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Deep Eutectic Solvents in Organic Synthesis

Scott T. Handy

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1. Introduction

As part of the push towards making Chemistry more environmentally compatible, there has been a major emphasis on the development of greener and more environmentally compatible solvents. Many different options have been explored, including water and supercritical fluids. [1] Each of these families has its own strengths, as well as significant limitations including reactivity to highly basic/nucleophilic reagents and limited solubility of entire families of reagents. These issues have resulted in the great interest displayed in room temperature ionic liquids (RTILs) over the last couple of decades. [2] In particular, the easily ability to tune the properties of these RTILs has attracted much attention. At the same time, essentially all of these RTILs suffer from very high cost compared to conventional solvents, which is a serious deterrent to more wide-spread application. Relatively recently, a potential solution to this problem has been reported – deep eutectic solvents (DES). [3,4,5] Although the specific cost of a DES depends upon its components, the most typical DES, such as choline chloride/urea or choline chloride/glycerol, are comparable in cost to typical organic solvents such as acetonitrile or N,N-dimethylformamide, thus eliminating much of the concern with their use.

Although many DES are theoretically possible, the current examples fall into three main families. The first is exemplified by the prototypical DES – a 1:2 molar ratio of choline chloride and urea – and involves the mixture of a salt and a hydrogen-bond donor. [6] Thousands of variation have been reported and many more can be readily imagined. [7-11] The second family is quite similar and involves the combination of a salt with a metal salt, as exemplified by choline chloride and zinc chloride again in a 1:2 molar ratio. [12-14] Much fewer examples have been studied, although this approach is expected to be quite general. The third family is more complex, involving the combination of a carbohydrate, an urea, and an ammonium salt in varying ratios. [15] The exact choice of components and their ratio does not appear to be readily predictable, but many options have already been reported, making their application relatively straightforward.

All three of these families share similar advantages, including costs comparable to conventional organic solvents, very low volatilities, lower toxicities, recyclability, and, for many components, being based on biorenewable materials. Considering the variety of salts and hydrogen-bond donors or metal salts that can be used, the properties of DES can also be tuned to control a number of fundamental properties, including Lewis or Bronsted acidity, polarity, and solvent miscibility. By exploring further variations of DES, an even greater range of solvent properties should be accessible.

Beyond being theoretically interesting materials, DES have found many significant areas of application. One of the first of these was the area of electroplating and related metal recovery and separations. [16] Tremendous research has been reported in this area and has resulted in some very promising applications. Similarly, DES have been found to be excellent solvents for enzymatic reactions, affording much higher activity and stability than organic solvents or RTILs, or sometimes even water. [17-20] Indeed, their abilities are so significant that they have been termed as potential solvents for the development of prebiotic chemistry. [21]

Despite all of these interesting applications of DES, one rapidly growing facet is their use in Organic Synthesis. Many new reports are appearing on a weekly basis, so this review attempts to cover applications reported through the middle of July of 2014.

2. Choline Chloride/Urea DES

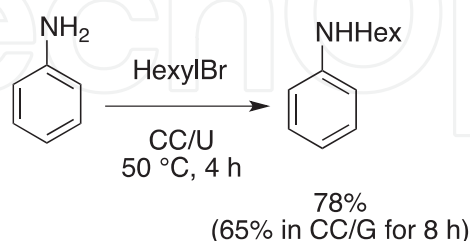
As one of the earlier deep eutectics reported, choline chloride/urea (CC/U) has been one of the most extensively explored in virtually all areas of application, including Organic Synthesis. [6] Part of its attraction is the availability of choline chloride in very large quantities (due to its use as a feed additive for poultry) at very low cost, as well as its low toxicity. The application of CC/U in Organic Synthesis covers a wide range of reaction types, with more continuously appearing.

Another important feature to note regarding CC/U is its ability to be recycled. In general there are two main options that have been reported. In one, the reaction products are separated by extraction with an immiscible organic solvent such as ether or ethyl acetate, resulting in a DES that can be reused following brief drying *in vacuo*. In the second option, this recycling involves dissolving the DES in water to separate it from the reaction product and then removing the water *in vacuo* to recover the DES. This is a fairly energy-intensive process, particularly on larger scale and may not always be worth the expense and effort. Still, the majority of reports use this option for recycling due to its avoidance of organic solvents and easy product isolation.

2.1. Alkylation, substitution, reduction, halogenation, and polymerization in CC/U

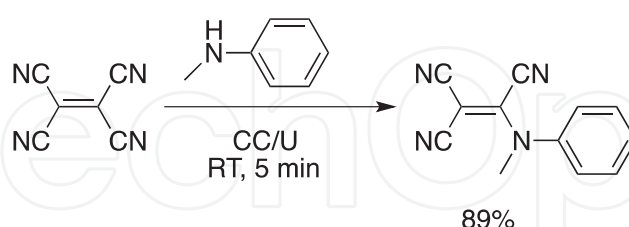
One interesting area of application has been in alkylation and nucleophilic substitution chemistry. Thus, Shankarling and co-workers have reported the simple alkylation of anilines using simple alkyl bromides in the absence of any added base. [22] (Scheme 1) Yields were high under mild conditions and generally short (< 4 hour) reaction times. In addition, the DES

could be readily recycled several times by extraction of the product with ethyl acetate and displayed little loss in activity (the yield for the reaction in Scheme 1 falling from 78% to 65% over 5 recyclings). Interestingly, a related DES, choline chloride/glycerol (CC/G), afforded a similar 65% yield, but required twice as long. The potential for expanding the scope of this chemistry to other nucleophiles (such as phenols and thiols) has not yet been reported, but seems promising.



Scheme 1. Alkylation of Anilines

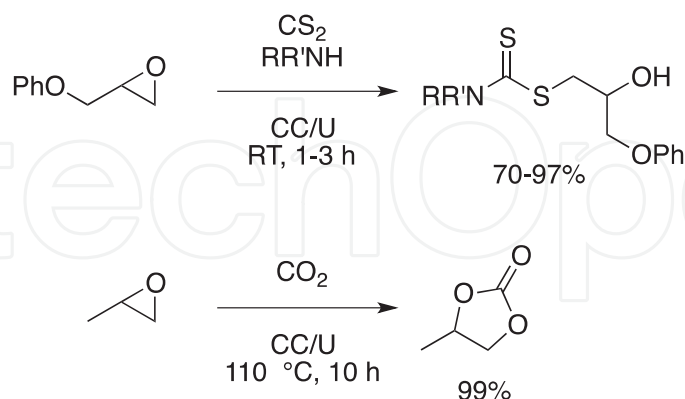
Switching to nucleophilic substitution chemistry, an unusual substitution of tetracyanoethylene with either anilines or indoles was reported by Shankarling and co-workers. [23] In a comparison of lipase and DES mediated reactions, it was shown that the DES conditions generally afforded better yields and better recyclability compared to the enzymatic conditions. A variety of other DES were also examined, and good yields were obtained in most cases. For the reaction seen in Scheme 2, yields fell modestly over 4 recyclings, going from 89% yield to 73% yield. This solvent recycling involved recovery of the DES from the aqueous layer of extraction at the end of the reaction, with care taken to remove the HCN generated in these reactions. The products of these reactions displayed interesting spectral properties, which, when combined with their straightforward synthesis, may raise useful future applications.



Scheme 2. Tetracyanoethylene Substitution

Two related nucleophilic ring openings of epoxides have been reported. Azizi and Gholibeglo have reported the synthesis of dithiocarbamates from the three component coupling of an epoxide, an amine, and carbon disulfide in a combination of CC/U at room temperature. [24] (Scheme 3) The dithiocarbamates could be isolated in good yield from a wide range of amines (mostly secondary, with a few primary examples as well). In addition, alkyl halides or enones could be employed in place of the epoxides to afford an even wider range of dithiocarbamate

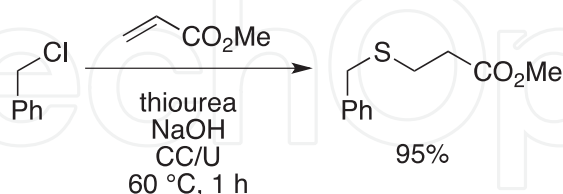
products under the same reaction conditions. The DES could be recycled several times using the water extraction option with only a modest decrease in activity.



Scheme 3. Epoxide reactions

The second epoxide reaction was the fixation of carbon dioxide with propylene oxide in the presence of CC/U. [25] (Scheme 3). In this case, CC/U supported on molecular sieves was found to be superior to simple CC/U, affording very high yields and much reduced reaction times (4-5 hours compared to 10 hours without support). The supported system had the added benefit of being readily recyclable via simple filtration of the catalyst and retained the same levels of activity for 5 recyclings.

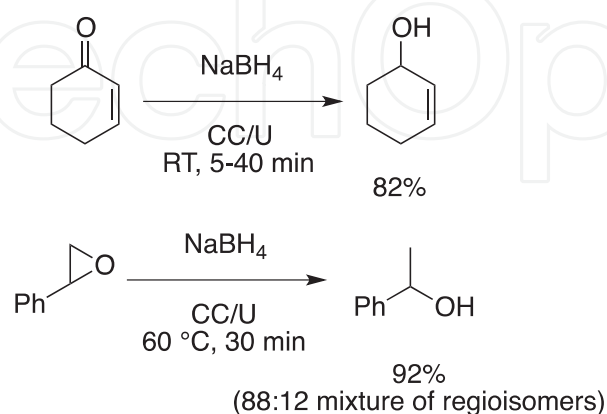
A final nucleophilic reaction in CC/U is a three component thia-Michael reaction. [26] (Scheme 4) In this case, the combination of an alkyl halide, thiourea, a Michael acceptor, and sodium hydroxide afforded very good yields of the thia-Michael products after short (< 2 hours) reaction times at 60 °C. A wide range of alkyl halides, including one example of a secondary one (bromocyclopentane) worked as did a range of Michael acceptors, including acrylates and cyclohexenone.



Scheme 4. Thia-Michael reactions

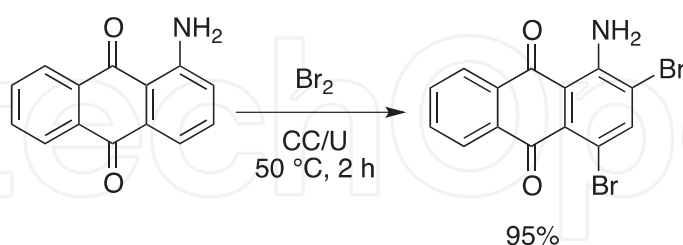
A highly unusual discovery was made by Azizi and co-workers when they studied the reduction of carbonyls and epoxides in CC/U with sodium borohydride. [27] (Scheme 5) Despite the potential for reaction with the urea, they noted clean and rapid reduction of both carbonyls and epoxides. Both aldehydes and ketones reacted well, with enones giving clean 1,2-reduction. Epoxides also reacted well at 60 °C, with even styrene oxide affording primarily the product of reduction at the less hindered end (88:12 ratio of 1-phenylethanol:2-phenyle-

thanol). Interestingly, these reaction conditions demonstrated very good chemoselectivity, with aldehydes and ketones being reduced at room temperature in the presence of imines or epoxides and epoxides being reduced at 60 °C in the presence of imines. The products were isolated via partitioning between water and ether and generally required no further purification.



Scheme 5. Reductions

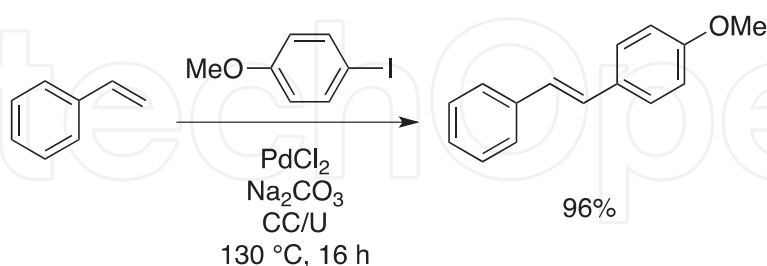
Another usual area of application is in the bromination of 1-aminoanthraquinones. [28] (Scheme 6) A series of these compounds were brominated by treatment with bromine in CC/U at 50-60 °C for 2 hours. In cases where the 4 position was unsubstituted, 2,4-dibromo products were obtained in good yield. Recycling of the DES was also reported via extraction with water followed by evaporation. Although little mechanistic information is discussed, it seems possible that the brominations are being mediated by the transient formation of N-bromo urea. The potential for this system to mediate the bromination of other compounds has yet to be studied, but could be of considerable utility.



Scheme 6. Brominations

Transition-metal-catalyzed couplings, though extensively studied in other DES, have been little explored in CC/U. The only report is found in the original patent on DES and reports some studies of the Heck coupling in CC/U. [29] (Scheme 7) The results were rather unsurprising and afforded results for aryl iodides comparable to those obtained in many conventional solvents. Appropriate selection of base and palladium source were critical for optimal results, with palladium chloride and sodium carbonate giving a 96% yields after 16 hours,

compared to 90% after 1.5 days using sodium acetate as base or 60% after 2 days using sodium acetate and palladium acetate. The patent reports that the catalyst and solvent can be reused, but no details are provided. Still, this does demonstrate that CC/U could be expected to be an inexpensive recyclable solvent/catalyst system for palladium-catalyzed coupling reactions.



Scheme 7. Heck coupling

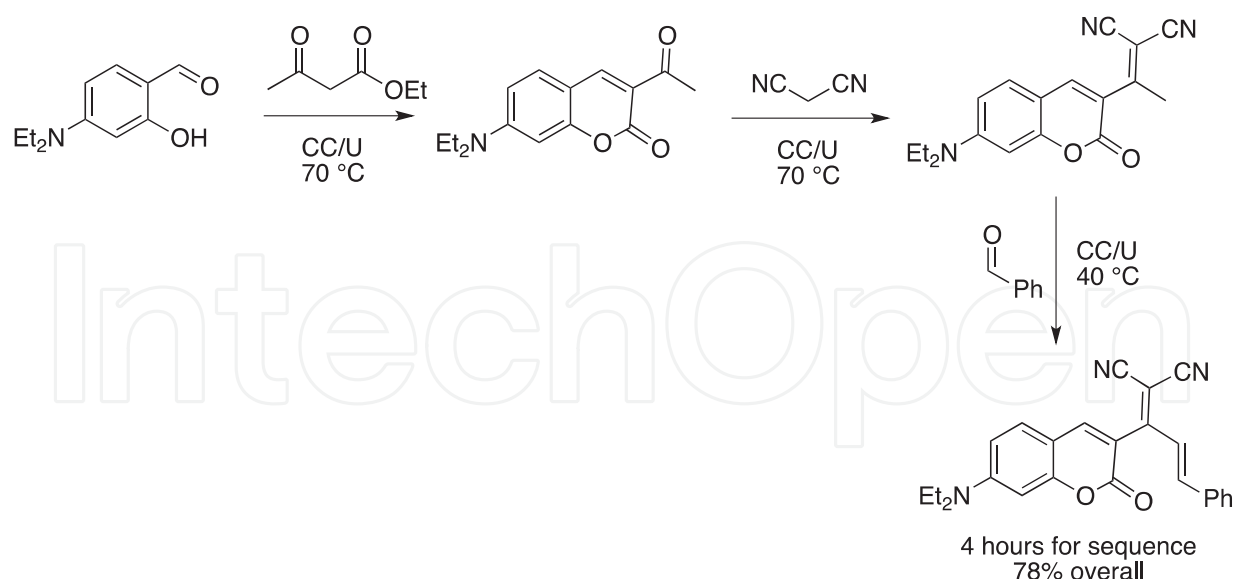
This same patent also reported the application of CC/U to free-radical polymerization. [29] Styrene was polymerized using 1 mol% of AIBN in CC/U at $110\text{ }^\circ\text{C}$ for 16 hours to afford a polymer with average molecular weight of 12,000 and a polydispersity of 3.2. There has been little follow-up to this report.

2.2. Condensation reactions in CC/U

A major area of application for CC/U has been in the area of condensation-type chemistry. It appears that the combination of the potential for organocatalytic, H-bonding activation of aldehydes by urea (a known, but weak organocatalyst) and the desiccating properties of CC/U serve to benefit this family of reactions in ways that many other solvents do not. As a result, this section is focused on condensation applications of CC/U.

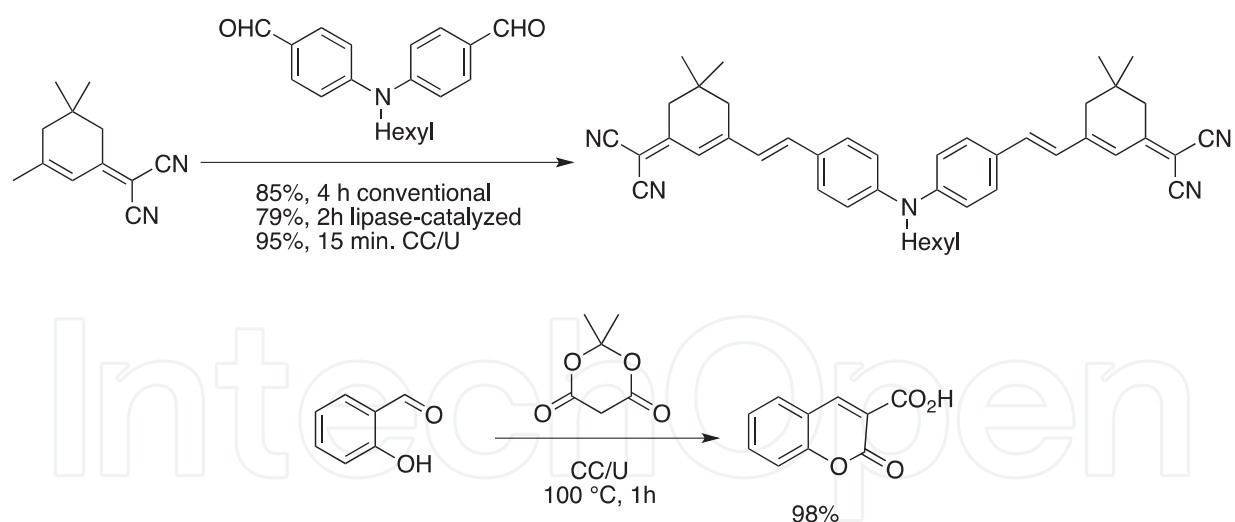
The first sub-set of condensation reactions are simple carbonyl reactions such as Knoevenagel, Perkin, Henry, and related aldol-type reactions. Perhaps the most elegant example of the application of CC/U to condensation reactions comes from a report by Shankarling. [30] (Scheme 8) In this paper, he reported a one-pot synthesis of coumarin styryl dyes via a sequence of two Knoevenagel condensations and one aldol-like condensation. All three condensation reactions were performed in CC/U at temperatures ranging from $30\text{--}75\text{ }^\circ\text{C}$ and all afforded the desired products in good to excellent yields after reaction times of < 2 hours (< 6 hours for the entire sequence). The CC/U could also be recycled using the procedure commonly employed in the Shankarling group of separation of the DES with water, followed by concentration *in vacuo* to afford the DES ready for reuse. The power and potential demonstrated in this paper have doubtless inspired at least some of the more recent applications of CC/U in this area.

In a related paper focusing just on the Knoevenagel condensation of diphenylamine aldehydes with a variety of active methylene compounds, three sets of reaction conditions were compared: conventional with piperidine as base, lipase-catalyzed, and CC/U mediated. In virtually all cases, the DES conditions afforded the highest yields and the shortest reaction times (< 30 minutes at room temperature). [31] (Scheme 9) As the focus of this paper was on the dyes that



Scheme 8. Condensation sequence

were synthesized and not as much the DES, no comment is made on recycling the DES, but it would seem likely from other papers that such recycling could be readily achieved with good results.



Scheme 9. Knoevenagel condensations

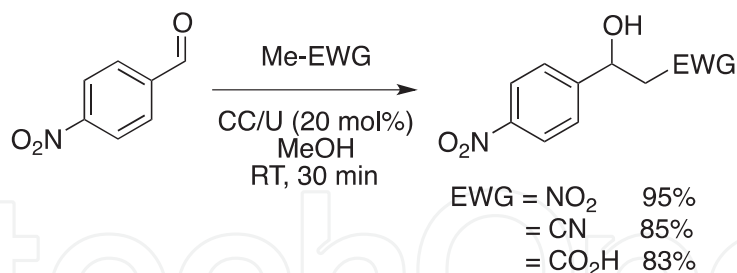
Another study of a different Knoevenagel condensation (salicyl aldehydes with Meldrum's acid and other active methylenes) also reported very good yields of the anticipated coumarins. [32] (Scheme 9) In this case, the reaction temperature was higher (100 °C), but still with short reaction times. Recycling of the DES using the water extraction/concentration method was mentioned, but no data was reported.

Another classic carbonyl condensation reaction that has been reported in CC/U is the Perkin reaction. [33] (Scheme 10) In this case, the reaction of an aromatic aldehyde with an anhydride (acetic anhydride in all but two cases) in CC/U at room temperature for 4-9 hours afforded the cinnamic acid derivatives in generally good yield. A comparison was made with conventional Perkin conditions (excess anhydride in the presence of sodium acetate at 140 °C), with the conventional conditions affording significantly lower product yields after longer reaction times in every case. The DES could be recycled with little loss in activity for 4 reactions using the water extraction/concentration method.



Scheme 10. Perkin reaction

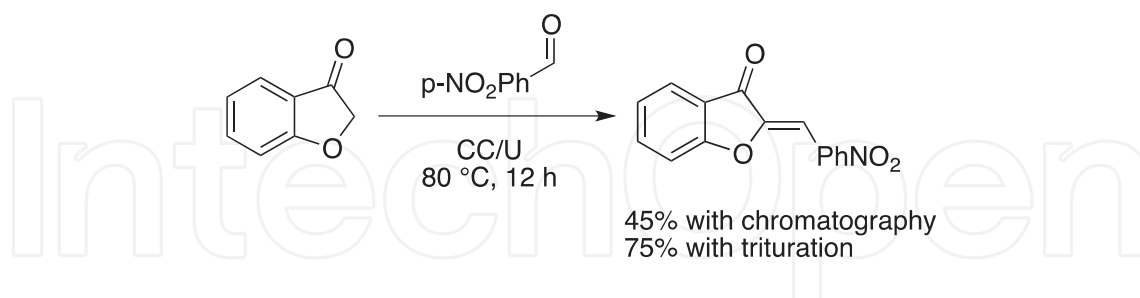
The Henry reaction and a couple of related examples using acetonitrile or acetic acid with aromatic aldehydes were reported by Shankarling. [34] (Scheme 11) Interestingly, the products in these cases were not elimination products, but rather the β -hydroxy products. Part of the reason for this outcome may stem from the fact that the DES was used as a catalyst in methanol for short reaction times at room temperature. It is possible that higher concentrations of DES may lead preferentially to elimination products (see, for example the aurone synthesis by Handy), although this feature has not yet been confirmed.



Scheme 11. Henry reaction

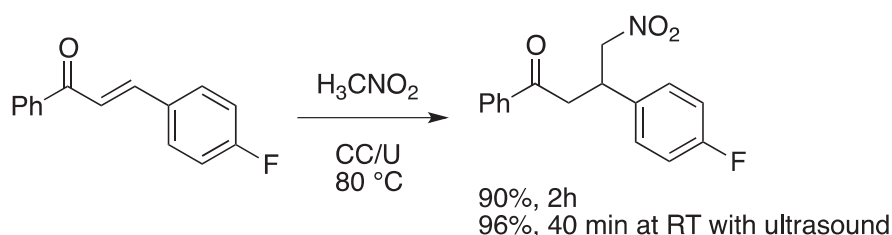
Also within the aldol family of reactions is the synthesis of aurones via condensation of an aromatic aldehyde and a coumarinone reported by Handy and Hawkins. [35] (Scheme 12) A wide range of aldehydes proved compatible with this method, including acid-sensitive ones such as furfural. The yields were quite variable, but subsequent research has demonstrated that much of the problem is associated with purification of the aurone products. By employing a modified purification using trituration with ether in place of the column chromatography, yields could be dramatically improved. For example, the reaction of coumarinone with p-nitrobenzaldehyde in CC/U followed by silica gel chromatography afforded the anticipated

aurone in 45% yield, while the same reaction purified by trituration with ether afforded the same product in 75% yield and analytically pure form.



Scheme 12. Aurone synthesis

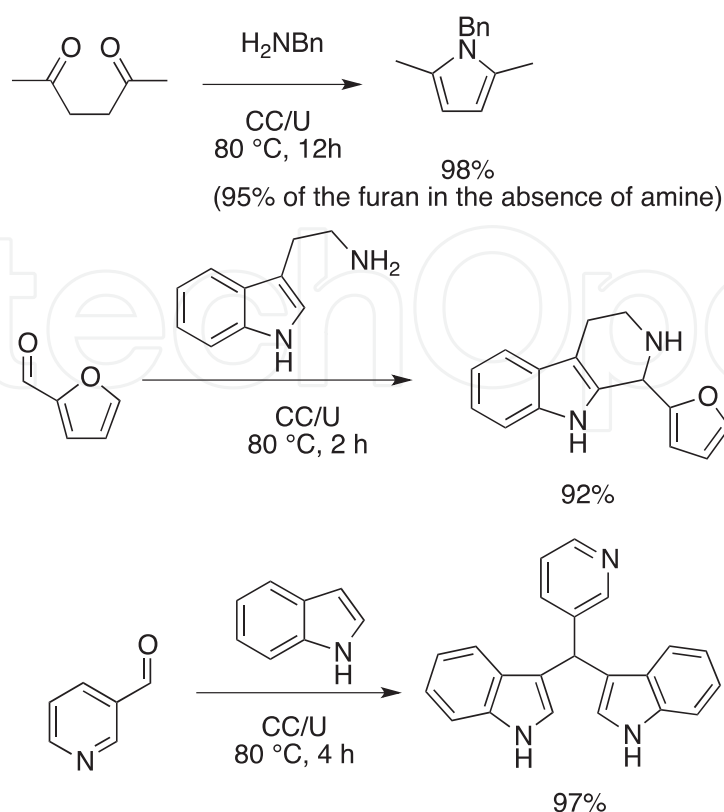
A final reaction from the carbonyl condensation family is the recently reported Michael addition of nitromethane and active methylene compounds (malononitrile, and ethyl cyanoacetate) to chalcones. [36] (Scheme 13) In this case, the use of a combination of CC/U and ultrasound afforded the Michael products in excellent yields after much shorter reaction times and at lower temperatures compared to the same reaction conditions in the absence of sonication. This beneficial combination of the DES and ultrasound is expected to be applicable to many other reactions run in CC/U and possibly other DES as well and certainly merits further exploration.



Scheme 13. Michael reaction

2.3. Heteroaromatic synthesis in CC/U

Another area that has found considerable application of CC/U as a catalytic solvent is in the synthesis of heteroaromatics via carbonyl condensation reactions. In a series of papers, the Handy group has reported several of these types of reactions, beginning with the Paal-Knorr synthesis of pyrroles and furans. [37] (Scheme 14) A variety of amines, including anilines could be condensed with 1,4-diketones in CC/U at 80 °C to afford the anticipated pyrroles in generally good yield. The one exception was the reaction of 2,5-hexanedione with poorly nucleophilic p-nitroaniline which afforded a 56% yield of the pyrrole with the mass balance being the 2,5-dimethylfuran. In the absence of amines, the diketones cleanly afforded the anticipated furans after longer reaction times. In addition, the DES could be recycled several times with little loss in activity by extraction of the products with ether and then brief drying *in vacuo*.



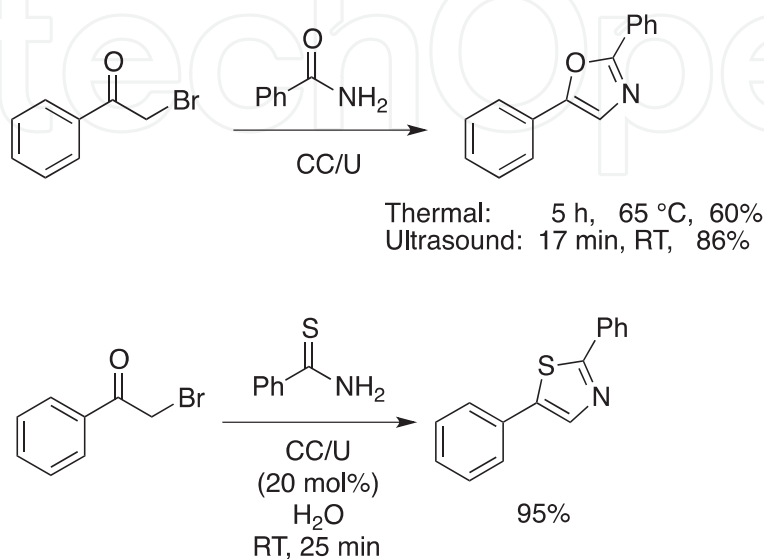
Scheme 14. Heteroaromatic syntheses from the Handy group

A second application was the Pictet-Spengler reaction. [38] (Scheme 14) The acid-free nature of these reaction conditions enabled the synthesis of a wide range of β -carboline derivatives including furyl and pyridyl substituted ones in excellent yield after 2 hours at $80\text{ }^\circ\text{C}$. As with the Paal-Knorr synthesis results, the products could be easily extracted using ether and the remaining DES recycled several times with minimal loss of activity after brief drying *in vacuo*.

A related reaction is the conversion of aldehydes to bis(indolyl)methanes by treatment with 2 equivalents of indole. Reaction in CC/U at $80\text{ }^\circ\text{C}$ for 4 hours afforded the bis(indolyl)methanes in excellent yield for a wide range of aromatic aldehydes including the more difficult to access pyridyl systems. [39] (Scheme 14) Interestingly, these reaction conditions proved ineffective with the more demanding aliphatic aldehydes and ketones, affording a complex mixture of aldol products and recovered starting material respectively. As with the previous two reports, the products were isolated via extraction with ether and generally required no further purification. The DES layer could be recovered and recycled following brief drying *in vacuo* with little loss in activity over 5 reactions.

Two related reports from the Shankarling group focus on related approaches to the synthesis of oxazoles and thiazoles. (Scheme 15) For oxazole synthesis, the combination of CC/U and ultrasound again displayed beneficial synergy. [40] Thus, treatment of an α -bromoacetophenone with an amide or urea affords the desired oxazoles. Thermal reactions ($65\text{ }^\circ\text{C}$) required 3.5-5 hours to afford modest yields, while the ultrasound reactions could be done at room

temperature and were complete in < 20 minutes to afford high yields of the products. CC/U recycling was also studied and proved to be quite convenient in this case as the products were extracted with methylene chloride (which is immiscible with CC/U) to directly afford the DES ready for recycling. There was no significant decrease in reaction yield over 5 reactions, indicating that the DES is stable to the ultrasound reaction conditions.



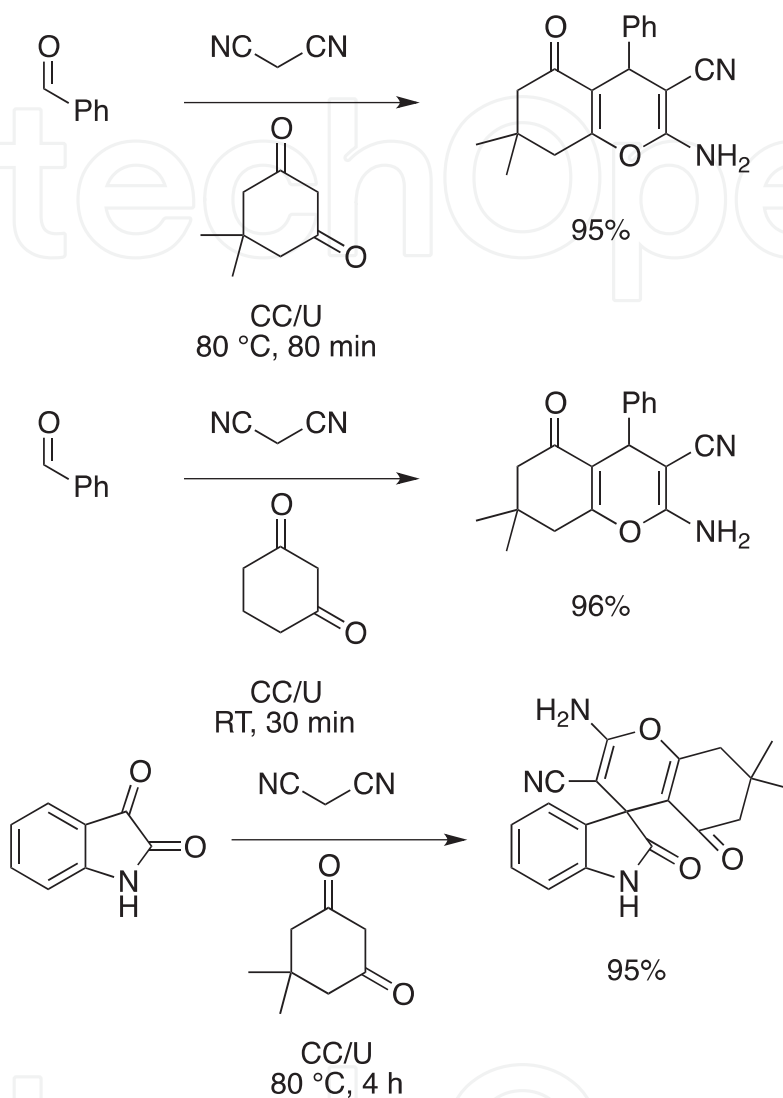
Scheme 15. Thiazole and Oxazole synthesis

The thiazole synthesis is quite similar. [41] (Scheme 15) Again, the combination of an α -bromoacetophenone and an amide or urea was combined in CC/U. There were two differences, though. First, DES and lipase catalyzed reaction conditions were compared, not ultrasound. Second, the DES was used as a true catalyst in aqueous solution at room temperature. Both methods afforded excellent yields of the thiazole products after short (< 20 minute) reaction times. DES recovery (via separation with water and concentration of the aqueous layer) was effective and the DES could be recycled several times with minimal loss in activity.

2.4. Multicomponent reactions in CC/U

A final condensation area that has received significant attention in CC/U is that of multicomponent coupling reactions (MCR). Many different options are imaginable, but virtually all of the reports have centered on reactions initiated by a Knoevenagel condensation, followed by some type of Michael addition. For example, Azizi and co-workers reported the MCR of aromatic aldehydes, malononitrile, and various active methylene compounds (including dimedone, acetylacetone, and acetoacetates). [42] All of these example afforded good yields after 1-4 hours at 80 °C, thus providing a simple and efficient route to compounds of this type. (Scheme 16) In addition, they explored a few other solvents under identical conditions and found that three acidic DES (CC with malonic acid, citric acid, or tartaric acid) afforded the anticipated products at slightly reduced yields (82%, 60%, and 68% respectively). Finally, the

temperature was important as the same reaction at room temperature in CC/U afforded only a 50% yield of the MCR product.



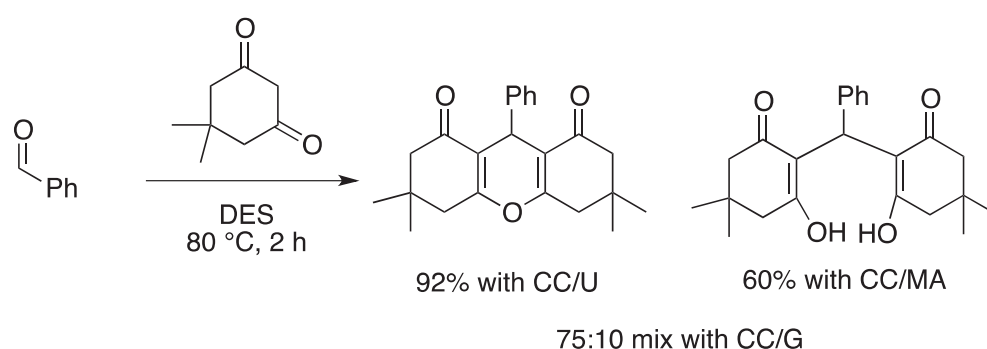
Scheme 16. Malononitrile multicomponent couplings

This temperature observation is quite interesting since another group reported the closely related condensation of aldehydes, malononitrile, and cyclohexane-1,3-dione in CC/U. In this case, they reported clean, high-yielding reactions at room temperature in 30 minutes. [43] (Scheme 16) Considering the very high viscosity of CC/U at room temperature, it is unclear how useful such reaction conditions would be, and the difference in reported results between the two groups is a concern.

A third related MCR is that of 1,2-diketones in place of the aldehyde to afford spirocyclic products. [44] (Scheme 16) A wide range of products were accessible as both malononitrile and methyl cyanoacetate were used in combination with dimedone, cyclohexane-1,3-dione, Meldrum's acid, and 1-naphthol. In general, very good yields were obtained when isatin was

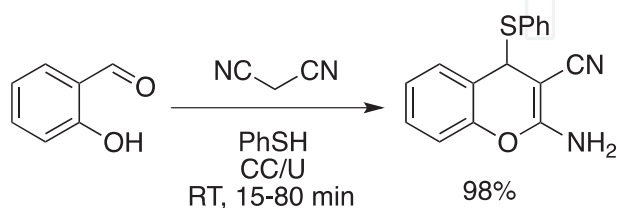
the 1,2-dikeone, although somewhat lower (50-60%) yields were obtained for other diketones. Recycling of the DES was also reported, again using extraction with water, followed by concentration *in vacuo*.

A very interesting report on MCR in CC/U focusing on the condensation of aldehydes with dimedone or cyclohexane-1,3-dione has also appeared. [45] (Scheme 17) In this careful study, the authors noted that the choice of DES controlled the type of product (open or closed) formed. In CC/U, a very high yield of the ring-open product was formed, while use of an acidic DES favored the closed form, with choline chloride/malonic acid (CC/MA) and choline chloride/ ZnCl_2 both affording solely the closed product. Interestingly, choline chloride/glycerol (CC/G) afforded a mixture of the two products, favoring the open form as did the presumably less Lewis acidic choline chloride/ SnCl_2 .



Scheme 17. Other multicomponent couplings

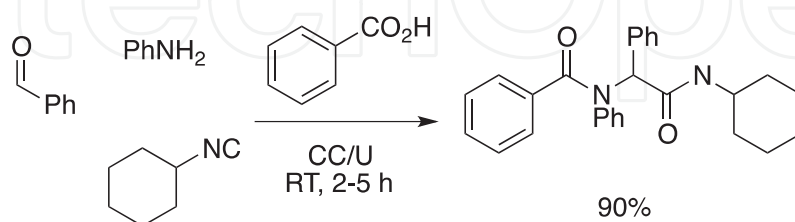
A somewhat different MCR in CC/U was reported based upon the initial condensation of malononitrile with salicylaldehyde, followed by Michael addition of a variety of nucleophiles to afford substituted chromenes. [46] (Scheme 18) The reactions proceeded quickly (all reactions < 4 hours, and most < 1 hour) and in generally excellent yield. Nucleophiles that were studied included many thiols, amines (secondary and one primary), cyanide and indole. The products could generally be isolated in pure form by diluting the reaction with water and then filtering to separate the product. In principle, this separation method should result in the ability to recycle the CC/U, but no recycling data was reported.



Scheme 18. Chromene multicomponent couplings

Finally, the parent MCR, the Ugi reaction, has also been reported in CC/U. [47] (Scheme 19) In this case, the use of a DES afforded much higher yields of the Ugi product than did reaction

under neat conditions or in water or several organic solvents. The mild conditions and short reaction times were complimented by the ease of product isolation (filtration after diluting with water) and recovery and recycling of the DES (via concentration of the water layer *in vacuo*). The recycled DES could be reused three times with only a slight drop in product yield. Finally, a wide range of anilines and aromatic aldehydes, as well as one aliphatic aldehyde and one ketone, all gave good yields of the Ugi products, indicating considerable scope to this method.



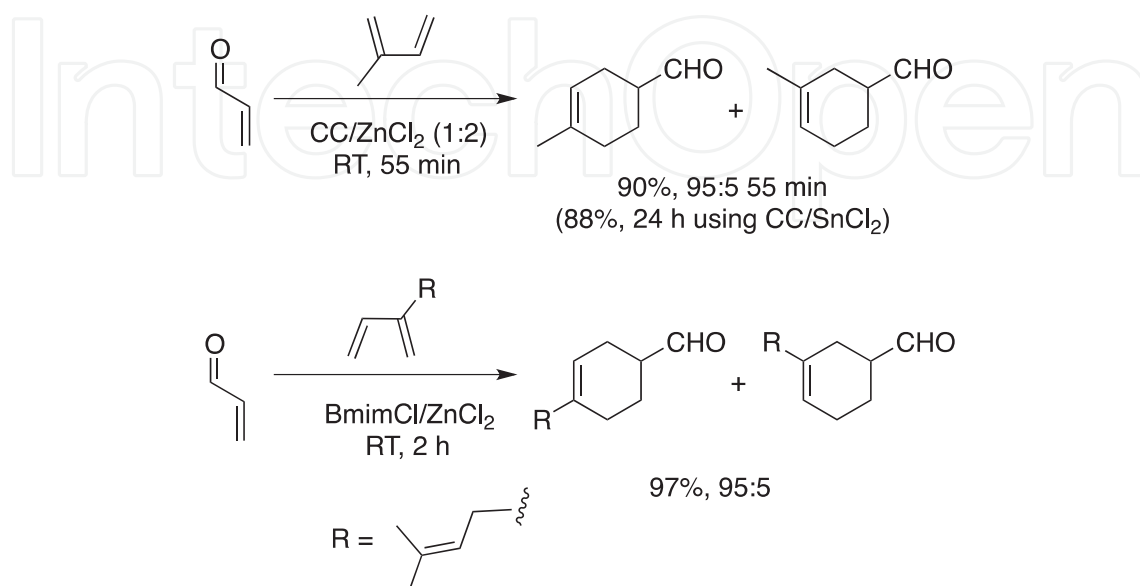
Scheme 19. Ugi multicomponent coupling

3. Lewis acidic DES

One of the early families of DES that was introduced are those composed of choline chloride and a metal salt, most typically zinc or tin chloride in a 1:2 molar ratio. These mixtures form complex metal chloride anions and give liquids that are Lewis acidic. In principle, this same concept should be applicable to combinations with a variety of other metal salts, such as iron, copper, and the lanthanides, although little has been reported along these lines. The obvious Lewis acidity of these DES has resulted in a number of applications in Organic Synthesis and should be applicable to even more than have been presently reported. One potential drawback to these DES is the fact that they would be expected to be moisture sensitive, although different authors have reported these DES as been either moisture sensitive or moisture insensitive. It is likely that there is some sensitivity, but it is likely less than that of the metal salts themselves, which may aid in their handling under normal laboratory conditions.

One reaction that shows considerable promise in these Lewis acidic DES is the Diels-Alder reaction. Considering the great utility that Lewis acids have demonstrated in the catalysis of Diels-Alder reactions, this is not surprising. Nevertheless, the first report by Abbott and co-workers did a fantastic job demonstrating their potential. [48] (Scheme 20) A number of reactions were studied between ester, ketone, and aldehyde substituted dienophiles and a range of simple dienes. Good yields were obtained (85+%) with good regioselectivities after modest (<5 h) reaction times at ambient temperature when CC/ZnCl₂ was employed as the solvent. The use of CC/SnCl₂ resulted in much slower reactions, but still good yields and regioselectivity. Product isolation was simple, involving decantation of the non-polar products from the DES, which could then be recycled at least 5 times with no appreciable loss in activity. A later study similarly noted good results when using zinc-containing DES. [49] A range of

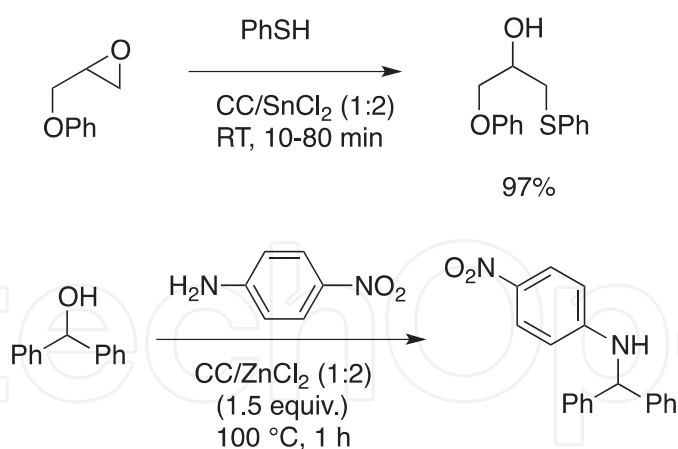
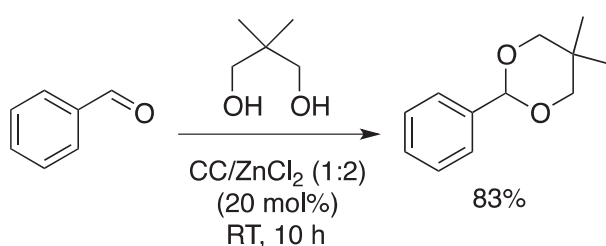
salts, including imidazolium and pyridinium ones were used in combination with varying ratios of zinc chloride. In all cases, 2:1 or higher molar ratios of zinc chloride to the other salt afforded the best yields and regioselectivities. Product isolation again involved decanting the less polar product layer to afford the DES layer which could be recycled.



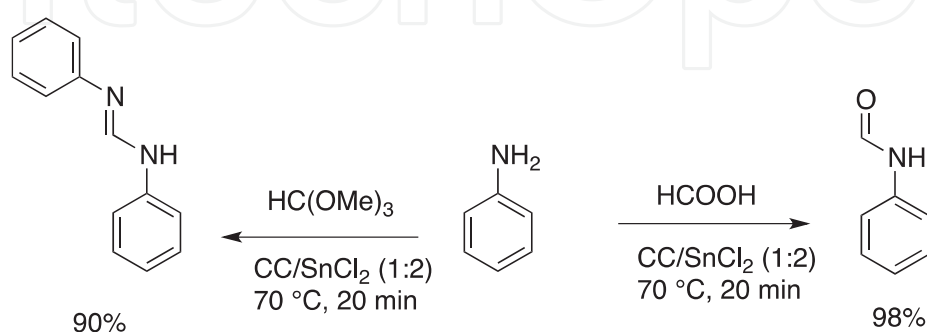
Scheme 20. Diels-Alder Reactions

Beyond Diels-Alder reactions, another obvious application is in the area of nucleophilic substitution chemistry. Azizi and Batebi have reported the ring opening of epoxides with a wide range of nucleophiles, including thiols, anilines, TMSCN, TMSN₃, and methanol. [50] (Scheme 21) These reactions generally afforded very good yields after short (<2 hours) reaction times at room temperature. In addition, the DES layer could be recycled at least 3 times with only a modest loss in activity following extraction of the product by diethyl ether. Another example of nucleophilic substitution chemistry in CC/ZnCl₂ involved the ionization and trapping of stabilized carbocations, such as diphenylcarbinol with a range of nucleophiles including anilines, amines, sulfonamides, and 1,3-dicarbonyl compounds. [51] Yields were good after 1 hour reaction times at 100 °C and the DES could be recycled at least 4 times with no loss in activity. It is worth noting that the DES is used more as a recyclable catalyst, as only 1.5 equivalents were employed. In addition, the DES was recovered by extraction with water and then dried *in vacuo* before reuse, which is operationally more difficult than the extraction option employed by Azizi.

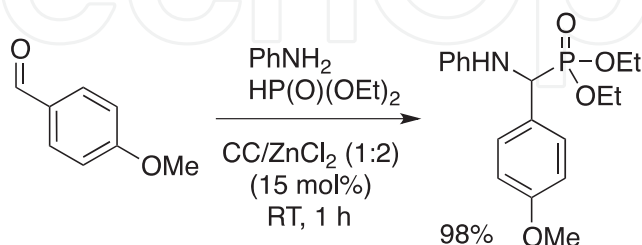
A related reaction is the ketalization of carbonyls using 2,2-dimethyl-1,3-propanediol using the CC/ZnCl₂ DES. [52] (Scheme 22) A wide range of aldehydes as well as two ketones were employed in this chemistry to afford the desired ketals in good yield after modest reaction times (10-20 h). Again, the DES was employed as a catalyst, with only 20 mol% being employed. Further, the DES could be readily recycled following separation of the product via extraction with ether.

**Scheme 21.** Nucleophilic Substitutions**Scheme 22.** Ketalizations

A rather unusual application of DES to synthesis is the preparation of either N-formylanilines or N-N'-diarylamidines starting from anilines. [53] (Scheme 2) In this case, CC/SnCl₂ was found to be the best solvent of those studied. Reaction in the presence of formic acid at 70 °C afforded the N-formyl products in good yield, while a slightly higher temperature (90 °C) in the presence of trimethyl ortho formate afforded the amidines instead. In both cases, product isolation involved simple extraction with ethyl acetate, which in principle should enable recycling of the DES, although this was not reported.

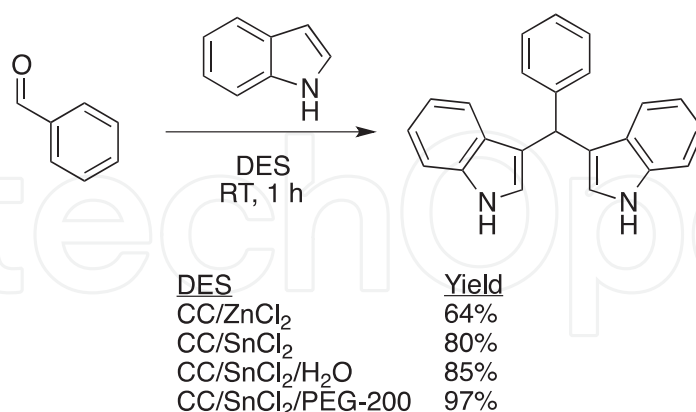
**Scheme 23.** Formylation and Amidine Formation

Various carbonyl condensation reactions have also been explored in Lewis acidic DES. The Kabachnik-Fields reaction of aldehydes, anilines, and phosphites has been conducted using CC/ZnCl₂ at room temperature to afford the desired products in good yield after short reaction times. [54] (Scheme 24) In this case, the DES was employed as a catalyst, with 15 mol% giving optimal results. The products could be readily extracted from the DES using MTBE and the DES recycled after drying *in vacuo*. A slight loss in activity (98% to 86% over five reactions) was observed, which may be due to mechanical loss of the DES over the course of five reactions.



Scheme 24. Kabachnik-Fields Reactions

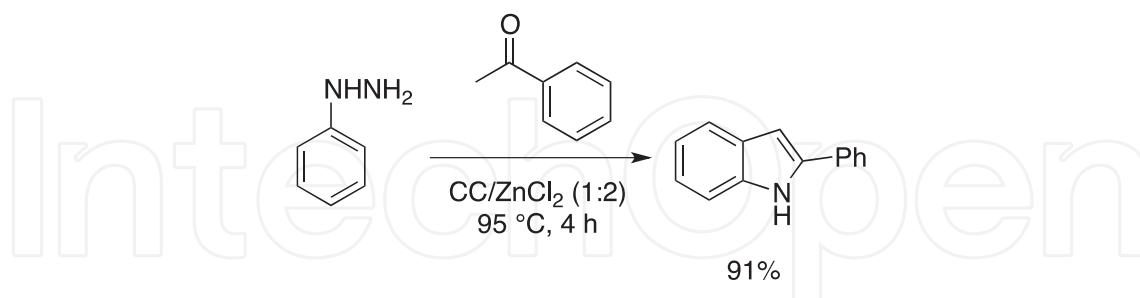
The synthesis of bis(indolyl)methanes (bim) has also been reported in a Lewis acidic DES. [55] (Scheme 25) Interestingly, in this case, CC/SnCl₂ proved superior to CC/ZnCl₂. Even better results were obtained when using either CC/SnCl₂ with water (1:2:3 molar ratio) or with PEG-200 (also a 1:2:3 molar ratio). Reaction times were short (<4 hours) at room temperature and yields high, even for the more problematic alkyl aldehydes. Finally, mention is made of recycling the DES, but no details are provided, although since the products are isolated via extraction with ether or ethyl acetate, this recycling should be straightforward.



Scheme 25. BIM Synthesis

In a final example, Abbott and co-workers have also explored the Fisher indole synthesis in CC/ZnCl₂. [56] (Scheme 26) Reaction yields were good and reaction times short (<4 hours), while employing 1-3 equivalents of the DES as the catalyst/solvent for the reaction. An interesting option for product isolation was used in this study, with the desired indoles being

obtained via sublimation from the DES. Recycling of the DES was reported, but activity decreased very rapidly, going from 91% to 72% to 34% over the course of three reactions.



Scheme 26. Fischer Indole Synthesis

4. Bronsted acidic DES

In addition to Lewis acidic DES, there is also the option to form Bronsted acidic DES by simply using a Bronsted acid as the proton donor component of the DES. In this way, a wide range of DES with varying acidity can be formed, with the most common options being various di- and tricarboxylic acids as well as tosic acid. (Figure 1) As with the simple CC/U DES, recycling of these systems has often been reported. In some cases, this simply involves product extraction with an immiscible organic solvent (even just decanting the product in one case), but more frequently is performed by dilution with water and then recovery of the DES from the aqueous layer. This is clearly an area in need of improved options and may benefit from many of the studies performed previously on traditional RTILs.

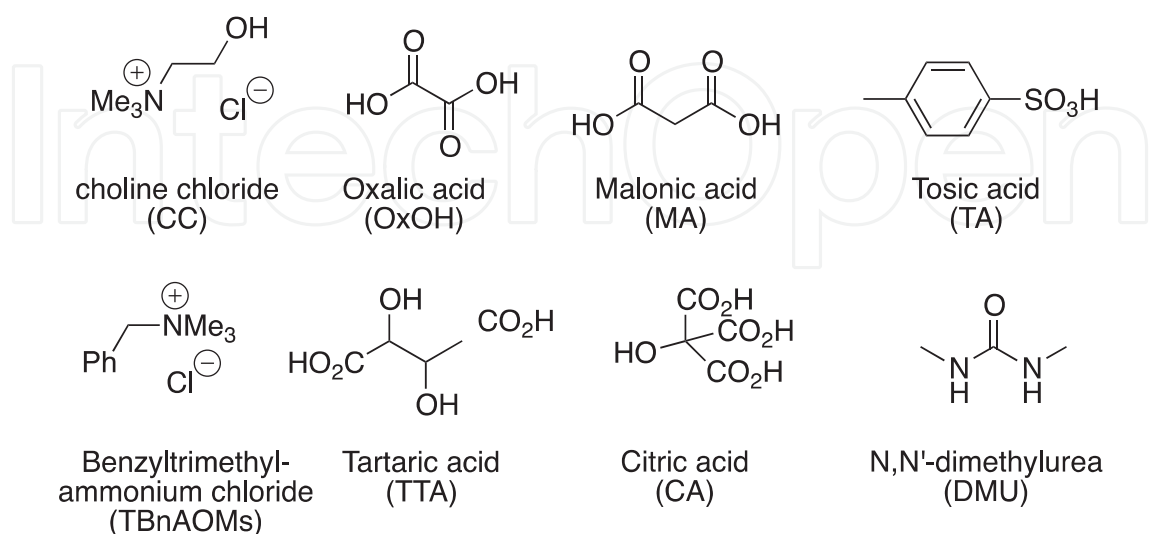
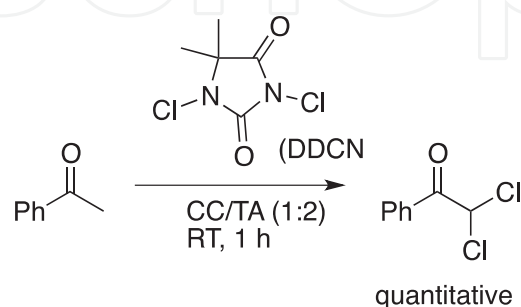


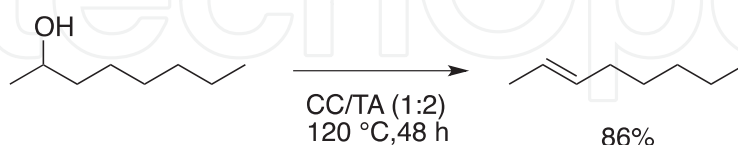
Figure 1. Common Acidic DES Components

One of the more unusual applications of acidic DES in Organic synthesis is the use of the choline chloride/tosic acid (CC/TA) system to effect the dichlorination of methyl ketones using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH). [57] (Scheme 27) Using methanol as the solvent, the chlorinating reagent cleanly affords the expected α -chloroketones in good yield. Upon switching the solvent to CC/TA, though, the dichlorination product is now obtained in nearly quantitative yield after a short 1 hour reaction time at room temperature. The scope of these conditions has not been extensively explored, but it does appear to be an interesting route to these unusual products.



Scheme 27. α -Chlorinations

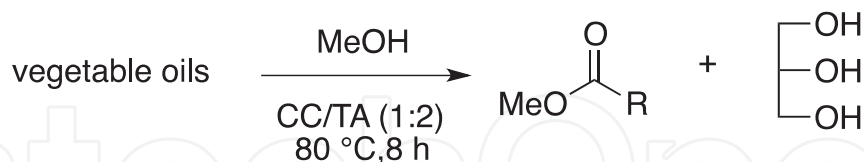
More traditional applications of acid catalysts have also been explored. In some unpublished work, Handy and co-workers have explored the use of CC/TA as a recyclable catalytic solvent for both the elimination of alcohols and the transesterification of esters. For the elimination of alcohols to afford alkenes, this reaction was found to proceed cleanly with simple alcohols such as 2-octanol and cyclohexanol, affording the alkenes in 85+% yields after reaction at 120 °C for 2 days. [58] (Scheme 28) 3° alcohols reacted more readily, with methylcyclohexanol affording the anticipated alkene after 12 hours at 80 °C. In all cases, product isolation involved simple decantation of the alkene, which formed a separate second layer. The remaining CC/TA layer could be reused 4 times with minimal loss of activity (still affording 80% of the alkene product from 2-octanol on the fourth recycling), although the build-up of water would eventually reduce the effectiveness of this acidic DES (usually by the 6th recycling).



Scheme 28. Eliminations

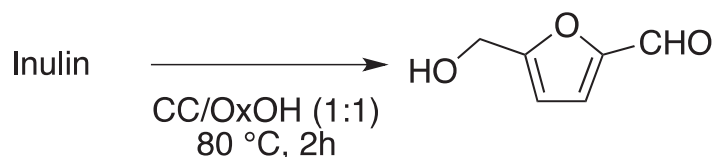
For transesterifications of various vegetable oils (corn, soy, and canola), the same CC/TA DES proved to be effective. [59] (Scheme 29) Yields of the methyl esters were high (>80%) after modest reaction times. Interestingly, the DES could be recycled up to 3 times without the need to remove the glycerol by-product before transesterification was seriously impeded (85, 80, and 76% recovery of the methyl esters for the first three uses of CC/TA, and then a drop to 50%

recovery on the fourth use). To date, attempts to remove the glycerol and regenerate the active DES have not proven to be successful.



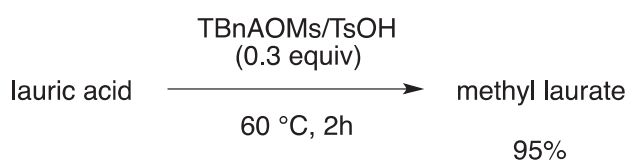
Scheme 29. Transesterifications

In related work, the dehydration of the carbohydrate inulin to form 5-hydroxymethylfurfural (HMF) in CC/Oxalic Acid has also been reported. [60] (Scheme 30) After extensive optimization of the reaction time, temperature and the acidic component of the DES, conditions were determined that allowed HMF to be isolated in 64% yield after only two hours of reaction at 80 °C. As has been reported several times, the inclusion of ethyl acetate aided in preventing decomposition of the HMF as it was formed. This feature also enabled product separate to be achieved by simple phase separation and the remaining DES to be recycled repeatedly with minimal loss of activity. The inexpensive nature of this catalyst system, coupled with the mild conditions and high yield of HMF from more complex carbohydrates (instead of the more easily converted fructose) holds considerable promise for the effective formation of the valuable biorenewable building block HMF.



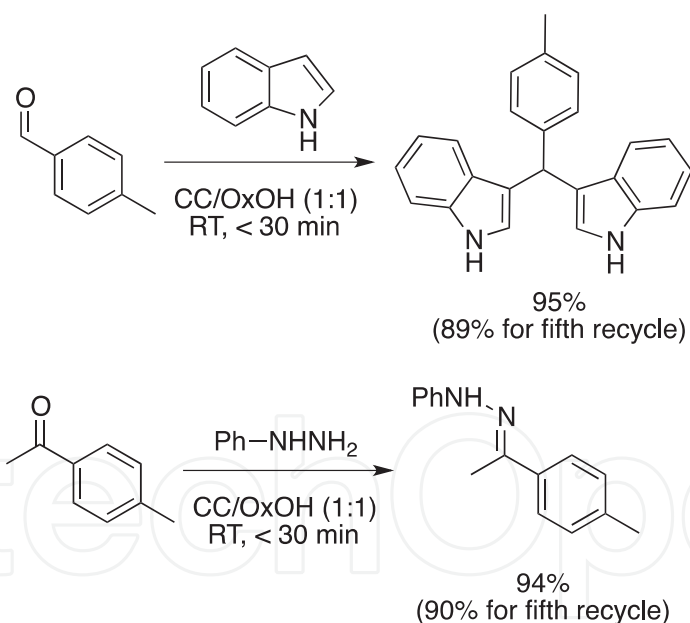
Scheme 30. HMF Formation

In addition to transesterifications, related acidic DES have been used for the Fischer esterification of carboxylic acids. [61] (Scheme 31) A series of new acidic DES were prepared from the combination of various ammonium salts and tosic acid, of which the equimolar combination of TBnAMsO and tosic acid was employed most frequently. It was very effective for the esterification with primary alcohols, affording the esters in near quantitative yields after short 2 hour reaction times at 60 °C. For secondary alcohols (such as isopropanol), the yields did drop to near 50% at the same time and temperature, but the esters could still be easily isolated. Of equal importance was the observation that the acidic DES, which was used as a catalyst (0.3 equivalents), could be recycled several times with only a modest loss in activity. Eventually, the build-up of water reduced this activity over the course of 8 recyclings, but the DES could be readily restored by simple dehydration *in vacuo* and then reused further. In addition, product isolation was very simple, requiring just phase separation of the upper organic layer to isolated the ester product and recovery of the acidic DES.



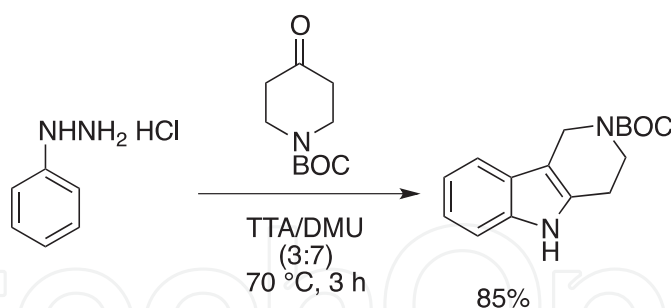
Scheme 31. Fischer Esterifications

Acidic DES have also been used studied in a number of carbonyl condensation type reactions, including the previously mentioned formation of bis(indolyl)methanes (bim) from aldehydes and indoles. [62] (Scheme 32) The DES in this case was again the combination of choline chloride and oxalic acid (CC/OxOH) and was used as a catalyst (10 mol%) for this transformation. The desired bims could be recovered in high yield after very short (5 minutes) reaction times at room temperature by dilution of the reaction with water and filtration. The DES could be recovered by evaporation of the aqueous layer and recycled several times with little loss of activity. The same paper also reported the synthesis of hydrazones from aryl aldehydes and acetophenones under the same reaction conditions. Another paper similarly reported the synthesis of bims by using TTA/DMU at 70 °C for 2-3 hours to afford the anticipated products in good yield. [63]



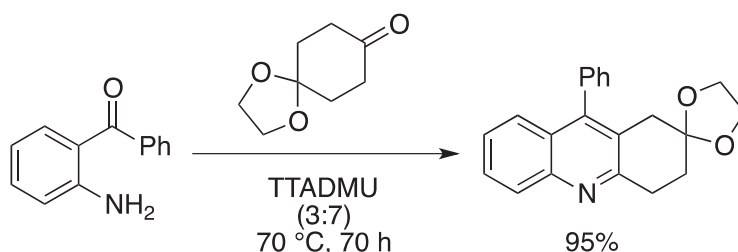
Scheme 32. BIM and Hydrazone Formation

In related work, the Fischer indole synthesis was reported in the tartartic acid/DMU (TTA/DMU) DES. [64] (Scheme 33) This reaction system afforded very good yields for a wide range of ketones, including ones with acid-sensitive functionality such as that seen in Scheme 33. The DES could be recovered from the aqueous layer after the reaction and recycled with minimal loss of activity over 3 uses. It seems likely that other acidic DES may behave similarly for this important reaction.



Scheme 33. Fischer Indole Synthesis

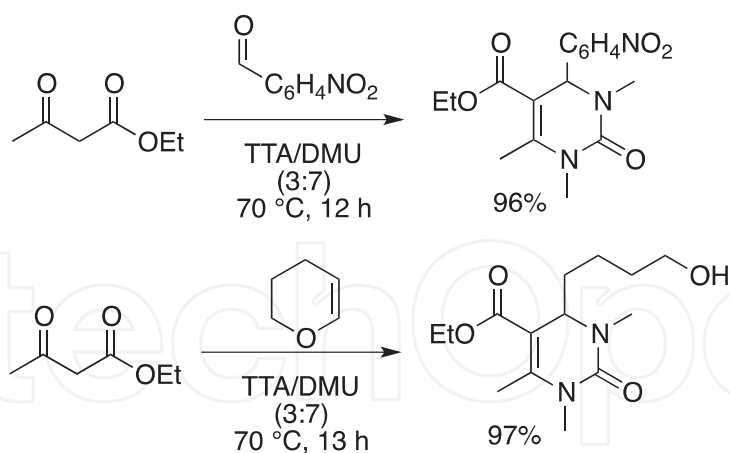
Another Heteroaromatic synthesis that has been reported in the same acidic DES is the Friedlaender synthesis of quinolones. [65] The combination of a ketone and an ortho-aminoacetophenone in TTA/DMU at 70 °C afforded the target quinolones in good yield. Again, acid-sensitive functionality, such as the ketal in the reaction in Scheme 34, survives these reaction conditions, demonstrating their functional group tolerance. The one drawback to these reaction conditions is the extremely long reaction times (often several days). Nonetheless, there is much promise for this approach.



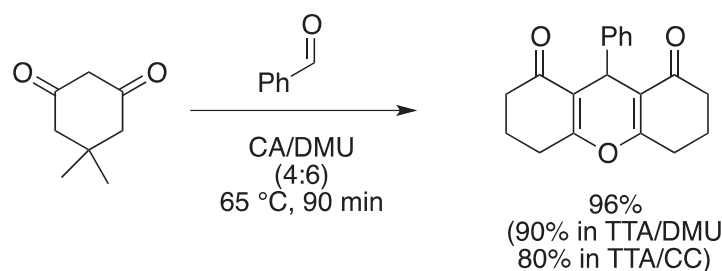
Scheme 34. Friedlaender Quinoline Synthesis

This same TTA/DMU acidic DES has found application in a number of multi-component reactions. In a pair of papers, Koenig and co-workers have reported the formation of dihydropyrimidin-2-ones or pyrimidopyrimidinediones by the combination of DMU and an aldehyde with ethyl acetoacetate and acetophenones respectively. [66, 67] (Scheme 35) In this case, beyond serving as a catalyst and solvent, the DES also serves as the source of the DMU. Non-methylated and thiocarbonyl versions of the products can also be accessed by switching to acidic DES with urea or thiourea respectively. Further, it was noted that vinyl ethers could be used as masked aldehydes, thereby affording access to hydroxyl-terminated alkyl substituents. In all cases, good to excellent yields are obtained after modest reaction times, thereby making this a very general route to these biologically interesting compounds.

A closely related acidic DES – citric acid/DMU – was found to be superior to TTA/DMU for the synthesis of 1,8-dioxo-dodecahydroxanthenes. [68] (Scheme 36) A wide range of aldehydes afforded good results under these reaction conditions and the DES could be recycled up to six times with little loss of activity. Recycling again involved the recovery of the DES from the aqueous layer via concentration *in vacuo*.

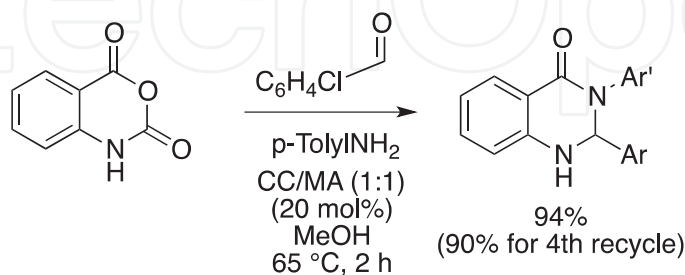


Scheme 35. Dihydropyrimidin-2-one and Derivatives Synthesis



Scheme 36. Xanthene Synthesis

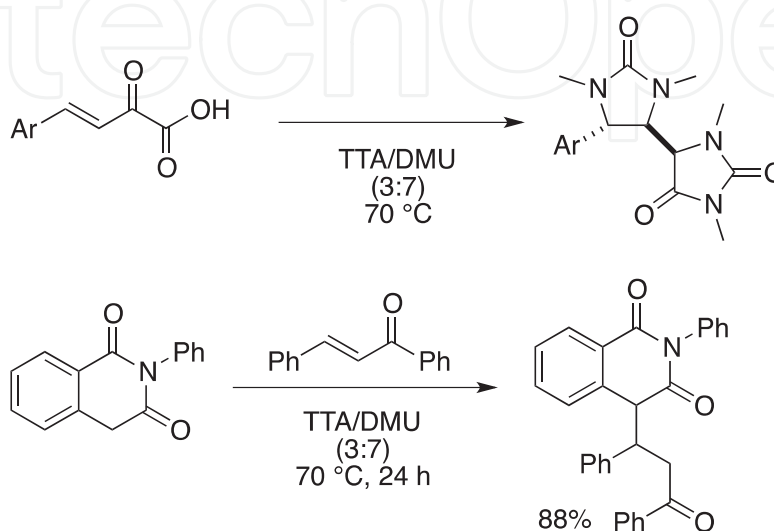
A final example of a multicomponent synthesis in an acidic DES comes from the Shankarling group who used CC/Malonic acid (CC/MA) to prepare 2,3-dihydroquinazoline-4-ones. [69] (Scheme 37) In this case, the DES is really employed as a catalyst (20 mol%) in methanol at 65 °C, instead of as a solvent as well. The DES can be recovered and recycled several times with little loss of activity by recovery from the aqueous layer, following product separation via extraction with ethyl acetate.



Scheme 37. 2,3-Dihydroquinazoline-4-one Synthesis

Finally, two different variations of conjugate addition have been reported in the TTA/DMU acidic DES. (Scheme 38) In the first, Koenig and co-workers have synthesized some complex

hydantoins in this DES, wherein the DES serves as solvent, catalyst, and the source of the urea component. The hydantoins are isolated in good yield as roughly 2:1 mixtures of the syn and anti isomers after several hours at 70 °C. [70] A more traditional Michael addition was reported using the same solvent system at 70 °C for relatively long reaction times (1-2 days). [71] Interestingly, several non-acidic carbohydrate-derived DES also afforded good results, indicating that the acidity may not be crucial for this reaction.



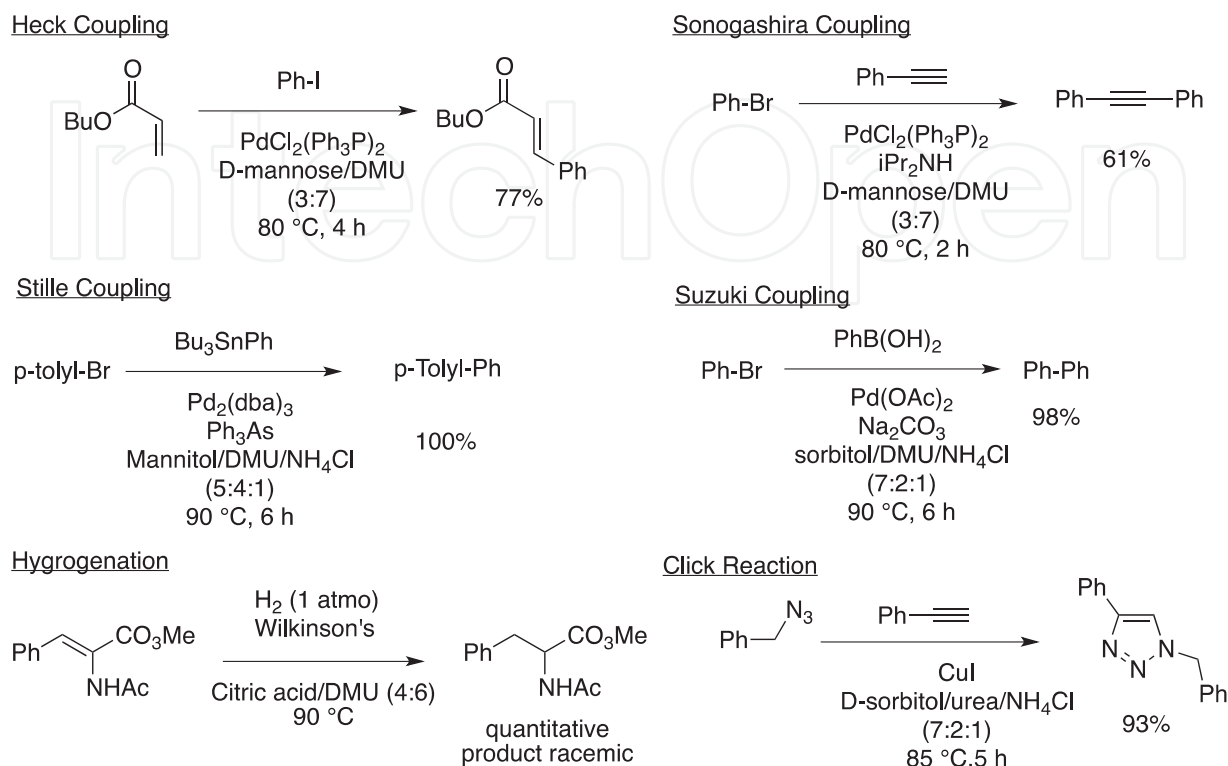
Scheme 38. Conjugate Additions

5. Carbohydrate-derived DES

Another major family of DES that have been extensively explored are those based upon carbohydrates. First popularized by Koenig and co-workers, they generally feature the combination of some carbohydrate (or reduced derivative as is the case with sorbitol and mannitol), a urea (most frequently N,N'-dimethylurea), and a chloride salt (most frequently ammonium chloride). [72, 74, 75] These DES frequently exhibit melting points in the 60-90 °C range and are easily prepared from bulk, biorenewable compounds. As a result, they feature an intriguing combination of being inexpensive, non-toxic, and environmentally compatible.

In terms of the chemistry explored in these solvents, much of it has been cross-coupling chemistry. Thus, Koenig and co-workers have employed various carbohydrate DES for Heck, Sonogashira, Stille, Suzuki, hydrogenations, and Click reactions. [74, 75] (Scheme 39) In general, these reactions performed similarly to those conducted in conventional solvents and were applicable, with slight variations in yield, across a considerable range of carbohydrate-derived DES. In a few cases recycling of both the palladium catalyst and the DES were mentioned, but with very little detail on how this recycling was performed. In the case of the Stille coupling between tributylphenyltin and p-bromoanisole, the reaction yield fell rapidly during recycling, going from 94% for the first reaction to 70% for the first recycling to 66% for

the second recycling which indicates either limited thermal stability of the catalyst or modest retention of the catalyst in the DES during product isolation.



Scheme 39. Metal-mediated Reactions in Carbohydrate-derived DES

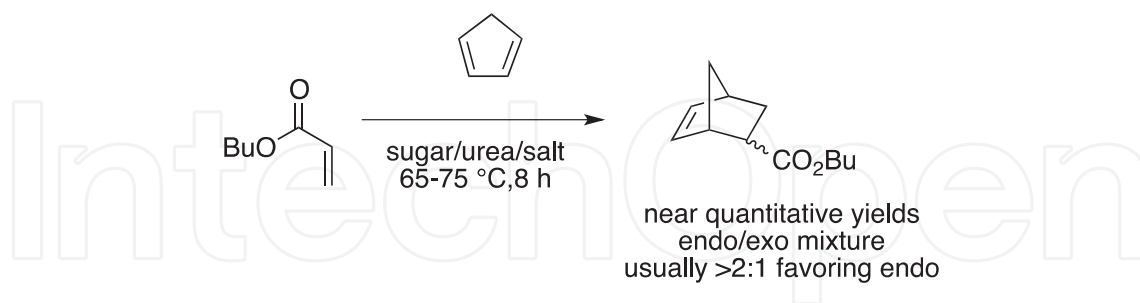
The Heck couplings were only reported using the more reactive aryl iodides, which work well under any of a wide range of reaction conditions. On the other hand, the Sonogashira couplings were reported for the less reactive aryl bromides and were performed in the absence of a copper co-catalyst, which does make these reaction conditions more potentially useful. [72] For the Suzuki coupling, a number of carbohydrate-derived DES were employed, with all affording generally good results for a range of electron-rich and deficient aryl bromides. [74] Across the examples studied, the sorbitol-based DES seen in Scheme 39 did afford modestly better results.

In the case of the hydrogenation reaction, although a chiral acid (citric acid) was used, the product that was obtained was racemic. [72] The use of other carbohydrate-derived DES for this particular reaction resulted in much poorer conversions.

Finally, for the copper-catalyzed Click reaction to form a triazole, the reaction could be either performed using a preformed azide (as shown in Scheme 1), or the azide could be generated in situ from sodium azide and benzyl bromide to afford the same product in 93% yield. [72]

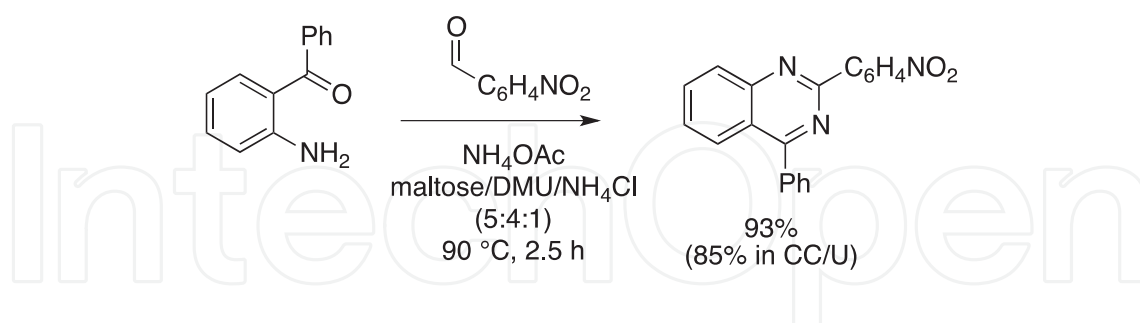
Beyond metal-catalyzed reactions, the Diels-Alder reaction of cyclopentadiene with butyl acrylate was also studied in a wide range of carbohydrate-derived DES. [72, 75] (Scheme 40) The reactions proceed in near quantitative yields in most cases and afforded modest endo selectivity. Unlike the earlier work by Abbott, this study did not report the results of any more

demanding Diels-Alder reactions, leaving the practical utility of these solvent systems in doubt. [48]



Scheme 40. Diels-Alder Reactions in Carbohydrate-derived DES

One example of the application of these carbohydrate-derived DES to the family of condensation reactions has also been reported. [76] Thus, the use of a maltose/DMU/ NH_4Cl DES for a catalyst-free Friedlander-type synthesis of quinazolines was reported. In general, the desired quinazolines were formed in high yield via a multi-component coupling of an aldehyde, an o-aminoacetophenone, and ammonium acetate. (Scheme 41) Interestingly, the omission of ammonium acetate severely decreased the yield of the desired quinazoline product with the reaction seen in Scheme 3 affording a 55% yield compared to a 93% yield in the presence of ammonium acetate. As a result, it appears that the ammonium chloride present in the DES is not able to serve as an effective nitrogen source for this reaction. Finally, these reactions worked well in a wide range of DES, including CC/U (more generally employed in condensation-type reactions). This result may indicate that the carbohydrate-derived DES could have a much broader range of application in condensation chemistry.



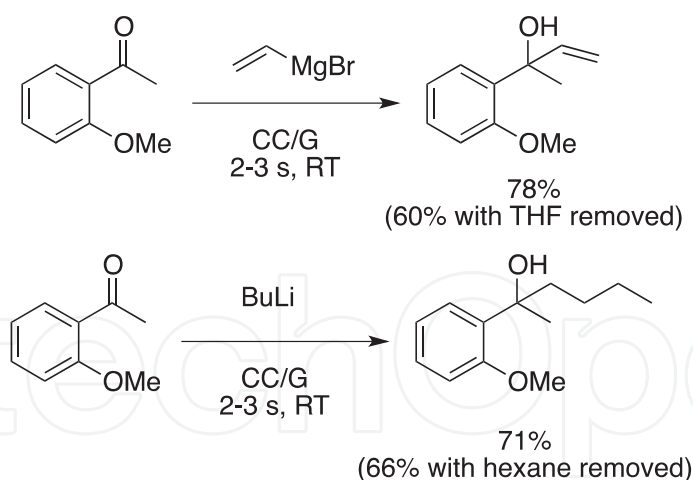
Scheme 41. Multicomponent Quinazoline Synthesis

6. Assorted DES

One of the exciting features of DES is the wide variety of materials that can be prepared. While many examples have been seen in the previous sections, a few additional ones provide excellent examples of this flexibility.

Recently, Del Monte and co-workers reported the use of an acrylic acid/Choline chloride DES as a combined reaction medium/reagent for frontal polymerization to form polyacrylic acids. [77] These polymerizations were initiated thermally using benzoyl peroxide and proceeded very efficiently to form the desired polymers. More interestingly, by dispersing or dissolving carbon nanotubes into this DES, carbon nanotube containing composites could be formed, resulting in materials with high biocompatibility and the potential for future applications as biomaterials. Indeed, this article serves as another reminder that the field of polymer science could benefit considerably from greater application of DES.

A very recent and very surprising result has appeared on the application of DES to main group organometallic chemistry. Although the generally protic nature of virtually all DES would be expected to be incompatible with organometallic reagent such as organolithiums and Grignards, it was noted that very rapid (2-3 seconds) additions to ketones could be achieved under ambient conditions with exposure to air. [78] (Scheme 42) Although several DES were studied, the optimal one was found to be choline chloride/glycerol (CC/G). Most reactions were performed using commercially available solutions of the organometallic reagents in ethereal or hydrocarbon solvents, but it was observed that the reactions still proceeded well when the organic solvent was removed *in vacuo* prior to addition. Unfortunately, attempts to generate the organometallic reagents in the DES failed, but this still constitutes a major advance in making organolithium and Grignard chemistry safer and more environmentally compatible. It will be interesting to note if the heightened reactivity observed in the present cases holds true for other organometallic reagents such as organozincs.



Scheme 42. Organometallic Chemistry in DES

7. Conclusion

In conclusion, in a few short years, DES have made a significant showing in Organic Synthesis. Given the broad range of such materials that can be imagined (neutral, Lewis acidic, and

Bronsted acidic), it is easy to picture continued growth in this area. Recycling has been demonstrated in many cases, although the frequently employed method of recovering the DES from the aqueous layer following extractive work-up of the reaction is undoubtedly energy intensive. It is likely that other superior methods for product separation and solvent recycling can be developed and should certainly be a topic for future focus. Additionally, the ability to tune the solvent properties by developing new DES is a fruitful option for study, although this may require the development of new design parameters beyond those currently in use. In any case, DES are here to stay.

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