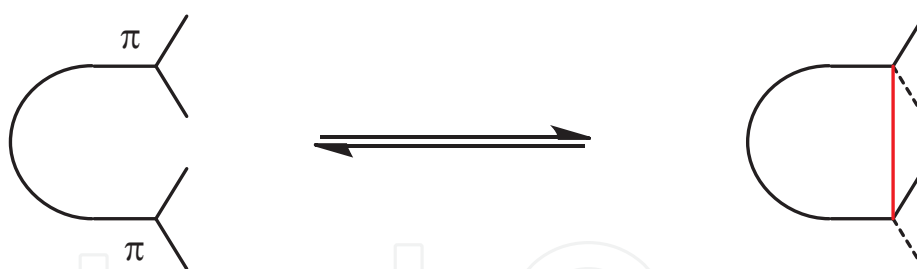
The Diels-Alder reactions involving at least one heteroatom in the dienophile (heterodienophile) [9] or in the diene (heterodiene) [10] are known as hetero-Diels-Alder reactions. For example, carbonyl groups can react successfully with dienes to yield pyranoid rings, a reaction known as the oxo-Diels-Alder reaction, or when a nitrogen atom can be part of the diene or the dienophile, the reaction is known as aza-Diels-Alder.



**Figure 4.** Molecular orbital interaction in [2+2] reaction.

#### 4. Electrocyclic reactions

Electrocyclic reactions are a type of pericyclic reaction which is unimolecular and in which the termini of a conjugated system become  $\sigma$  bonded to each other to form a shortened  $\pi$  system (Figure 5) [11].



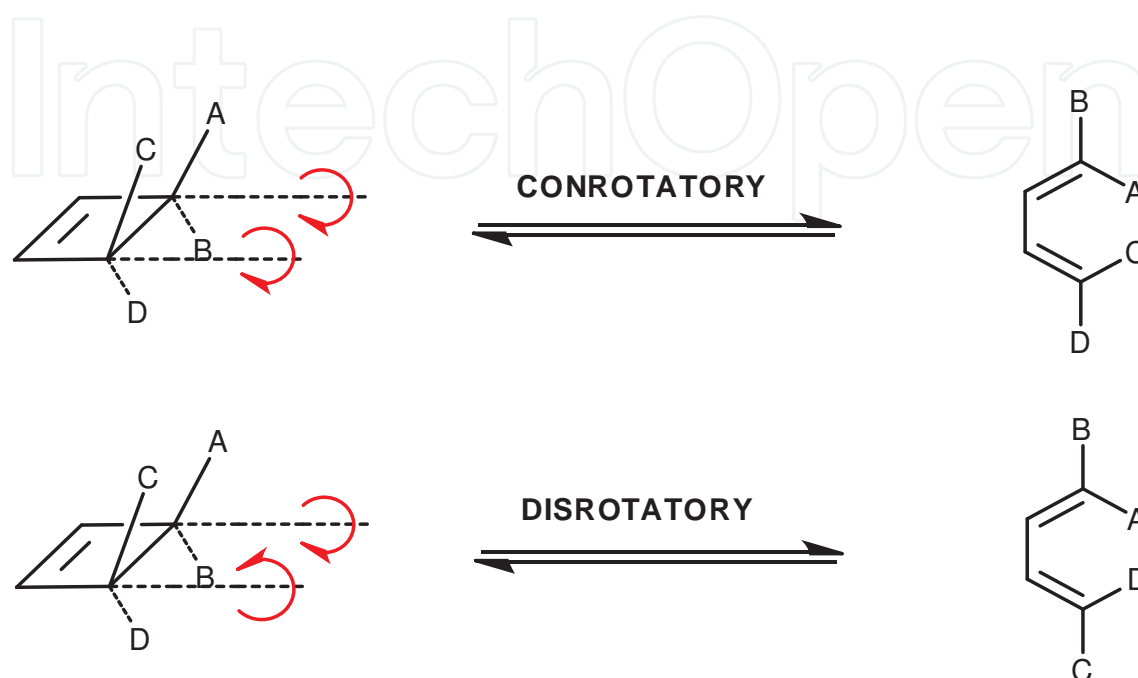
**Figure 5.** Representation of an electrocyclic reaction.

A typical example of this reaction is the electrocyclization of the 1,3,5-hexatriene to the conjugated cyclic diene (Figure 6).



**Figure 6.** Electrocyclization reaction of the 1,3,5-hexatriene.

When there are substituents at the end of an unsaturated system, these substituents have a definite stereochemistry at the cyclic structure depending on the rotation way of the overlapping molecular orbitals. This relationship might be disrotatory or conrotatory. Fixed geometrical isomerism imposed upon the open chain is related to rigid tetrahedral isomerism in the cyclic array (Figure 7).



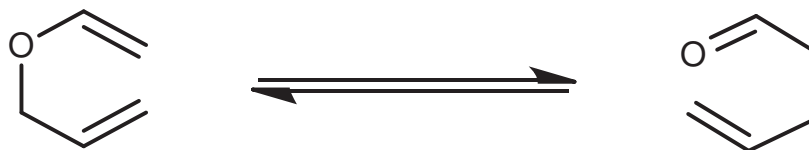
**Figure 7.** Stereochemistry at the cyclic structure depending on the rotation way of the overlapping molecular orbitals.

For this kind of reaction, the thermal reaction is now disrotatory, while the photochemical reaction is conrotatory. According to the Principle of Conservation of Orbital Symmetry by Woodward & Hoffmann [12], the thermal reaction will be conrotatory for  $4n$  systems and disrotatory for  $4n+2$  systems, and in the opposite way for photochemical reactions.

## 5. Sigmatropic rearrangements

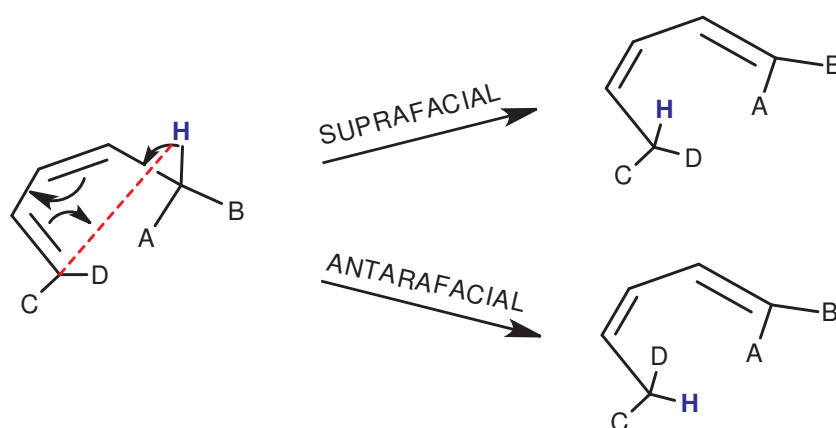
In a sigmatropic rearrangement, one bond is broken while another bond is formed across a  $p$  system. The numbering system  $[m, n]$  gives the number of atoms between the broken bond and the formed bond in both directions [13].

There are two different types of sigmatropic reactions: a) those that involve the migration of a hydrogen atom, and b) those that involve carbon, oxygen or other element atoms. In these reactions, the starting materials are acyclic, but the transition state is cyclic, with pronounced conformational effects. A classical reaction of this type is the Claisen rearrangement (Figure 8). Other typical reactions of this type are the Cope rearrangement and the Fisher indole synthesis.



**Figure 8.** The Claisen rearrangement.

Figure 10. In the hydrogen migration, the hydrogen atom can migrate either suprafacially or antarafacially across the conjugated system, leading to Hückel or Möbius topologies for the transition states. The typical migration for these systems is the [1, 5] hydrogen migration (Figure 9).



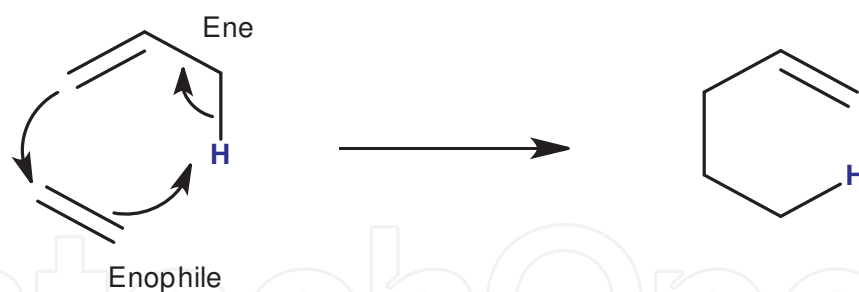
**Figure 9.** Suprafacial and antarafacial hydrogen migration across the conjugated system.

## 6. Group transfer reaction

A group transfer reaction is a process, where one or more groups of atoms are transferred from a molecule to another. Unlike other pericyclic reaction classes, group transfer reactions do not have a specific conversion of  $\pi$ -bonds into  $\sigma$ -bonds or vice versa. Typical examples of this process are the ene reaction and the reduction of a double bond by  $N_2H_2$  diimide reaction, which is a supra-supra reaction involving six electrons.

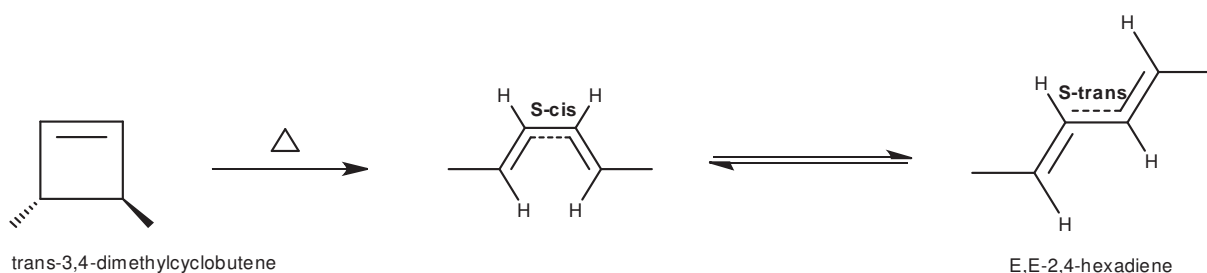
In the ene reaction, an alkene with an allylic hydrogen (the ene component) reacts with a compound containing a multiple bond (the enophile) like olefins, acetylenes, and benzyne or carbon-hetero multiple bonds such as  $C=O$ ,  $C=N$ ,  $C=S$ , and  $C\equiv P$  (carbonyl-ene reactions) in order to form a new  $\sigma$ -bond with migration of the ene double bond and 1, 5 hydrogen shift. The product is a substituted alkene with the double bond shifted to the allylic position (Figure 10) [14].





**Figure 10.** The ene reaction.

Due to the principle of microscopic reversibility, there is a parallel set of pericyclic "retro" reactions which perform the reverse reaction: retro Diels-Alder, retro-ene reaction and the retro-electrocyclic reactions. An example of the last one is the reaction in which the *trans*-3,4-dimethylcyclobutene is cleaved thermally to yield *E,E*-2,4-hexadiene. In this reaction, the cleavage of a  $\sigma$ -bond occurs to generate a longer conjugated system (Figure 11).



**Figure 11.** Thermal cleavage of the *trans*-3,4-dimethylcyclobutene.

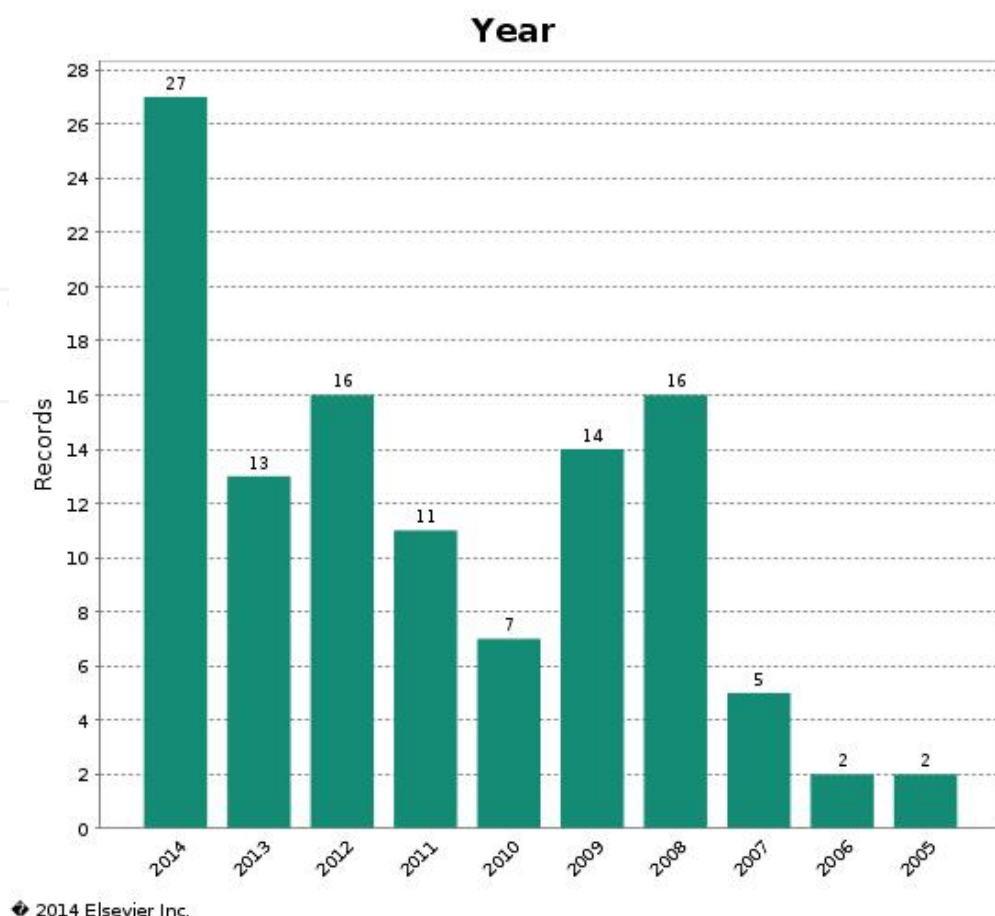
The cleavage of a  $\sigma$ -bond to generate a longer conjugated system is sometimes called a retro-electrocyclic reaction. As an example of the latter, cyclobutene is cleaved thermally to yield 1,3-butadiene, relieving the extensive strain in the cyclobutene system and gaining the resonance stabilization of the conjugated diene system.

## 7. IL-assisted cycloaddition reactions

Cycloaddition is a highly versatile protocol to generate new C-C bonds, being a handy tool for the synthesis of natural products [15, 16].

According to E-Village Compendex [17], in the last decade, 120 papers about IL-assisted cycloaddition reactions have been published with an important increment in the last years (Figure 12).

Among cycloaddition reactions, Diels-Alder reactions are by far the most studied, and also the most studied pericyclic reactions employing ILs. The Diels-Alder reaction is an important class of reaction that allows the synthesis of six-membered rings with accurate control on the

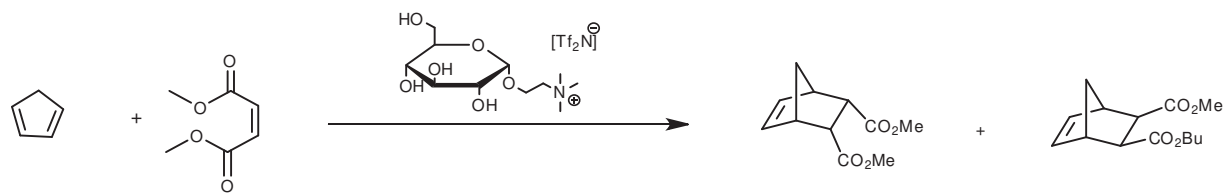


**Figure 12.** Papers published on IL-assisted cycloaddition reactions in the last decade.

stereoselectivities of the products. It is well known that the Diels-Alder reaction can be accelerated in the presence of a salt and because of their ionic features, ILs have shown good catalytic properties in this kind of reaction. Considering the environmental pollution provoked by using conventional organic solvents and catalysts, ILs have proved to be alternative solvents and catalysts for carrying out this kind of reactions [18].

Erfurt et al. studied the performance of hydrogen-bond-rich ILs obtained from D-Glucose, where chloroalcohols were used as raw materials and sources of hydroxyl groups for the synthesis of IL cations; bis(trifluoromethylsulfonyl)imide was used as an anion to catalyze the reaction between cyclopentadiene and either diethyl maleate or methyl acrylate. The studied ILs showed high activity even when present in catalytic amounts (4 mol% with respect to dienophile). An increase in the number of hydroxyl groups present in the IL structure resulted in higher reaction rates. The IL tends to form a crystal at temperatures in the range of  $-29$  to  $-16^{\circ}\text{C}$ , and is thermally stable from ambient temperature to at least  $430^{\circ}\text{C}$  (Figure 13) [19].

Tamariz and coworkers have studied extensively the synthesis of *exo*-heterocyclic dienes and captodative olefines and their applications in Diels-Alder reactions [20-25]. In one of their works, they studied the effect of several ILs in combination with non-conventional energy sources (microwaves and ultrasound) on this reaction. (*Z*)-*N*-substituted-4-methylene-5-

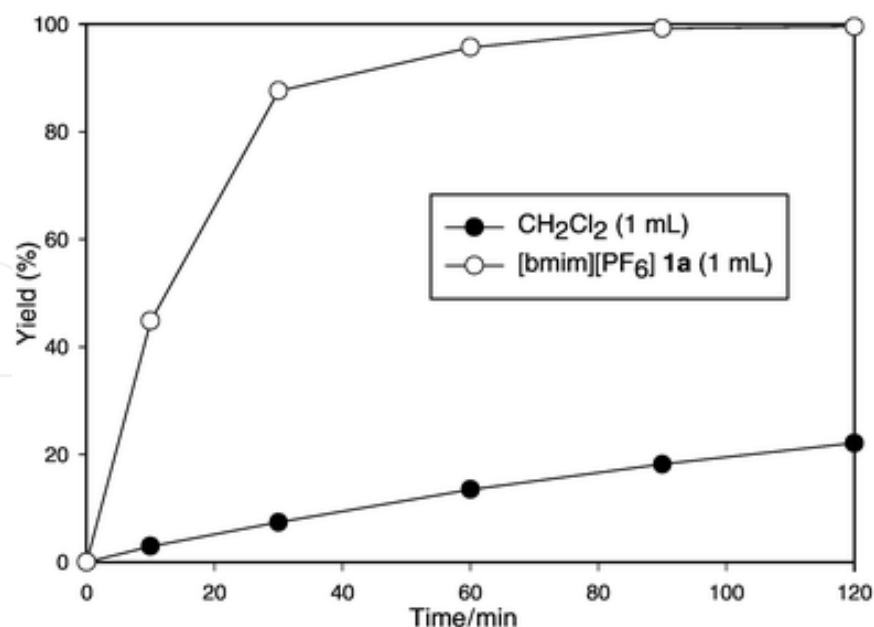


**Figure 13.** Diels-Alder cycloaddition using hydrogen-bond-rich ILs obtained from D-Glucose and chloroalcohols as catalysts.

propylidene-2-oxazolidinone dienes were prepared by means of a one-step synthesis, starting from 2,3-hexanedione and isocyanates. Diels-Alder cycloadditions of these dienes were carried out in the presence of dienophile methyl vinyl ketone, methyl propiolate, and a captodative olefin, using high polarity solvents, Lewis acid catalysts, and non-conventional energy sources. The reactions carried out with either H<sub>2</sub>O/MeOH mixtures or BF<sub>3</sub>·Et<sub>2</sub>O catalysts yielded the highest regio- and stereo-selectivities. The use of ILs, microwaves, and ultrasound did not significantly increase the selectivity [26].

Vidis et al., also found a low effect of ultrasound and microwave dielectric heating on the selectivity of Diels-Alder reactions in ILs, but a significant effect on the reaction rate [27].

ILs have also proved to be a powerful reaction medium (or additive) for significant rate acceleration in the Diels-Alder cycloaddition (Figure 14). In this sense, ILs were used as a medium in scandium-triflate-catalysed-Diels-Alder reactions, not only for facilitating the catalyst recovery, but also for accelerating the reaction rate and improving the selectivity [28].



**Figure 14.** Kinetic studies on the reaction between 1,4-naphthoquinone (1 mmol) and 2,3-dimethylbuta-1,3-diene (3 mmol) in the presence of 0.2 mol% of Sc(OTf)<sub>3</sub> at 20 °C in methylene chloride and IL (Reproduced from ref. 28 with permission from The Royal Society of Chemistry).

The DES concept was first described by Abbott and coworkers [30], which generally refers to a type of solvent composed of a mixture that forms a eutectic through two cheap and reliable components, which are capable of associating via links, by hydrogen bonding, to a melting point much lower than any of the individual components; a DES can be easily formed by mixing two or more simple components under given operating conditions, manifesting poor conductivity properties. In general, DESs are cheaper than classical ILs, and also feature some other properties that make them very attractive: water-chemical inertness, easy storage, easy preparation (eliminating problems of purification and residue formation), biodegradability and environmentally biocompatibility.

salts

Hydrogen bond donors

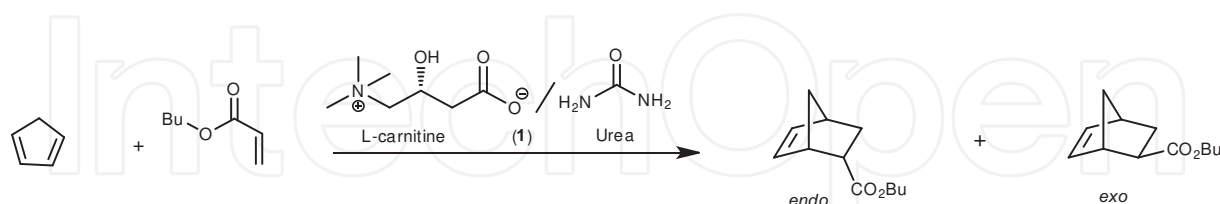
[Cl-].[N+](C)(C)CCO [Cl-].CC[NH3+] NC(=O)N NC(=S)N O=C1NCNC1

[Cl-].[N+](C)(C)C CC(=O)OCC[N+](C)(C)C CC(=O)N CC(=O)N NC(=O)N

[Cl-].[N+](C)(C)C(C)(C)C [Br-].c1ccccc1P+(c2ccccc2)c3ccccc3 OCCO CC(=O)N NC(=O)C(F)(F)F

DESs have shown a very good performance as solvents and catalysts for many organic reactions [32], including Diels-Alder cycloaddition. Particularly, Ilgen and König used DES **1**, obtained from L-carnitine/urea melt, to carry out the D-A reaction between cyclopentadiene and *n*-butylacrylate (Figure 16). The L-carnitine melt shows a very high polarity property to obtain adducts with an excellent yield of 93% with an *endo/exo* selectivity of 3.5/1. High yields

(72-95%) were obtained from D-glucose and lactose melt, respectively [33]. These DESs were also used for Heck and Sonogashira cross-couplings and Cu-catalyzed reactions. The 1, 3-dipolar cycloadditions also proceed cleanly in sugar and L-carnitine based melts, but the applicability of L-carnitine melts for standard organic reactions is limited by their lower thermal stability [34].



**Figure 16.** Diels-Alder cycloaddition between cyclopentadiene and *n*-butylacrylate using L-carnitine/urea melt as DES.

Employed IL	Reagents involved in the D-A reaction	Observations	Ref.
Trihexyl-tetradecylphosphonium m	Cyclopentadiene and dienophiles from the group of $\alpha,\beta$ -unsaturated esters, bis(trifluoromethylsulfonyle)aldehydes and ketones.	Several phosphonium-IL-metal chlorides, triflates and bis-triflimides catalyzed very efficiently this reaction. The catalyst can be recycled.	[35]
1-(1-butyl)-3-methylimidazolium tetrafluoroborate ([BMIM][BF <sub>4</sub> ])	Cyclopentadiene and naphthoquinone	The second-order rate constants for cycloaddition reaction were determined in various compositions of the IL with water and methanol. Rate reaction constants in pure solvents are in the order of water > [BMIM]BF <sub>4</sub> > methanol. Reaction rate constant increases with solvophobicity (Sp), hydrogen-bond donor acidity and hydrogen-bond acceptor basicity parameters.	[36]
[BMIM][BF <sub>4</sub> ]	N-ethylmaleimide and 2,3-dimethyl-1,3-butadiene	The Diels-Alder reaction was studied in a microemulsion (IL-H <sub>2</sub> O/AOT/isooctane). The apparent second-order rate constants were determined by spectrophotometry. Those in the IL-microemulsion are five times higher than that in isooctane, and $k_2$ in pure IL is at least 10 times higher than that in isooctane. AOT: Sodium bis(2-ethylhexyl)sulfosuccinate.	[37]
[BMIM][PF <sub>6</sub> ]	Functionalized 2(1H)-pyrazinones	Significant rate-enhancements for both inter- and intramolecular hetero-Diels-Alder reactions were observed for the reaction in IL-doped CH <sub>2</sub> Cl <sub>2</sub> , comparing the standard protocols to the microwave-heated transformations.	[38]
[BuPy]Cl:AlCl <sub>3</sub> (mole fraction) = 0.6	Cyclopentadiene with methyl acrylate	The acidic chloroaluminate IL can further enhance the catalytic power of an expensive silyl borate catalyst for	[39]

Employed IL	Reagents involved in the D-A reaction	Observations	Ref.
		carrying out Diels–Alder reactions. Less amount of catalyst in the above ionic liquid is required to obtain optimum results.	
Several pyridinium based ILs: 1-butyl pyridinium [BP] <sup>+</sup> , 1-hexyl pyridinium [HP] <sup>+</sup> , 3-methyl-1-butyl pyridinium [3MBP] <sup>+</sup> , 3-methyl-1-hexyl pyridinium [3MHP] <sup>+</sup> , 3-methyl-1-octyl pyridinium [3MOP] <sup>+</sup> , and 4-methyl-1-butyl pyridinium [4MBP] <sup>+</sup> . The anions were tetrafluoroborate [BF <sub>4</sub> ] <sup>−</sup> and bis(trifluoromethylsulfonyl) [NTf <sub>2</sub> ] <sup>−</sup>	(E)-1-phenyl-4-[2-(3-methyl-2-butenyloxy) benzylidene]-5-pyrazolone	The reaction rates decrease with the increasing viscosity of the ILs. As evident from the anionic effect, the solute-solvent specific interactions play a role in governing the kinetics of the reaction. The lower viscosities of the bistrifluoromethanesulfonimide [NTf <sub>2</sub> ] <sup>−</sup> based ILs as compared to those based on tetrafluoroborate [BF <sub>4</sub> ] <sup>−</sup> anion fail to accelerate the reaction rates.	[40]
Pyridinium-based ILs, 1-butyl-pyridinium tetrafluoroborate, 1-butyl-3-pyridinium tetrafluoroborate, and 1-butyl-4-methyl pyridinium tetrafluoroborate	Anthracene 9-carbinol and N-ethyl maleimide	The reaction rates decreased, caused by gradually increasing the volume fraction of ILs in solvents for all three ILs. A temperature-dependent study of kinetics of the D-A reaction was carried out in the binary mixtures of ILs in water and was explained by the entropy-enthalpy compensation effect based upon activation parameters. Kinetics of the D-A reaction in highly aqueous medium was noted to be entropically driven.	[41]
[EMIM]BF <sub>4</sub> [BMIM]BF <sub>4</sub> [BDMIM]BF <sub>4</sub>	Ester-tethered 1,3,9-decatriene	The intramolecular D-A reaction of an ester-tethered 1,3,9-decatriene system was significantly accelerated in the studied ILs. Under the present conditions, the D-A reaction proceeded smoothly without the use of Lewis acid catalysts to give cis-fused bicyclic lactones in good yield with high diastereoselectivity	[42]
Several chiral ILs synthesized from camphorsulfonic acid and camphene	Acrylic acid and cyclopentadiene	Chiral ILs were used as solvents in the D-A reaction of acrylic acid and cyclopentadiene and showed good yields and diastereoselectivities.	[43]

Employed IL	Reagents involved in the D-A reaction	Observations	Ref.
1-ethyl-3-methylimidazolium-(S)-2-pyrrolidinecarboxylic acid salt [EMIM][Pro]	A set of cyclic $\alpha,\beta$ -unsaturated ketones and arylamines with formaldehydes	The chiral IL catalyzed the one-pot direct asymmetric aza D-A reaction in up to 93% yield with up to >99/1 dr and >99% ee. Moreover, the catalytic system can be recycled and reused six times without any significant loss of catalytic activity.	[44]
Triethylammonium acetate (TEAA)	Heteroarylaldehyde, pyrazolone with enol ether	A highly efficient, rapid one-pot procedure has been developed for a three-component domino intermolecular Knoevenagel-intermolecular hetero-Diels-Alder reaction to afforded indolyl- and quinolylpyrano[2,3-c] pyrazoles from corresponding TEAA under microwave irradiation. The reaction advantageously precedes in highly regio- and stereoselective ways in combination with the ease of IL recovering.	[45]
Triethylammonium acetate (TEAA)	O-allylated acetophenones/ propiophenone with several 5-pyrazolones	One-pot procedure for the synthesis of some new angular benzopyrano[3,4-c]pyrano-fused pyrazoles, all of which incorporate a tertiary ring junction carbon by means of domino-Knoevenagel-hetero-Diels-Alder reaction TEAA-mediated one-pot method for the synthesis of a new family of angularly fused polyheterocycles providing efficient and improved reaction conditions for unactivated dienophile propargyl, needing no additional catalyst, required for allyl- and prenyl-based substrates is another advantage of this method.	[46]

**Table 1.** Summary of recent papers studying IL-assisted-D-A reactions.

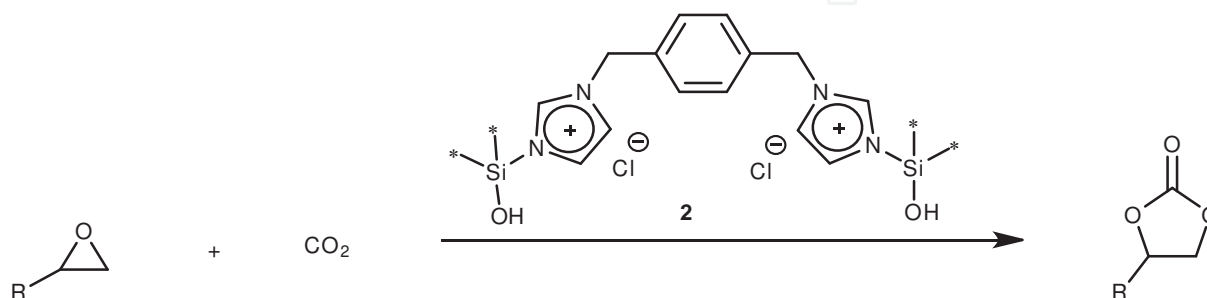
Another well studied cycloaddition reaction is the one involving the cycloaddition of  $\text{CO}_2$  with epoxides [47]. The cycloaddition of  $\text{CO}_2$  is a very important reaction because it allows  $\text{CO}_2$  fixation, which is a hot topic in current research. The fixation of  $\text{CO}_2$  to generate valuable chemicals such as cyclic carbonates is meaningful. Cyclic carbonates are used as polar aprotic solvents, electrolytes in lithium secondary batteries, precursors for the formation of polycarbonates, and intermediates in the production of pharmaceuticals and fine chemicals. According to studies on this reaction mechanism, the cycloaddition between  $\text{CO}_2$  and epoxides catalyzed by ILs takes place through a stepwise mechanism and is not properly a pericyclic reaction [48], however, because of the importance of this reaction, it is briefly discussed here.

In a recent paper, a polymer grafted with an asymmetrical dication, IL-based on imidazolium and phosphonium ([P-Im- $\text{C}_4\text{H}_8\text{Ph}_3\text{P}$ ] $\text{Br}_2$ ) was synthesized, and for the first time, it was evaluated as a catalyst for the synthesis of cyclic carbonates from epoxides and  $\text{CO}_2$  without using any co-catalyst and solvent. The catalyst showed higher activity than the monocation imidazolium and phosphonium ILs. At low catalyst loading (0.38 mol%), high yield (96.8%) and selectivity (99.5%) of propylene carbonate can be obtained at  $130^\circ\text{C}$  and 2.5 MPa in 4 h.



The author proposed that both the nucleophilic attack of bromine anions and their activation could explain the good activity of the catalyst. Furthermore, the catalyst showed excellent stability and reusability. It can be reused for up to five runs without any significant loss of catalytic activity after simple filtration [49].

Very recently, a new method for the synthesis of main chain poly-imidazolium salts (**2**) was developed from bisimidazole and silicon tetrachloride. These types of silicon-based poly-imidazolium-salt-poly-ILs were found to be the most efficient metal-free heterogeneous catalysts (TOF=90 h<sup>-1</sup>) for the fixation of CO<sub>2</sub> with epoxides into cyclic carbonates under metal- and solvent-free conditions (Figure 17) [50].



**Figure 17.** Synthesis of cyclic carbonates under metal- and solvent-free conditions using silicon-based-poly-imidazolium-salt-poly-ILs as catalysts.

## 8. IL-assisted electrocyclic reactions

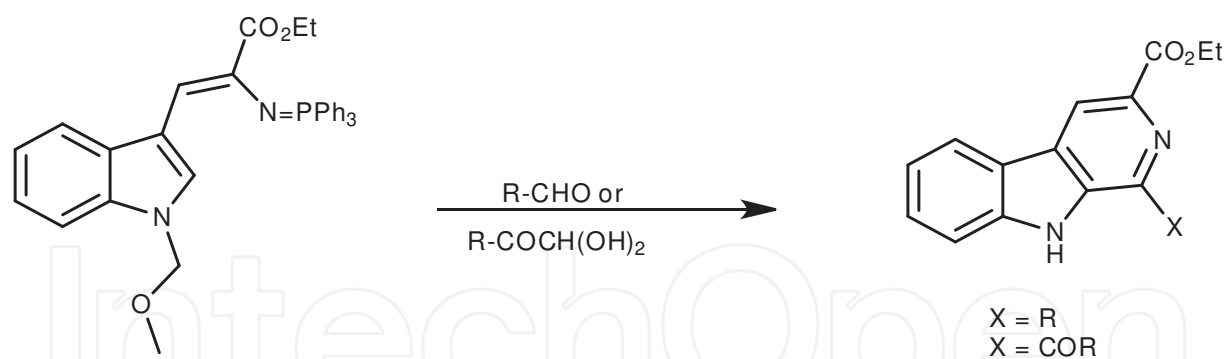
ILs are also a very useful option for the development of electrocyclic reactions. Some examples of this reaction using ILs will be discussed below.

The use of microwaves as conventional heating source to carry out chemical reactions is very useful for obtaining high yields of products with short reaction times. In recent years, many reactions have been reported, where the use of microwaves as a heating source and ILs as solvents or catalysts for reactions has been combined. Because of their ionic nature, ILs are heated very quickly when subjected to microwave irradiation. This is an excellent feature to perform very rapid and efficient reactions that match the "green concept" [51-53].

In 2012, Freneda and Blazquez studied the synthesis of  $\beta$ -carboline (pyrido[3,4-*b*]indole) using the microwave-assisted-tandem-aza-Wittig/electrocyclic-ring-closure methodology in ILs. This efficient procedure using microwave irradiation in combination with the IL [BMIM][BF<sub>4</sub>] used as the solvent was useful for the preparation of aryl/aroxy-1-substituted-9H-pyrido[3,4-*b*]indoles (Figure 18).

The pyrido-annulation process involved the simultaneous deprotection of an *N*-methoxymethyl group using IL/microwave-assisted irradiation with good yields (65–90%) and short reaction times (15–25 min) as shown in Table 2 [54].





**Figure 18.** Synthesis of  $\beta$ -carbolines (pyrido[3,4-*b*]indole) using the microwave-assisted tandem-aza-Wittig/electrocyclic-ring-closure methodology in ILs.

R-CHO	R-COCH(OH) <sub>2</sub>	Time (min)	Yield (%)
4-MeOC <sub>6</sub> H <sub>4</sub>		15	79
4-ClC <sub>6</sub> H <sub>4</sub>		20	70
C <sub>6</sub> H <sub>5</sub>		20	73
C <sub>6</sub> H <sub>5</sub> -(CH <sub>2</sub> ) <sub>2</sub>		20	65
	C <sub>6</sub> H <sub>5</sub>	15	88
	4-MeOC <sub>6</sub> H <sub>4</sub>	15	90
	N-MOM-indol-3-yl	25	76

<sup>a</sup> (R-CHO/ R-COCH(OH)<sub>2</sub>): 1:1, MW, power: 1 W, T: 200°C.

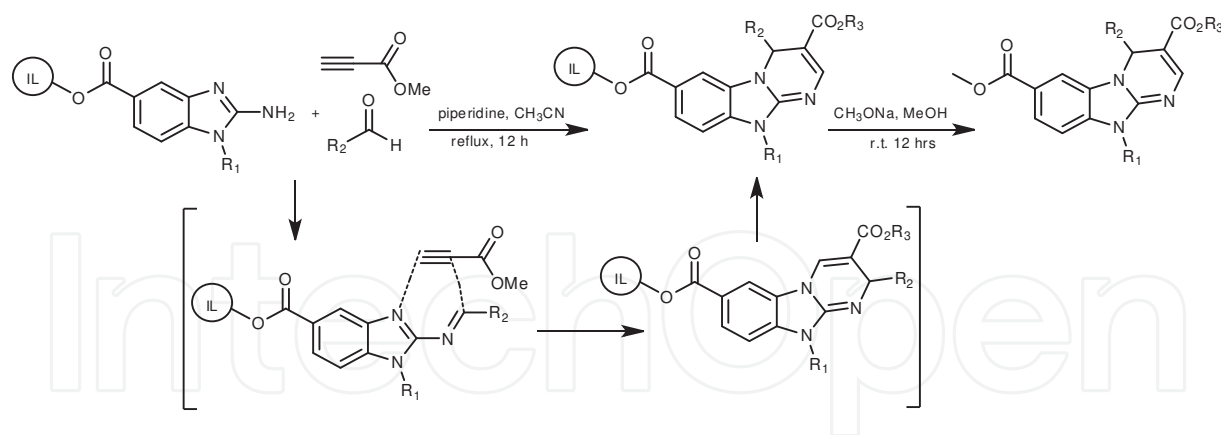
**Table 2.** Time and yields of  $\beta$ -carboline synthesis using microwave-assisted-tandem-aza-Wittig/electrocyclic-ring-closure methodology in [BMIM][BF<sub>4</sub>].<sup>a</sup>

## 9. IL-assisted sigmatropic rearrangements

Another useful application of ILs in organic syntheses is as soluble supports to immobilize certain organic substrates. The high polarity and ionic character of IL supports have proved to exert synergistic effects and reaction rate enhancements.

Dihydropyrimidine and benzimidazole derivatives are key structural elements in many biologically active natural products and pharmaceutical compounds. Some of them constitute key intermediates which have widespread applications in drug research. Recently, an efficient IL-supported synthesis of novel benzimidazole-fused-dihydropyrimidine derivatives catalyzed by Lewis bases was published.

3-Hydroxyethyl-1-methylimidazolium tetrafluoroborate, as an ionic soluble IL support, was employed for immobilizing 2-amino benzo[*d*]imidazole. Twenty primary amines and aldehydes were evaluated in this parallel protocol, furnishing the products with high purity and yields (72-98%) (Figure 19).



**Figure 19.** One-pot parallel synthesis of [1,5]-sigmatropic rearrangement involving immobilized 2-amino benzo[d]imidazole.

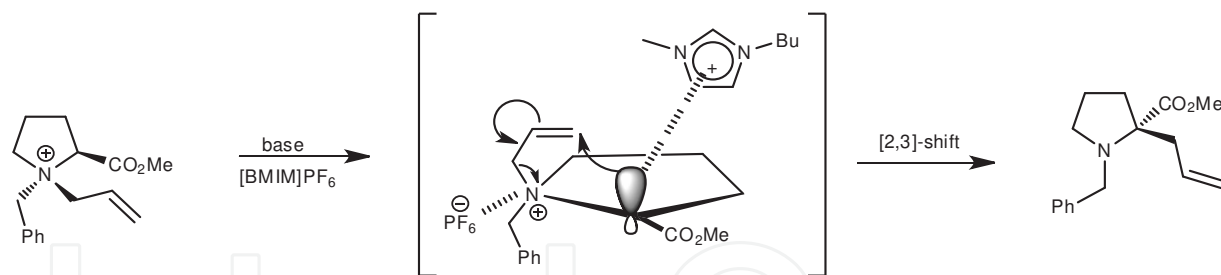
The novel multicomponent reaction between IL-anchored, 2-aminobenzoimidazoles, aldehydes, and electron-deficient dienophiles, described below, involve a [1,5]-sigmatropic rearrangement, which was compatible with a wide range of substrates to furnish the new scaffolds. The use of the IL as a soluble support facilitates purification by simple precipitation along with advantages such as high loading capacity, homogeneous reaction conditions and monitoring of the reaction progress by conventional NMR spectroscopy [55].

In 2011, an example of [2,3]-sigmatropic rearrangement was published, showing the cyclopropanation of 5-(allyloxymethyl)- and 5-(methallyloxymethyl)-5-ethyl-1,3-dioxanes with methyl diazoacetate catalyzed by  $\text{Rh}_2\text{OAc}_4$  or  $\text{Cu}(\text{OTf})_2$  in the presence of [BMIM]Cl, [BMIM]BF<sub>4</sub> and [BMIM]PF<sub>6</sub>, which proceeded regioselectively at the C=C bond and led to the formation of the corresponding cyclopropane-containing 1,3-dioxanes in yields up to 62% [56].

In another example of [2,3]-sigmatropic rearrangement, an efficient enantioselective approach towards the construction of quaternary indolizidines from proline building block co-catalyzed by the IL 1-butyl-3-methylimidazolium hexafluorophosphate was shown. In this work, the author explored N → C chirality transfer under [2,3]-shift of a proline derivative ammonium, yielding stereogenic at nitrogen. The rearrangement was stereospecific because the [2,3]-migrations were restricted to the same face, and the stereoselectivity arose from the previous N-alkylation step. A mechanism was proposed in which the use of an IL showed an improvement in the yields of the Stevens rearrangement due to a possible stabilization and/or activation of zwitterionic species in solution by the IL (Figure 20) [57].

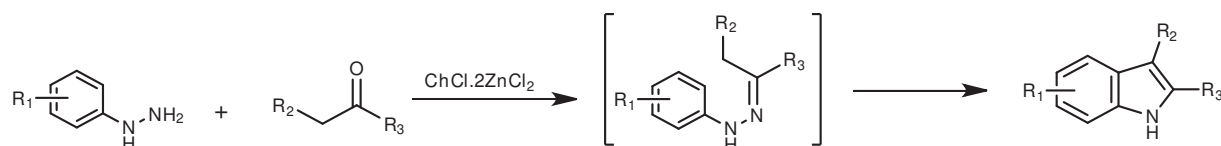
Another type of sigmatropic rearrangement explored with the assistance of an IL is the [3,3]-sigmatropic rearrangement involved in the Fisher indole synthesis.

Widespread occurrence of indoles in natural products and biologically active compounds has led to a continued interest in the practical synthesis of the indole nucleus. Despite the diverse and creative approaches that have been developed so far, the classical Fischer indole synthetic methodology, which involves hydrazone formation and subsequent [3,3]-sigmatropic rearrangement remains the benchmark method.



**Figure 20.** Proposed mechanism for IL stabilization of zwitterionic species in the Stevens [2,3]-sigmatropic rearrangement.

Calderon-Morales et al. carried out the one-pot conversion of phenylhydrazine and ketone to the indole. The Fischer indole synthesis with one equivalent of the IL Choline chloride  $2\text{ZnCl}_2$  ( $\text{ChCl}_2 \cdot \text{ZnCl}_2$ ) with direct product isolation by vacuum sublimation was used. Since an IL has very low vapor pressure, then the vapor pressure of the solution of the indole product in the IL would be expected to be about the same as the vapor pressure of the indole itself. Following this procedure, ten indole derivatives were obtained in high yield with one equivalent of  $\text{ChCl}_2 \cdot \text{ZnCl}_2$ ; exclusive formation of 2,3-disubstituted indoles is observed in the reaction of alkyl methyl ketones, and the products readily sublime directly from the IL. For example, in the case of 2-phenylindole, a 91% yield of product could be obtained by direct vacuum sublimation of the IL reaction mixture, while for 2,3-dimethylindole, a 56% yield was obtained, using this method. In unsymmetrical cases, regiospecific formation of a single product arising from the formation of the most substituted enamine intermediate is observed (Figure 21) [58].



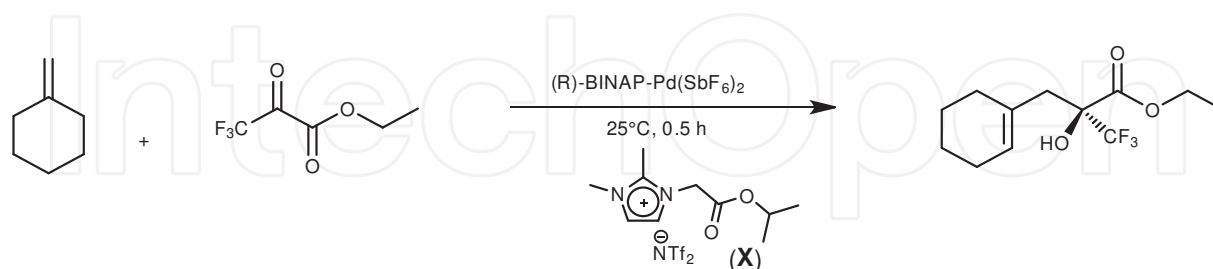
**Figure 21.** Fischer indole synthesis using  $\text{ChCl} \cdot 2\text{ZnCl}_2$ .

The Fischer indole synthesis of different ketones using chloroaluminate IL as a solvent as well as a catalyst has been also described [59].

## 10. IL-assisted group transfer reactions

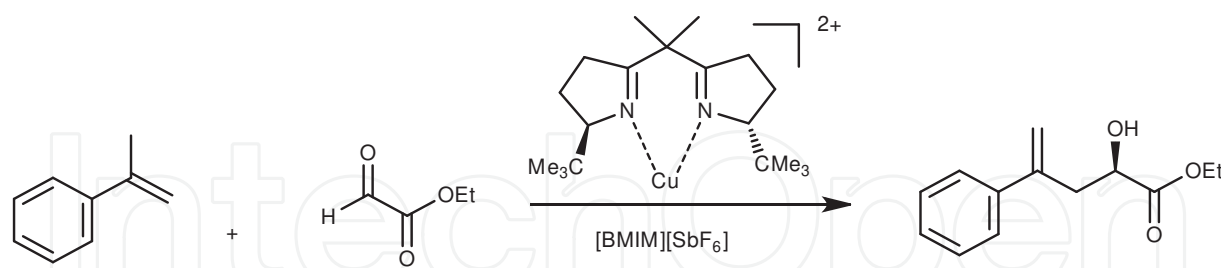
The ene reaction has been one of the most explored group transfer reactions using ILs. Gore et al., reported, in 2013, a tandem ionic liquid asymmetric catalysis study: carbonyl-ene reactions with trifluoropyruvate with five alkenes catalysed by  $[\text{Pd}\{(\text{R})\text{-BINAP}\}](\text{SbF}_6)_2$  were carried out. The synthesized and evaluated ILs showed low antimicrobial toxicity. Excellent yields and enantioselectivities (up to 96% yield and 94% ee) were obtained using IL (**X**) as a solvent. These results were either superior or comparable to those associated with conventional volatile

solvents (*e.g.*  $\text{CH}_2\text{Cl}_2$ ). Substrate scope studies revealed identical enantioselectivity when using methylenecyclopentane in either IL **4** or  $\text{CH}_2\text{Cl}_2$ . Furthermore, the IL **4** immobilized catalyst  $[\text{Pd}\{(\text{R})\text{-BINAP}\}](\text{SbF}_6)_2$  reaction medium was recycled and reused up to 7 times without losing activity (Figure 22) [60].



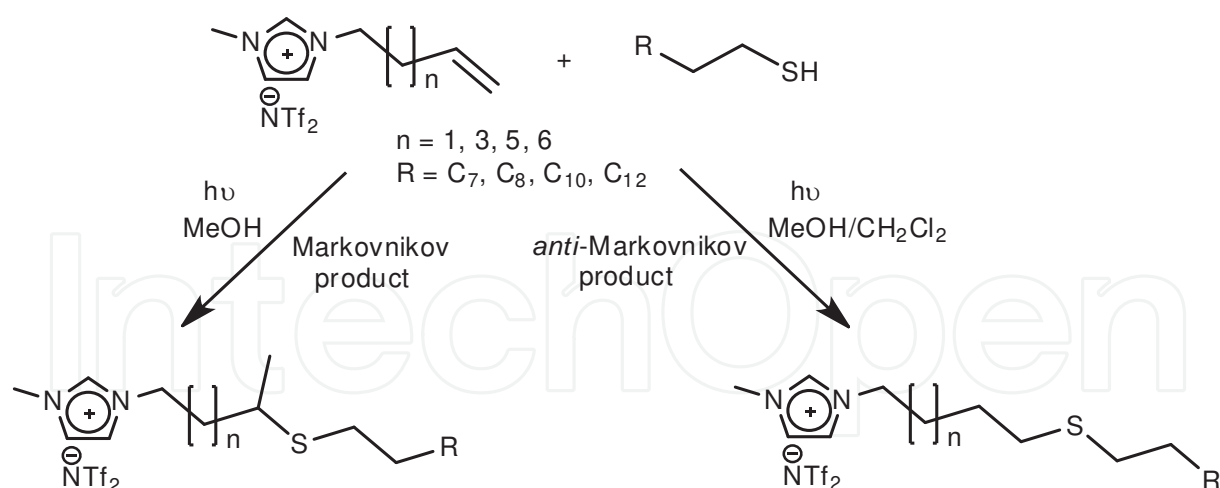
**Figure 22.** Enantioselective carbonyl-ene reaction using the IL (**X**) as solvent.

In 2012, Kim et al. reported an optimal hydrophobic IL as a solvent for highly enantioselective-glyoxylate-ene reactions catalyzed by a chiral bis(oxazoline)-copper complex. [BMIM] with  $\text{BF}_4$ ,  $\text{PF}_6$ , OTf and  $\text{SbF}_6$  were evaluated as solvents. The reactivity and stereoselectivity were highly dependent upon the properties of the IL, being the last one the best IL according to the yield (93%) and selectivity (94% *e/e*). Reactions between olefins and ethyl glyoxylate in [BMIM] $\text{SbF}_6$  at ambient temperature provided remarkably enhanced reactivity and stereoselectivity, which greatly exceed those of the corresponding reactions in dichloromethane. Furthermore, the metal-ligand complex was readily recycled up to eight times, while exhibiting no significant decrease in reaction efficiency (Figure 23) [61].



**Figure 23.** Catalytic enantioselective ene reaction of  $\alpha$ -methyl styrene and ethyl glyoxylate with the copper complex as catalyst and IL as solvent.

Very recently, the synthesis of ILs using the ene pericyclic reaction was also described. In this interesting work, a series of new lipid-inspired ILs was synthesized through thiol-ene "click" reaction with a single-step process. This synthesis offers considerable promise as an efficient and orthogonal method to construct structurally diverse imidazolium-type ILs with linear and branched cationic tails, as well as versatility in the placement of the sulfur heteroatom. Profound solvent effect on this ene-reaction regioselectivity has been observed (Figure 24) [62].



**Figure 24.** Synthesis of lipid-inspired ILs through thiol-ene "click" reaction as a single-step process.

## 11. Conclusions

As seen through this chapter, ionic liquids offer a great potential for the development of pericyclic reactions. Ionic liquids have shown to be powerful as catalysts, cocatalysts, solvents and additives in these reactions and in most cases, highly improved results regarding the yields and reaction rates have been observed and in the case of chiral reactions, excellent enantiomeric excesses have also been found. So far, in the case of cycloaddition reactions and particularly for the Diels-Alder reaction the results are very abundant, however, these are still scarce for the rest of pericyclic reactions. Both the results obtained so far and research trends are aimed at developing new methods featuring high efficiency and more environmental suitability with the use of ILs.

## Author details

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