Application of Chiral Ionic Liquids for Asymmetric Induction in Catalysis

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Abstract: Here we present the state-of-the-art for asymmetric catalysis using chiral ionic liquids (CILs) as source of chiral information. The current review covers reactions using typical homogeneous catalysts e.g. organocatalysts, transition metal complexes and solid catalysts for heterogeneous catalysis in solvent-systems with chiral ionic liquids.

INTRODUCTION

Most of the chemical production processes in industry involve catalysts (>90%) and the majority are heterogeneous processes [1]. This is due to practical aspects like purification of products or intermediates. However, solid catalysts are disadvantageous if asymmetric reactions such as asymmetric hydrogenation need to be carried out. In that case, chiral organometallic complexes or organocatalysts acting in homogeneous manner are clearly superior to the heterogeneous type of catalyst. Further attempts for asymmetric induction in principle use substrates, reagents and auxiliaries bearing the chiral information successfully [2], or chiral reaction media, the latter one less successfully [3]. Other investigations involved asymmetric induction by chiral particles of achiral substances, like chiral quartz (SiO_2) or glycine crystals, for example in asymmetric photochemical reactions in the solid state [4, 5]. In the absence of chiral molecules also circularly polarized light can be used as chiral force such as the synthesis of hexahelicene with left or right circularly polarized light [4, 5].

There are reports though, which are describing the immobilization of chiral homogeneous catalyst on solid support [6]. However, in most cases homogeneous catalysts do not fulfill the necessary requirements (catalyst stability, catalyst recycling, separation from product and intermediates) for industrial processes like continuous-flow processes. For years, the industrial adaptation only seemed practical if homogeneous catalysts are immobilized on solid supports or soluble polymers which can be easily separated from solution [6]. Combining the advantages of solid catalysts (stability, recyclable, purification, long life-time) [6, 7] and the advantages of homogeneous catalysts (chemo-, regio- and asymmetric reaction controls) [6, 7] lead to chiral ionic liquids (CILs) as an reaction media for the immobilization of the catalyst. Nowadays, CILs seem to be the most adequate

materials potentially fulfilling all the desired requirements for a heterogeneous-type solid catalyst as well as typical molecular complex catalysts or organocatalysts for asymmetric catalysis. Recently, their unique material and solvent properties and the growing interest in a sustainable, "green" chemistry has led to an amazing increase in interest in such salts [8].

Ionic liquids (ILs) are well-organized three-dimensional media. It has been shown that intramolecular C-H•••π interactions results in a well-organized *3D* structure where ionic channels are formed by cations and anions [9]. This supramolecular arrangement render them in a plethora of applications and opportunities [10]: a media for metal nanoparticles formation and stabilization [11], the formation of organized liquid clathrates [12], and in many different physicochemical processes [13]. There are many different reviews on the subject of ILs that can attend many readers with distinctive needs [14].

Not before 1999 the first CIL, an imidazolium salt with a lactate as chiral anion was published by *Seddon*, and in the following years most of the CILs had chiral cations derived from the "chiral pool" [15]. Their chirality origin is from axial, central or planar chirality. Additionally, it can be found in both cation, and the anion – the so called *doubly chiral IL*. As a consequence of a very well organized *3D* structure, CILs have an intrinsic potential for enantioselective reactions, especially because in a well organized media it is reasonable to expect some chiral transmission. Whether considering that ILs can participate in the transition state or stabilizing charged (or polar) intermediates, it is expected that chiral induction takes place in that media.

The chiral transmission using CILs as the single source of chirality may take place through two different pathways: (1) the CILs indeed participate in the reaction intermediates or transition states [16], *e.g.* some proline TSCILs (task-specific CIL) and (2) through ion-pairing formation [17].

The attempts to use chiral solvents as source of chirality goes back to the 1970s, when *Seebach* and *Oei* performed electrochemical reduction of ketones in a chiral amino ether which led to a rather low enantioselectivity of ~24% *ee* [18]. Further investigations in the past decades gave also comparably low asymmetric induction which resulted in the ac-

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cepted conclusion that chirality transfer from chiral solvents is rather low [3]. Later on, it was not necessary to wait again several decades for further advantages in catalysis using chiral solvent. This conclusion seemed to be unchanged at least until middle of 2004. Then, the first motivating result was published by *Vo-Thanh* and coworkers [19]. The middle of May 2006 can be dated as the breakthrough of catalysis using CIL as single source of chirality. Almost parallel *Leitner* [20], *Afonso* [21], *Malhotra* [22], *Cheng* [23], and all their respectively coworkers presented their contribution to this research field with remarkably high enantiomeric excesses in different reactions. Nowadays, many applications of CILs in different areas of research may be found in the open literature. CILs are used for enantioselective separation of pharmaceutical products by capillary electrophoresis,[24] to tune some kinetics aspects on the asymmetric hydrogenation of some specific compounds [25], chiral stationary phase for the liquid chromatographic resolution [26], enantiomeric recognition properties [27], influence on the excited-state properties [28], and others. Furthermore, the importance of CILs are reflected in various publications showing simply their syntheses, characterizations and properties [29, 30, 31] Several reviews can be found describing the development in the syntheses and applications of CILs [15]. In the present review we focus on the application of CILs in asymmetric catalysis and not on the synthesis/design of CILs which are more intensively discussed in previous reviews [15].

1. ORGANOCATALYSIS

1.1. Baylis-Hillman Reaction

Vo-Thanh and coworkers presented the pioneering work about a DABCO (1,4-diazabicyclo[2.2.2]octane) catalyzed asymmetric Baylis-Hillman reaction between benzaldehyde and methyl acrylate **3** (Scheme **1**, Table **1**). Enantioselectivities up to 44% *ee* were obtained using a chiral cation, based on ephedrine, as source of chirality [19].
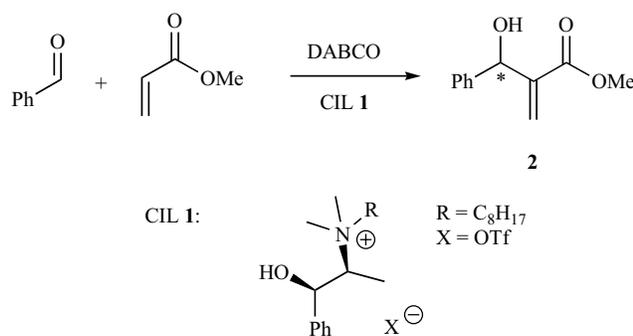
Scheme 1. Asymmetric induction by the CIL **1** in a Baylis-Hillman reaction (up to 44% ee) [19].

They pointed out the necessity of an excess of the CIL **1** to obtain an enhanced enantioselectivity but this was accompanied by an decreasing yield. The latter one was explained by the insolubility of benzaldehyde under the reaction conditions. Furthermore, no influence to the enantiomeric excess was recognized using different alkyl chain lengths in the IL. Instead, the choice of the anion seems to play an important role, in the decomposition pathway of the CIL, where the IL **1** with the triflate anion is superior towards the stability of

the CIL [32]. Furthermore, the alcohol function in the IL is propitious for the chirality transfer, using a CIL with an ester group the enantiomeric excess dropped to 6% *ee*. They presumed, that the OH group acts as a coordination point for a carbonyl function in the substrate via hydrogen bridges. Noteworthy, unmodified ephedrine as chiral catalyst gave only 9% *ee*.

Table 1. Asymmetric Baylis-Hillmann Reaction in the Presence of Chiral IL 1 [19]

Entry	IL 1 (eq.)	Conversion (%)	Yield (%)[a]	(R)-1 ee (%)[b]
1	0.5	86	76	20
2	1	85	78	23
3	1.5	85	73	28
4	3	65	45	32
5	3	88	60	44[c]

Conditions: benzaldehyde:methyl acrylate:DABCO = 1:1:1.
T = 30 °C, t = 4 days. [a] Determined by GC; [b] determined by chiral HPLC; [c] t = 7 days.

Leitner presented an enantioselective Aza-Baylis-Hillman reaction with enantiomeric excesses up to 84% *ee* in CIL with nucleophilic Lewis-bases as organocatalysts [20]. These results stay in one row with the best results obtained in conventional solvents (94% *ee* and 83% *ee*) [33]. In contrast to *Vo-Thanh*, they used a chiral anion derived from the chiral pool (Scheme **2**).
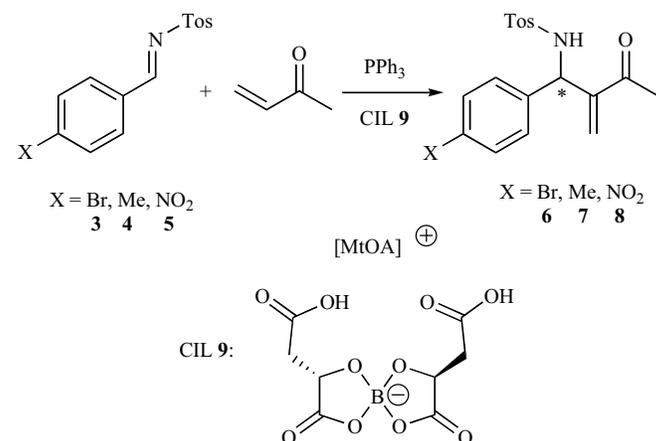
Scheme 2. Enantioselective aza-Baylis-Hillman reaction (up to 84% ee). [MtOA]+ = Methyltrioctyl ammonium [20].

In their investigations they also confirmed the mentioned importance of OH groups as hydrogen-bond donors for the stability of reaction intermediates. So, OH groups in alcohol and acid functionalities can indeed act as a coordination point between the CIL and a carbonyl group in the reactants. Though, this allows asymmetric induction into the reactants. Noteworthy, dilution experiments in conventional organic solvents with equivalent amounts of CIL resulted in racemic products, and this indicates the necessity to use the CIL as solvent for effective chirality transfer.
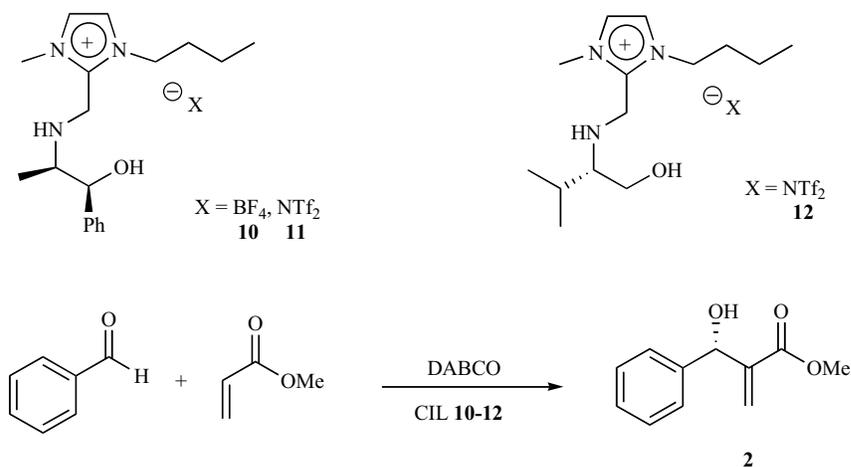
Scheme 3. Asymmetric version of the Baylis-Hillman reaction using CILs [34].

Best CIL: 100% yield, syn:anti = 99:1 , 99% *ee*
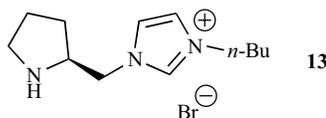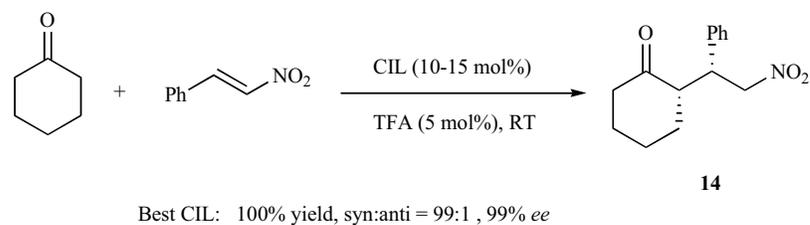
Scheme 4. Asymmetric nitro-aldol reaction with chiral TSIL-catalysts [23].

Following *Vo-Thanh*'s attempts to induce chirality in Baylis-Hillman reaction, *Headley* and co-workers presented novel CILs **10-12** for this application (Scheme **3**) [34].

In many examples, a co-solvent were used yielding the Bailys-Hillman adduct in reasonable yields (5-80%) and 0-14% of enantiomeric excess. However, without the presence of a co-solvent (using pure CILs), the author got the best yields (80-82%) and the best enantiomeric excess (5-25%). The best reaction conditions (CIL **10**, 4 °C and 7 days) were tested using different aldehydes and acrylates. Yields were moderate to high (38-91%) but enantiomeric excess (2-24%) were fairly low.

2. MICHAEL ADDITION REACTION

The first approach to use typical organocatalysts incorporated in CILs for enantioselective catalysis was presented by *Cheng* and co-workers [16c, 23]. In contrast to the previously discussed asymmetric catalyses in here, they incorporated directly typical chiral organocatalysts into side-chains to generate chiral functional ionic liquids (FILs) as task-specific ILs (TSILs). Those TSILs were used as organocatalysts (10-15 mol%) for Michael addition of nitroolefins with TFA (trifluoroacetic acid) as co-catalyst (5 mol%), (Scheme **4**).

In most cases the yields were up to quantitative and the enantiomeric excesses were usually over 90% *ee*, with some exceptions (lowest *ee*: 70%). In contrast to the previously discussed results, here, *Cheng et al.* observed that incorporation of protic groups (hydrogen bond donors) in the CILs resulted in a decrease of activity and selectivity. Otherwise in accordance to the observation by *Afonso* [21], and *Malhotra* [22], they also recognized a strong influence of (achiral) anions onto the transfer of the chiral information. Concerning activity and selectivity the PF_6-anion is the less recommendable anion due to lower yields and enantiomeric excesses. The group also recycled their chiral TSIL-catalysts by precipitation in five successful runs with high enantioselectivities and high yields. Advanced studies showed that salicylic acid gives also good results as co-catalyst in combination with a CIL **15** bearing a benzimidazolium-backbone (Scheme **5**, Table **2**) [16c].

A novel type of pyrrolidine-based chiral ILs with chirality on the cation was developed by *Headley et al.* to catalyze the Michael addition of aldehydes and nitrostyrenes. Using these ILs as organocatalysts, it is possible to obtain products in high diastereoselectivities, good enantioselectivities and moderate yields (depending on the groups R_1 and R_2) with a good recyclability of the system (Scheme **6** and Table **3**) [35].

Scheme 5. Asymmetric Michael addition catalyzed by CIL 15 (15 mol%) and salicylic acid as co-catalyst (5 mol%) [16c].

Table 2. Asymmetric Michael Addition Catalyzed by CIL (15 mol%) and Salicylic Acid as co-catalyst (5 mol%) [16c]

Entry	R	Ar	t (h)	Yield (%)[a]	*dr* (a:b)[b]	*ee* (%)[c]
1	Me	Ph	10	89	6.2:1	97
2	Me	4-ClPh	10	89	6.1:1	99
3	Me	2-ClPh	10	99	>10:1	97
4	Me	2-NO$_2$Ph	3	93	4.4:1	97
5	*t*-Bu	Ph	12	88	7.9:1	98
6	Ph	Ph	10	63	12:1	96

[a] Isolated yields; [b] determined by ^{1}H NMR; [c] determined by chiral HPLC.

R$_1$ = *n*-Bu; R$_2$ = H; Ar = Ph: **23**
R$_1$ = *n*-Bu; R$_2$ = H; Ar = *p*-Tol: **24**
R$_1$ = R$_2$ = Me; Ar = Ph: **25**
R$_1$ = *n*-Pr; R$_2$ = H; Ar = Ph: **26**
R$_1$ = *i*-Pr; R$_2$ = H; Ar = Ph: **27**

Scheme 6. Pyrrolidine-based CIL employed as catalysts in asymmetric Michael addition [35].

A mild and efficient procedure for asymmetric Michael additions of cyclohexanone to chalcones catalyzed by an amino acid IL **28** was investigated (Scheme **7**, Table **4**) [36]. The authors used here directly the proline-anion as chiral catalyst with an imidazolium-cation as counterion.

In a general way, yields were reasonable (30-96%), and diastereomeric ratios moderate to very good (20:80 to 4:96 favoring *syn* isomer). Enantiomeric excesses ranged from 17-94%. To achieve better results, the author performed the reaction in methanol as a solvent. It is worth noting that the use of DMSO as a solvent gave the product with the inverse configuration. However, the most interesting aspect of the study was an unexpected solvent-dependent inversion of the enantioselectivity using MeOH and DMSO. Further investigations are necessary to understand these unexpected results.

Table 3. Asymmetric Michael Additions of Aldehydes and Nitrostyrenes Using CIL 22 as Catalysts at 4 °C [35]

Entry	R₁	R₂	Ar	Yield (%)	Syn/Anti	ee (%)
1	n-Bu	H	Ph	64	97:3	68
2	n-Bu	H	p-Tol	60	96:4	67
3	Me	Me	Ph	58	----	82
4	n-Pr	H	Ph	49	89:11	64
5	i-Pr	H	Ph	53	96:4	66

$R_1 = R_2 = Ph$: **29**
$R_1 = 4\text{-MeC}_6H_4$; $R_2 = Ph$: **30**
$R_1 = 4\text{-ClC}_6H_4$; $R_2 = Ph$: **31**
$R_1 = Ph$; $R_2 = 4\text{-H}_2NC_6H_4$: **32**
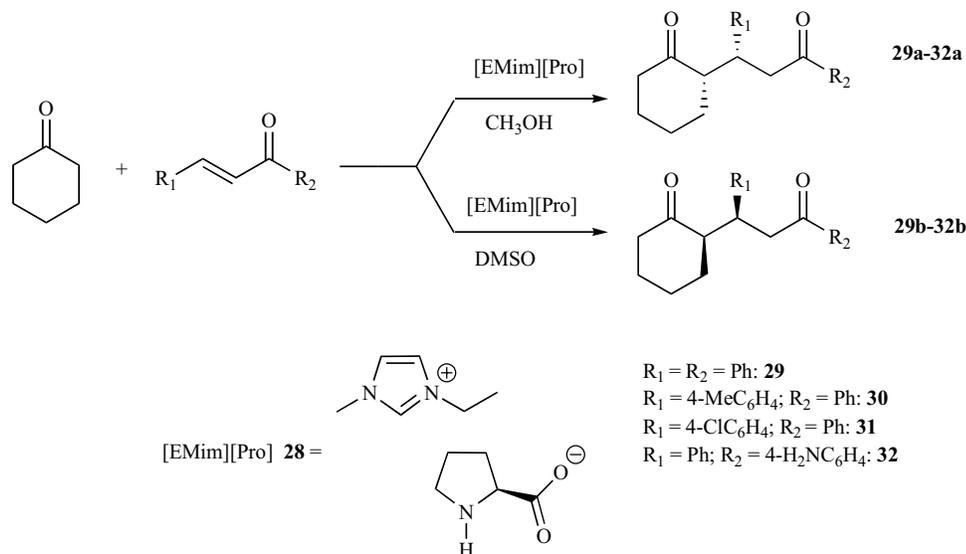
Scheme 7. Asymmetric Michael addition using a CIL bearing a chiral anion [36].

Table 4. Asymmetric Michael Addition of Cyclohexanone and Chalcones Catalyzed by a CIL 28 at Room Temperature (Selected Data) [36]

Entry	R₁	R₂	Solvent	t (h)	Yield (%)[a]	Anti/Syn[b]	ee (%)[b]
1	Ph	Ph	CH₃OH	4	98	20:80	86
2	4-MeC₆H₄	Ph	CH₃OH	4	90	5:95	37
3	4-ClC₆H₄	Ph	CH₃OH	4	98	4:96	60
4	Ph	4-NH₂C₆H₄	CH₃OH	8	87	4:96	94
5	Ph	Ph	DMSO	4	95	12:88	-78
6	4-MeC₆H₄	Ph	DMSO	4	98	16:84	-72
7	4-ClC₆H₄	Ph	DMSO	4	94	10:90	-65
8	Ph	4-NH₂C₆H₄	DMSO	8	85	4:96	-91

[a] Isolated yield; [b] dr and ee determined by HPLC. The signal (-) means inversion of configuration.

In further works, some pyrrolidine-based chiral pyridinium ILs **33-36** were synthesized and tested as efficient promoters of the asymmetric Michael addition (Scheme **8**, Table **5**) [37]. These CILs **33-36** have been found to be recyclable and efficient organocatalysts for the addition reactions of ketones to nitroolefins with high yields, high enantioselectivities, and diastereoselectivities.

The obtained yields were higher than 74% and diastereomeric ratios over 95:5 favouring the *syn*-isomer. Additionally, the enantiomeric excesses of the major isomer were higher than 86%. The best condition developed required 5 mol% of trifluoroacetic acid at a temperature of 4 °C.

X = BF$_4$, PF$_6$, NTf$_2$, Cl
33   34   35   36

14
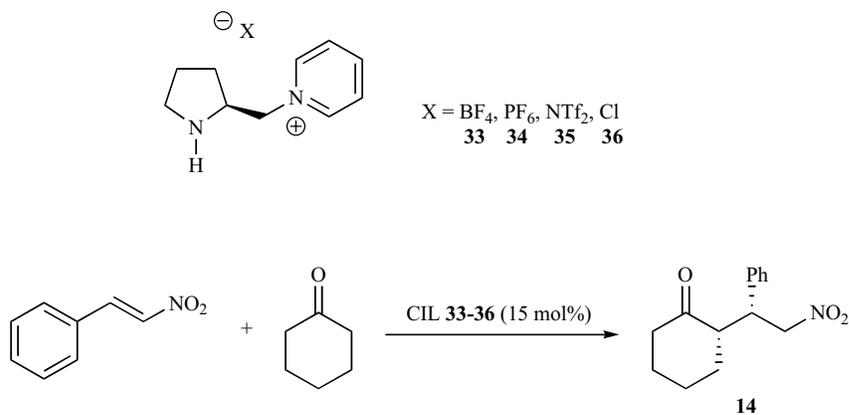
Scheme 8. Asymmetric Michael reaction using CILs 33-36 [37].

Table 5. Michael Reaction between Cyclohexanone and Nitrostyrene with CILs 33-36 at Room Temperature (Selected Data) [37]

Entry	Catalyst	TFA (mol %)[a]	t (h)	Yield (%)[b]	ee, syn (%)[c]	Syn/Anti[d]
1	36	----	36	74	99	98:2
2	36	5	36	91	99	97:3
3	33	----	36	75	94	> 99:1
4	33	5	16	95	98	99:1
5	34	----	72	90	93	99:1
6	34	5	48	92	86	95:5
7	35	----	43	81	95	96:4
8	35	5	16	95	93	96:4
9[e]	33	5	30	92	99	> 99:1

[a] TFA (trifluoroacetic acid); [b] isolated yield; [c] determined by HPLC; [d] determined by ^{1}H NMR; [e] T = 4 °C.

38-44

CIL **37** =
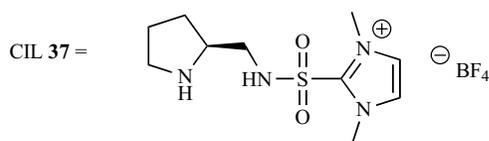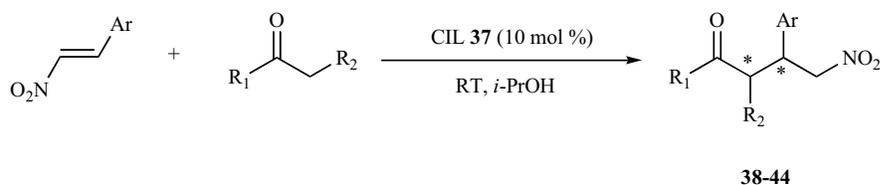
Scheme 9. CIL supported pyrrolidine sulfonamide organocatalyst 37 for the asymmetric Michael reaction [38].

A new class of CIL supported (*S*)-pyrrolidine sulfonamide organocatalyst **37** was developed by *Headley* and co-workers and shown to be a very effective catalyst for the asymmetric Michael addition reactions of ketones and aldehyde with nitroolefines with high enantio- and diastereoselectivities (Scheme **9**, Table **6**) [38].

Reactions yields ranged from 10-95% and in almost all cases an organic solvent was present in the reaction media. The authors obtained very good diastereoselectivity for all reactions favoring the *syn* isomer (up to 99:1), with *ee* ranging from 14 to 99%. A series of different aldehydes were also tested under the best reaction conditions with high yields, diastereo- and enantioselectivity.

From the same group, further results were published in this area with pyrrolidine-based functionalized CILs and showing to be effective and reusable organocatalysts for the asymmetric Michael addition reactions of aldehydes with nitrostyrenes (Scheme **10**, Table **7**) [39].

Table 6. Asymmetric Michael Addition of Ketones and Nitro Olefins Catalyzed by CIL 37 (Selected Data) [38]

Entry	Product	t (h)	Yield (%)[a]	ee (%)[b]	*Syn/anti*[c]
1	**14**	16	91	90	95:5
2	**38**	20	90	95	98:2
3	**39**	17	90	99	99:1
4	**40**	17	87	94	93:7
5	**41**	24	96	90	97:3
6	**42**	24	96	99	99:1
7	**43**	36	75	14	----
8	**44**	24	97	80	92:8
9	**25**	16	85	75	----
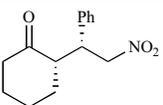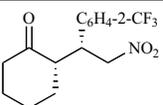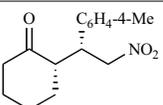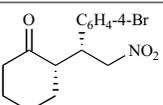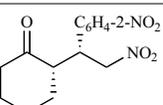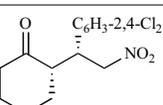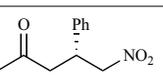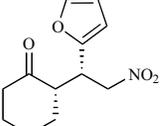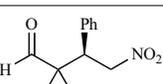
[a] Isolated yield; [b] determined by chiral HPLC; [c] determined by ^{1}H NMR.
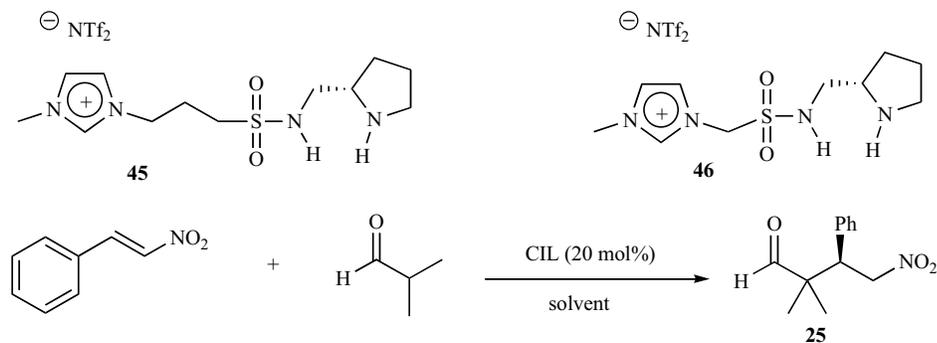
Scheme 10. Asymmetric Michael Addition using a functionalized CIL 45-46 [39].

In many cases, the authors used an organic solvent to perform the reaction. Yields varied from 5-90%. Enantiomeric excess could not be determined in some cases, while in other cases, it was above 80%. It was also tested the reaction of cyclohexanone with nitrostyrene catalyzed by both CILs (**45, 46**). In this case, these organocatalysts result in high yields (up to 99%), good enantioselectivities (up to 85%), and high diastereoselectivities (*syn/anti* ratio up to 97:3). It is worth

Table 7. Asymmetric Michael Addition of Dimethylacetaldehyde with Nitrostyrene (Scheme 10) Catalyzed by a CILs 45/46 at Room Temperature (Selected Data) [39]

Entry	Solvent	Additive	Catalyst	t (days)	Yield (%)[a]	ee (%)[b]
1	MeOH	----	**45**	6	80	67
2	MeOH	5% TFA	**45**	6	< 5	N. D.
3	THF	----	**45**	6	17	75
4	THF	5% TsOH	**45**	6	< 10	N. D.
5	MeOH	----	**46**	6	86	79
6	MeOH	5% TFA	**46**	3	90	84

[a] Isolated yield; [b] determined by HPLC analysis; N. D. = not determined.
(TsOH = *p*-toluenesulfonic acid)
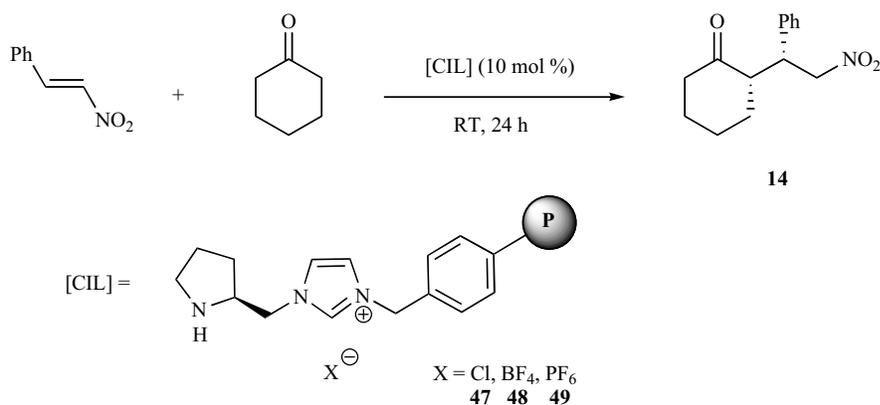
Scheme 11. Asymmetric Michael addition reactions catalyzed by the CILs 47-49 [40].
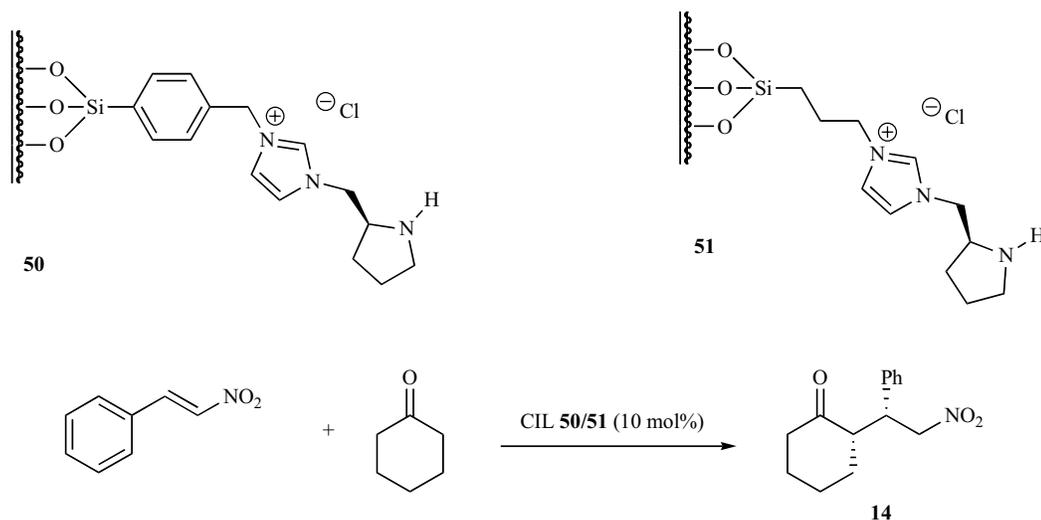
Scheme 12. Asymmetric Michael addition using a silica-gel supported CIL [41].

noting that despite the fact that the best conversion was obtained using methanol as the solvent, the use of ether as the solvent gave the best *ee* (82%) at temperature of 4 °C, without the presence of any acid as additive.

Following in the field of organocatalysis, *Wang et al.* published the synthesis of polymer-bound pyrrolidine-based chiral ILs **47-49** and their application as catalysts in the

asymmetric Michael addition reactions (Scheme **11**) obtaining high yields (> 91%) and both excellent enantioselectivities (> 99% *ee*) and diastereoselectivities (> 99:1 *dr*) [40].

Noteworthy, these reactions can be carried out under solvent-free conditions and the catalyst could be reused several times without loss in its catalytic activity.

Table 8. Selected Examples of the Asymmetric Michael Reactions of Nitrostyrene with Cyclohexanone in Different Solvents Catalyzed by CIL at Room Temperature in 36 h [41]

Entry	CIL	Solvent	Yield (%)[a]	ee (%)[b]	dr[c]
1	**50**	EtOH	71	98	99:1
2	**50**	EtOH	68	97	99:1
3	**50**	DMF	76	98	98:2
4	**51**	DMF	72	98	98:2
5	**50**	CH_2Cl_2	61	98	98:2
6	**51**	CH_2Cl_2	56	96	98:2
7	**50**	H_2O	51	98	98:2
8	**50**	Hexane	72	98	98:2
9	**50**	Neat	91	99	99:1

[a] Isolated yields; [b] determined by HPLC; [c] diastereomeric ratio *dr* (*syn/anti*) determined by ^{1}H NMR.

R = Ph: **54**
R = Cy: **55**
R = 4-BrC$_6$H$_4$: **56**
R = 2-ClC$_6$H$_4$: **57**
R = 4-O$_2$NC$_6$H$_4$: **58**
R = 4-NCC$_6$H$_4$: **59**
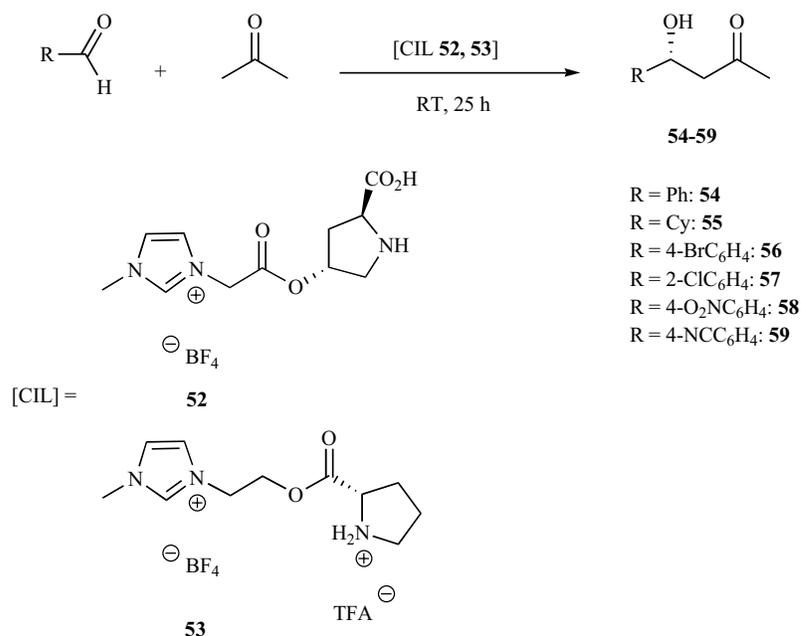
Scheme 13. CIL-catalyzed asymmetric aldol reaction [45].

Further studies were published later on by the same group using silica gel supported pyrrolidine-based CIL (**50, 51**) as recyclable organocatalyst for asymmetric Michael addition to nitrostyrenes (Scheme **12**, Table **8**) [41].

The reactions generated the corresponding products in moderate to good yields (up to 91%), excellent enantioselectivities (> 96% *ee*), and high diastereoselectivities (> 98:2 *dr*). In addition, the catalyst could be reused at least five times without a significant loss of catalytic activity and stereoselectivity. Both organocatalysts gave similar results, but a slight advantage using a propyl group as spacer could be noted.

Previously works on CIL-catalyzed Michael additions with organic co-solvents reported much lower enantiomeric excesses (< 15% [42], and < 25% [43],). More recent examples for this reaction, can be found elsewhere [44].

3. ALDOL REACTION

In 2006, *Chan* and coworkers have described the syntheses of new proline-based CILs (**52, 53**) and the application of these ILs in asymmetric aldol reaction between ketones and aldehydes under mild conditions (Scheme **13**) [45]. In particular for the reaction of 4-cyanobenzaldehyde and acetone, the CIL **52** gave better results in yield (59%) and *ee* (72%) in contrast to those obtained with CIL **53** (10% yield and 11% *ee*). Therefore, one may denote that the acidic proton of proline (CIL **52**) have an important role in the catalytic aldol process. A few examples of this work are summarized in Table **9**.

Zlotin et al., presented new chiral ionic liquids (**60-64**) with imidazolium or pyridinium cations bearing amino acid moieties. Such salts are capable to catalyze (15 mol% CIL) the asymmetric aldol reaction between aldehydes and ke-

Table 9. Asymmetric Direct Aldol Reactions of Different Aldehydes with Acetone Using The CIL 52 as Organocatalyst (Selected Data) [45]

Entry	R	Yield (%)	ee (%)
1	Ph	50	76
2	Cy	43	85
3	4-BrC$_6$H$_4$	58	73
4	2-ClC$_6$H$_4$	92	71
5	4-O$_2$NC$_6$H$_4$	64	85
6	4-NCC$_6$H$_4$	59	72
7[a]	4-NCC$_6$H$_4$	10	11

[a] CIL **53** was used

Table 10. Selected Results of Asymmetric Aldol Reactions Using the Synthesized CILs (60-64) [46]

Entry	Catalyst	t (h)	Conv. (%)	Anti/Syn	ee (anti, %)
1	60	15	> 99	98:2	98
2	61	15	----	----	----
3	62	15	97	97:3	99
4	63	20	84	87:13	91
5	64	20	89	90:10	97

The conversions and diastereomeric ratio were determined by ^{1}H NMR and the ee by HPLC.

tones in water at room-temperature (Table **10**, Scheme **14**) [46]. It was established that the hydrophobic alkyl groups available in the organocatalysts improved the reaction efficiency under the examined conditions. The catalyst with the anion PF$_6^-$ can be readily regenerated and utilized multiply without a decline in the conversion, *dr*, and *ee* values.

All yields ranged from good to excellent (58-99%). Both, diastereomeric and enantiomeric rates (favoring *anti* isomer) were very good ranging from *dr* 87:13 to 98:2 and *ee* from 91% to >99%. Interestingly, the use of pyridinium-based CILs (**61-64**) gave better results than imidazolium-based. However, no significant difference was observed among them.

In a previous work by *Zlotin* and co-workers, similar proline based CILs also displayed a good efficiency to promote asymmetric aldol reaction (Scheme **15**, Table **11**) [47].

The observed conversions, nevertheless, were ranging from 20% to 95% with high diastereomeric (up to 97:3 – *anti* isomer) and enantiomeric excesses (80-99%). One may note that the only difference was the anion effect associate with the aldol process, and the use of PF$_6$-anion gave the best results in terms of selectivity. Recently, it has been described the pronounced anion effect in some cases [48].

Cheng and co-workers presented a combinatorial synthesis towards a CIL-library. They used reagents from the chiral pool and generated chiral cations and chiral anions (including zwitterionic compounds), via ring-opening alkylation of the corresponding cyclic sulfates and sulfamidates. Such CILs were tested as organocatalysts in asymmetric aldol reactions (Scheme **16**, Table **12**) [16b, 49].

It is worth noting that the use of doubly CILs gave good yields (up to 97%) and poor *anti*-diastereomeric (from 50:50 to 70:30) and enantiomeric excess (7-55% for *anti* isomer and 4-73% to *syn* isomer). The CIL with the anion *o*-carboxyl-benzoic acid **80** showed the best *anti*-selectivity (70:30) and *ee* (55%, for the *anti*-isomer and 73% for the *syn* isomer).

Further examples for enantioselective aldol reaction with CILs as organocatalysts are published elsewhere [50, 51].

4. HOMOGENEOUS TRANSITION METAL CATALYSIS

Where *Vo-Thanh* and *Leitner* focussed on organocatalysis, *Afonso* and coworkers investigated transition metal catalysis with CIL (e. g. **84**) as source of chirality [21, 52]. To obtain low melting point salts using anions from the chiral pool which usually form solid salts, they have chosen the [*dmg*] cation tetra-*n*-hexyl-dimethylguanidinium which is less prone to crystallize (Scheme **17**). For the evaluation of the CILs for asymmetric catalysis, rhodium catalyzed intramolecular carbenoid C-H insertion (not shown here) and Sharpless asymmetric dihydroxylation using osmium catalysts were performed, the latter shown in Scheme **17**.

In both reactions high to almost quantitative yields were obtained, but the enantioselectivities differs from each other extremely. In the dihydroxylation of alkene impressive *ee*'s were obtained (72% *ee* and 85% *ee*), otherwise lower selectivity in the C-H insertion was obtained (27% *ee*). Most no-
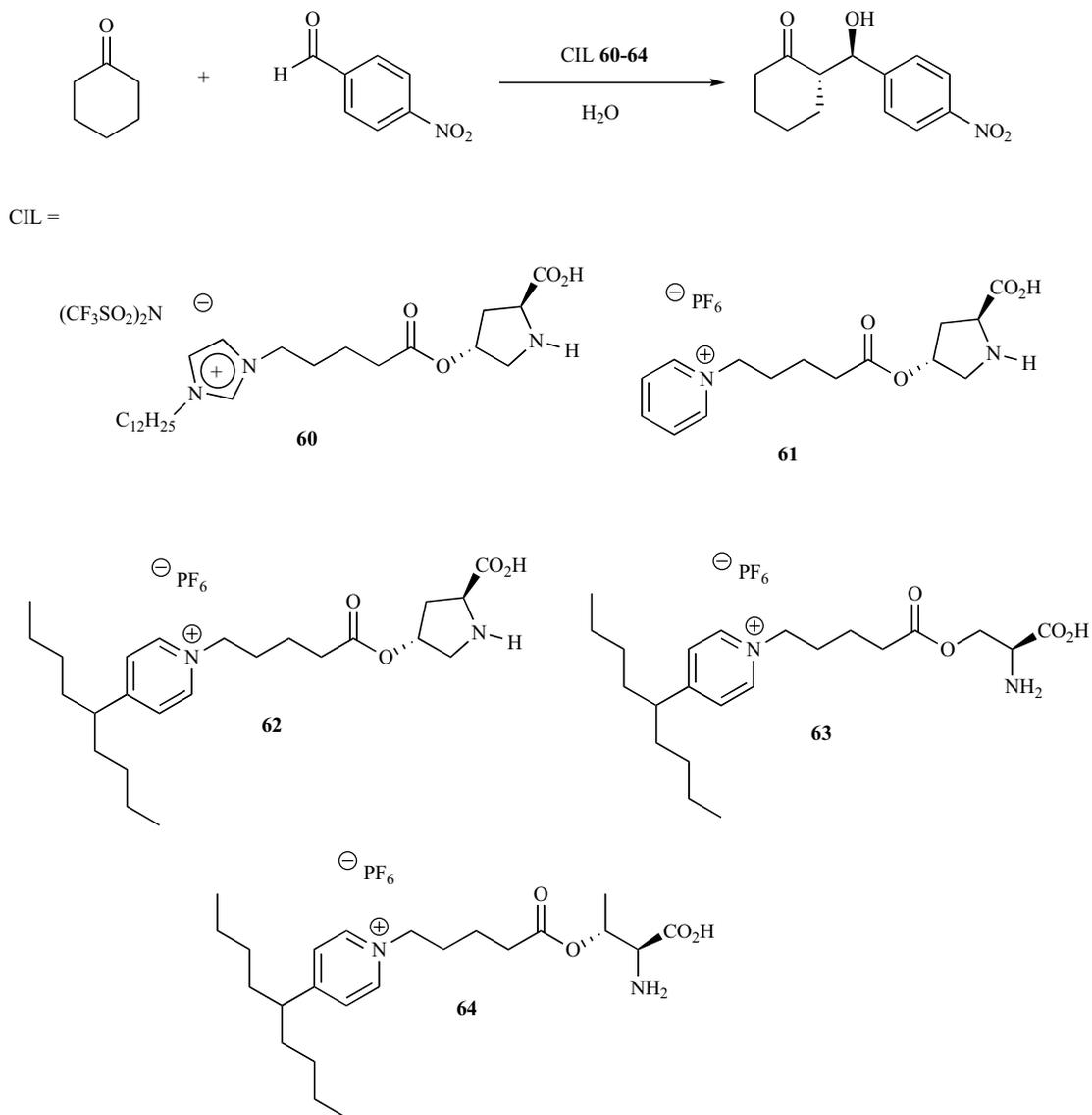
Scheme 14. Asymmetric aldol reaction (top) and selection of amino acid derived CILs 60-64 [46].

R = *p*-O$_2$NC$_6$H$_4$: **66**
R = *p*- CH$_3$O$_2$C$_6$H$_4$: **67**
R = C$_6$H$_5$: **68**
R = *p*-CH$_3$OC$_6$H$_4$: **69**
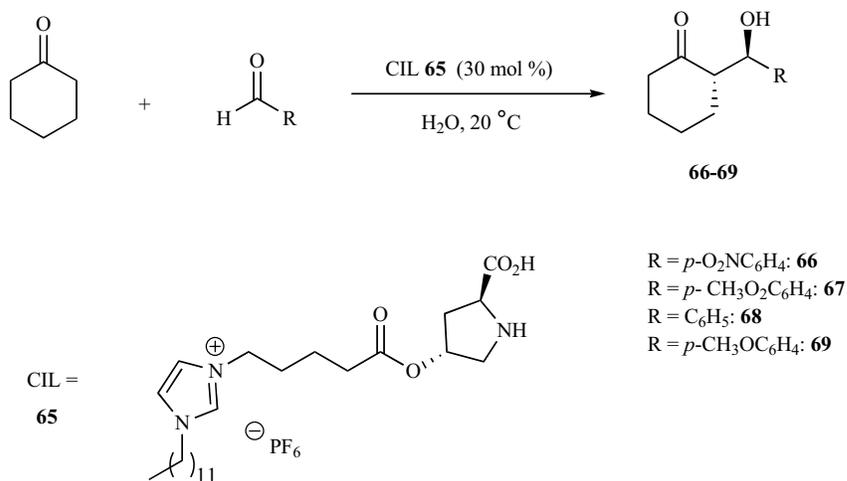
Scheme 15. Catalytic asymmetric aldol reaction by proline-derived CILs [47].

Table 11. Catalytic Aldol Reactions of Cyclohexanone and Different Aldehydes with CIL as Organocatalysts in the presence of Water (Selected Data) [47]

Entry	R	t (h)	Conv. (%)	Anti/Syn	*ee*, anti (%)
1	p-NO$_2$C$_6$H$_4$	10	> 95	97:3	> 99
2	p-CH$_3$O$_2$CC$_6$H$_4$	10	86	97:3	> 99
3	C$_6$H$_5$	36	67	93:7	88
4	p-CH$_3$OC$_6$H$_4$	64	20	84:16	80
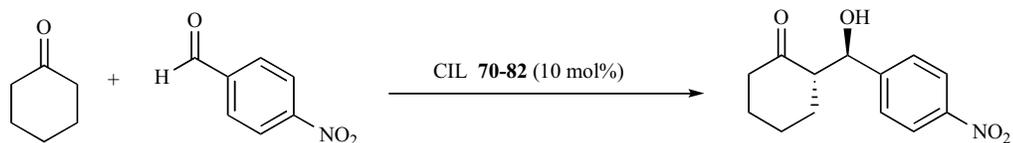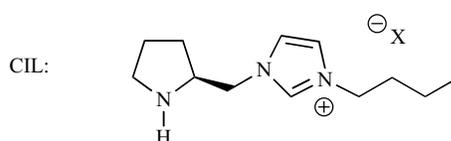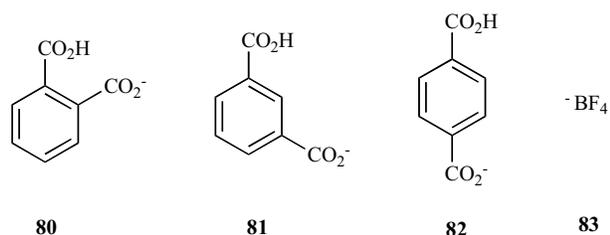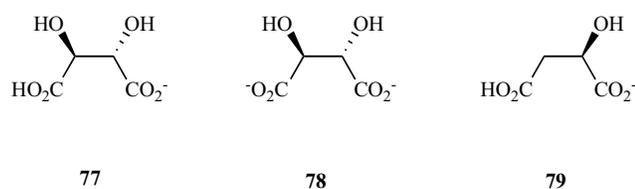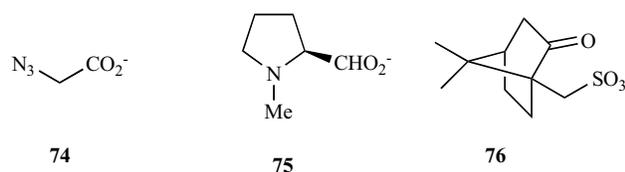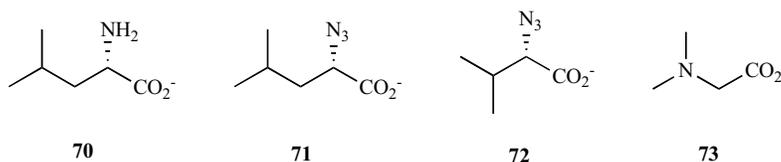
Scheme 16. Excerpt from CIL-library for asymmetric aldol reaction [49].

Table 12. Aldol Reactions Catalyzed by the CILs (Selected Data) [49]

Entry	Catalyst	t (h)	Yield (%)	Anti/Syn	ee, anti (%)	ee, syn (%)
1	**83**	30	92	46:55	26	71
2	**72**	36	90	64:36	7	4
3	**71**	60	94	60:40	15	46
4	**74**	36	97	60:40	21	6
5	**77**	36	94	50:50	23	58
6	**78**	50	90	57:43	35	34
8	**80**	23	94	70:30	55	73

R = *n*-Bu (**85**), 95%, 85% *ee*
R = Ph (**86**), 92%, 72% *ee*

CIL (R = *n*-hexyl) **84** =

[*dmg*]   [(R)-mand)]
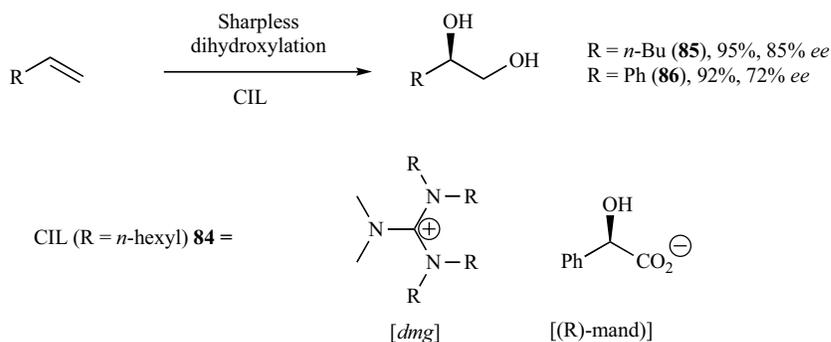
Scheme 17. Sharpless asymmetric dihydroxylation in CIL [21].

Cu(OTf)₂ (3 mol%), Et₂Zn

CIL **87**, -20 °C, 15 h

88

CIL **87**:

BF₄
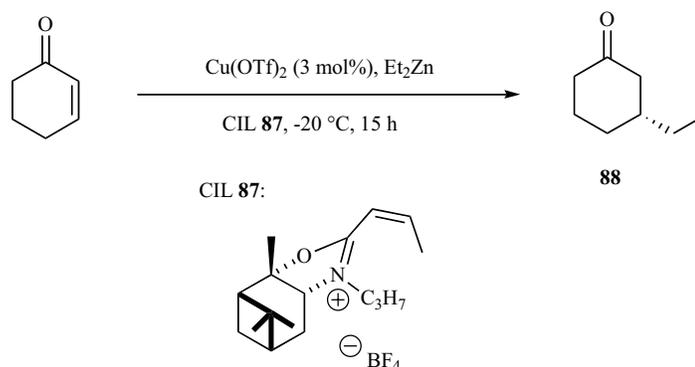
Scheme 18. Asymmetric copper-catalyzed diethyl zinc addition to enones (up to 76% ee) [22].

tably, the asymmetric dihydroxylation still gave high yields and moderate enantiomeric excesses (40% *ee*) using catalytic amounts of the CIL **84** dissolved in *t*-BuOH/H₂O. This result differs totally from those reported by *Vo-Thanh* and *Leitner*, where only almost racemic material was obtained. The better results for the asymmetric dihydroxylation might be due to the strong electrostatic interaction and hydrogen bonding between the CIL, reactants and the catalyst.

Malhotra and *Wang* performed copper catalyzed enantioselective 1,4 addition of diethylzinc to enones [22]. Notably, the CIL **87** derived from the chiral pool contains the chirality in a cationic oxazolinium salt with a pinene backbone (Scheme **18**). The investigators also observed that the concentration of the CIL **87** has an influence to the enantiomeric excess. With low catalytic amounts of the CIL **87** (< 10 mol%), the enantioselectivity was also low (17-38% *ee*). Increasing the amount of CIL **87** to 35 mol%, the enanti-

omeric excess rised up to 76% *ee* with cyclohexenone and cyclopentenone (Scheme **18**, Table **13**).

Table 13. Effect of CIL 87 (mol %) on the Alkylation of Cyclohex-2-enone with Diethylzinc[a] [22]

Entry	CIL (mol%)	ee (%)
1	3	17
2	5	23
3	10	38
4	15	51
5	25	74
6	35	76*

[a] 3 mol% Cu(OTf)₂, T = -20 °C, t = 15 h. *Conversion: 90%.
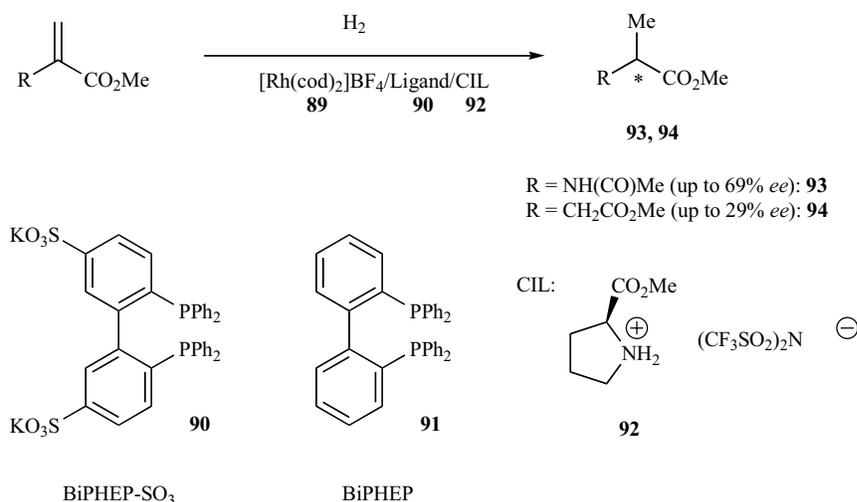
Scheme 19. Rh-catalyzed hydrogenation in CIL 92 [53].

The authors believed that the chiral induction is due to the formation of a "chiral pocket" with the CIL and the Cu metal, influencing the selectivity of the alkyl transfer. They also observed that different achiral anions have a great influence to the enantiomeric excess (BF$_4$: 76% *ee*, PF$_6$: 35% *ee*). Noteworthy, the CIL can be used as additive or co-solvent in asymmetric catalysis.

In 2007, another enantioselective catalytic hydrogenation with an achiral transition metal catalyst was presented by *Leitner* and co-workers [53]. In contrast to the previously discussed hydrogenation of a prochiral ketone, here, acrylates are enantioselectively hydrogenated by a rhodium catalyst with achiral BiPHEP ligands (biphenylphosphine; e. g. **90**) and CILs based on amino acids (Scheme **19**). To enhance the solubility, and also for immobilization, anionic sulfonated ligands were used.

Furthermore, different additives were applied to optimize the enantiomeric excess. The highest value 69% *ee* was obtained using the BiPHEP-SO$_3$ ligand **90**, a proline based CIL **92** and triethylamine as basic additive. Instead, the addition of water gave a similar enantiomeric excess (47% *ee*) as without additive (49% *ee*), (see: Table **14**).

Table 14. Selected Data for the Rh-catalyzed Hydrogenation of methyl 2-acetamidoacrylate in CIL 92[a] [53]

Entry	Ligand	Additive	ee (%)
1	90	-	49 (S)
2	-	-	*rac*
3	90	H$_2$O	47 (S)
4	90	NEt$_3$	69 (S)
5	91	NEt$_3$	52 (S)

[a] Substrate/cat = 250, p(H$_2$) = 40 bar. Full conversion was achieved in all experiments unless otherwise noted. Conversion and enantioselectivity were determined by GC (Lipodex E).

They showed also that a base enhances collaborative effects in the catalytic system between the rhodium metal and the CIL **92**, where neutral additives (H$_2$O) and acids have no effects or gave lower enantiomeric excesses. Notably, also the non-sulfonated ligand BiPHEP **91** gave remarkable results (52% *ee*) when NEt$_3$ was added. This indicates that the predominated asymmetric induction is not due to direct interaction of the ligand backbone with the CIL **92**. It seems most likely the addition of base, free amino acid esters may act as monodentate (N) or bidentate (N,O) ligand (from the CIL). Directly coordinating to the rhodium centre which allows asymmetric induction. In additional experiments, they showed that the catalytic system is recyclable at least over three runs, where the product was separated by extraction with supercritical CO$_2$.

Recently, *Leitner* and co-workers presented their advances in rhodium complex catalyzed asymmetric hydrogenation of dimethyl itaconate (R = CH$_2$CO$_2$Me) using CIL **92** as source of chirality (Scheme **20**) [54]. The detailed investigations focused on applying *rac*-binap (*rac*-**95**), *(R)*-binap (*R*-**95**) and *(S)*-binap (*S*-**95**) as ligands for rhodium catalysis with (S)-proline methyl ester based CIL Me-Prol.NTf$_2$ **92** as co-solvent and source of chirality. Most interestingly all ligands showed similar selectivities for the hydrogenation of dimethyl itaconate (64-71% *ee*), where with *(R)*-binap *R*-**95** the *(R)*-enantiomer (*R*-**95**) was obtained (Table **15**).

They explained the almost identical selectivity using *rac*-binap *rac*-**95** and *(S)*-binap *S*-**95** with *chiral poisoning* of the respective Rh/binap complexes with the *(S)*-proline-CIL **92**. Where in the system with *rac*-binap (*rac*-**95**), the rhodium complex fragment with *(R)*-binap is more stable in presence of the *(S)*-proline-CIL **92** (as ligand) and consequently this complex is much less reactive than the [Rh{(S)-binap}]-complex. Using the benchmark substrate methyl *N*-acetamido acrylate (R = NH(CO)Me) the best selectivity reached 41% *ee*. Here, they showed the influence of the selectivity using *(R)*-binap *R*-**95** and different ratios between (S)-proline-CIL **92** and the co-solvent dichloromethane.

The optically active orthopalladated phenanthrylamine phase transfer catalyst has been produced and explored for asymmetric glycine alkylation in CIL (Scheme **21**) [55].
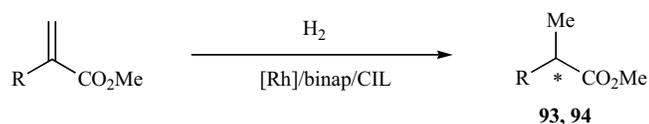
R = NH(CO)Me (up to 41% *ee*, **89**): **93**
R = CH$_2$CO$_2$Me (64 - 71% *ee*, **96, 97**): **94**

95: *rac*-binap,
(S)- or *(R)*-binap

CIL **92**:
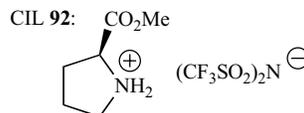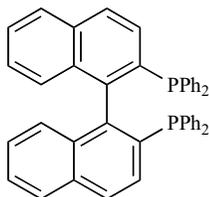
(MeProl.NTf$_2$)

[Rh] = [Rh(acac)(cod)   **96**
    = [Rh(acac)(CO)$_2$] **97**
    = [Rh(cod)$_2$BF$_4$ **89**

Scheme 20. Rh-catalyzed hydrogenation in CIL [54].

Table 15. Selected Data for the Rhodium-Catalyzed Asymmetric Hydrogenation of Dimethyl Itaconate[a] [54]

Entry	Ligand 95	[Rh]	*ee* (%)
1	*rac*-binap	96	67 (*S*)
2	*rac*-binap	97	65 (*S*)
3	(*R*)-binap	96	71 (*R*)
4	(*R*)-binap	97	66 (*R*)
5	(*S*)-binap	96	64 (*S*)
6	(*S*)-binap	97	70 (*S*)

[a] Reaction conditions: [Rh]=0.01 mmol, binap/[Rh]=1:1, substrate/[Rh] = 300:1, p(H$_2$) = 40 bar, MeProl.NTf$_2$ **92** (0.2 mL), CH$_2$Cl$_2$ (1 mL), 16 h, RT. Full conversion in all entries.

98

X = OAc

99

100
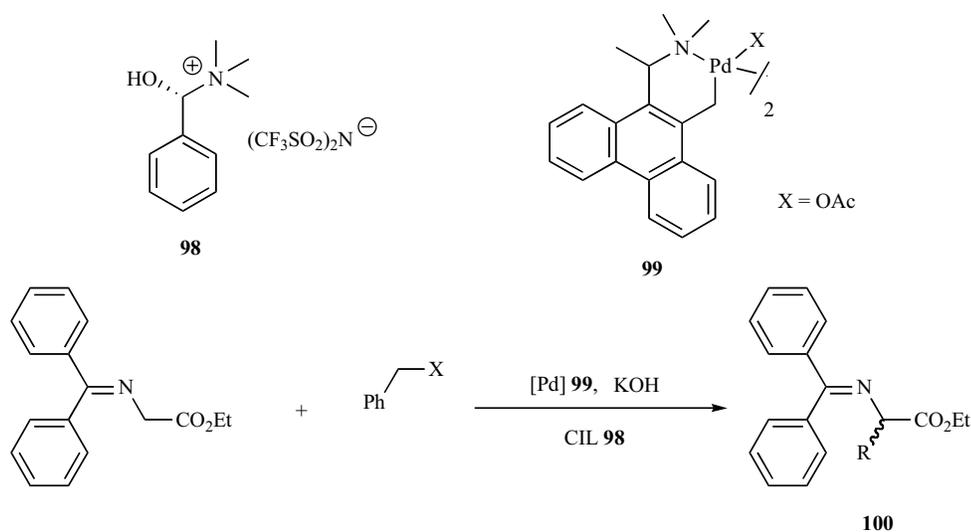
Scheme 21. Asymmetric alkylation reaction in CIL 98 using chiral orthopalladated phenanthrylamine (R = benzyl) [55].

Apparently, the chiral ionic liquid **98** has a cooperative effect to boost the enantiomeric excess content of an asymmetric reaction. Yields were very good (85-92%) and enantiomeric excesses fair (20-26%). In organic solvents and non-chiral ILs, the *ee*'s were lower (9-16%). Interestingly, the CIL can not alone induce enantioselectivity under biphasic conditions, it acts as a chiral booster to increase the *ee* when used along with the orthopalladated complex.

5. HETEROGENEOUS TRANSITION METAL CATALYSIS

In 2007, the first paper dealing with a solid catalyst for heterogeneous asymmetric catalytic hydrogenation in CIL **101** was published by *Wasserscheid et al.* [17]. The authors performed ruthenium catalyzed (Ru/C) asymmetric hydrogenation of a prochiral imidazolium salt in presence of a chiral anion derived from the chiral pool (Scheme **22**).
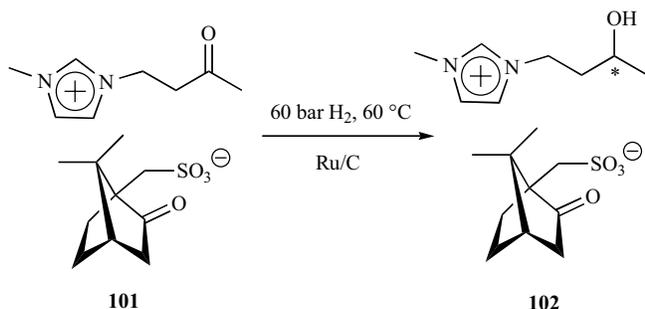
Scheme 22. Asymmetric hydrogenation of prochiral imidazolium cation with achiral solid ruthenium catalyst (80% ee) [17].

The enantioselectivity reached 80% *ee*, where the reaction was performed in ethanol as solvent to decrease the viscosity of the CIL **101**. In accordance to the previous results presented inhere, the higher the concentration of the source of chirality, the enantiomeric excess in the product. In their investigation of this reaction, they also excluded that the asymmetric induction might be due to chiral modification of the surface of the solid achiral Ru/C catalyst. They pointed out that the effective asymmetric induction in this reaction must be based on strong ion-pairing effects between the chiral anion and the prochiral cation.

In 2009, *Wasserscheid* and co-workers published their extended studies on this issue, investigating some varying camphorsulfonate ILs with prochiral cations shown in Fig. (**1**) [56]. As noted before, the viscosity of the reaction plays a role, furthermore, the nature of solvent to decrease the viscosity, too. In most cases, the enantioselectivity was much better using ethanol as solvent than water. Comparing these solvent systems, this effect was explained by the higher dissociation of water, resulting in a different solvatization of the chiral ion pairs, than in ethanol. Thus, the ethanol-system is superior to the water-system. Furthermore, they found out that the concentration of CIL in the solvent plays an important role for the chirality transfer, where neither low nor very high concentrations are suitable for asymmetric induction in the cation. High concentrations result in ion cluster formation which suppresses the efficiency of the chirality transfer. Furthermore, the alkyl-chain length (spacer), where the prochiral centre is incorporated, plays an important role. The IL with a 2-butanone **101** side-chain was hydrogenated with 94% *ee*, instead, a 2-hexanone side-chain in CIL **103** was hydrogenated with 45% *ee* under identical reaction conditions with 0.3 [mol/L] CIL in ethanol, this concentration represents also the lowest degree of dissociation for these systems (Fig. (**1**), Table **16**).
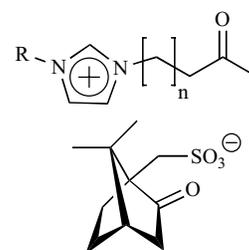
CIL **101**: n = 1 , R = Me
CIL **103**: n = 3 , R = Me
CIL **104**: n = 1 , R = H

Fig. (1). Tested prochiral CILs 101, 103 and 104 [56].

In conclusion, the prochiral centre must be closed to the imidazolium cation (ionic centre) for an efficient chirality transfer from the chiral anion, using the ion-pairing effect, and the concentration of the CIL in the solvent should result in the lowest possible degree of dissociation.

Table 16. Selected Data for the Hydrogenation of Prochiral Cations Over Ru/C [56]

Entry	CIL	Solvent	*ee* %
1	**101**	EtOH	94
2	**101**	Water	4
3	**104**	EtOH	54
4	**104**	Water	38
5	**103**	EtOH	45
6	**103**	Water	not given

Conditions: T = 60 °C , p = 60 bar (H$_2$), t = 15 h,
IL/solvent [mol/L] = 0.3, conversion > 95%.

6. DIELS-ALDER REACTION

Moreover, we like to include outstanding examples which uses CILs in an asymmetric aza-Diels-Alder reaction [57]. Previous reports about asymmetric aza-Diels-Alder are generally promoted by chiral Lewis acid catalysts [57]. *Vo-Thanh* and co-workers presented a reaction system without the need of (chiral) Lewis acid catalysts and organic solvents but recyclable chiral reaction medium. The diastereomeric excesses reached 72% *de* (yield: 30%) or 66% *de* (yield: 77%) (Scheme **23**). As previously reported by *Vo-Thanh* in 2004 [19], and *Leitner* in 2006 [20], the presence of hydrogen bond donors, like hydroxy groups, enhance the reactivity and selectivity also in here, in the aza-Diels-Alder reaction.

Vo-Thanh and co-workers recently published further results with novel CIL about their asymmetric aza Diels–Alder reaction of Danishefsky's diene with some chiral imines (Scheme **23**, Fig. (**2**)) [58, 59].

The strategy of using a CIL-containing a chiral moiety and a hydroxyl function derived from isosorbide being efficient to promote chiral induction in the aza Diels-Alder reactions. Yields ranged from 5-75% and diastereomeric excesses from 32-69% *de*. Choosing R$_1$ = R$_2$ = H, the authors obtained the products with 75% yield and 69% *de*. Additionally, the system could be reused at least four times without
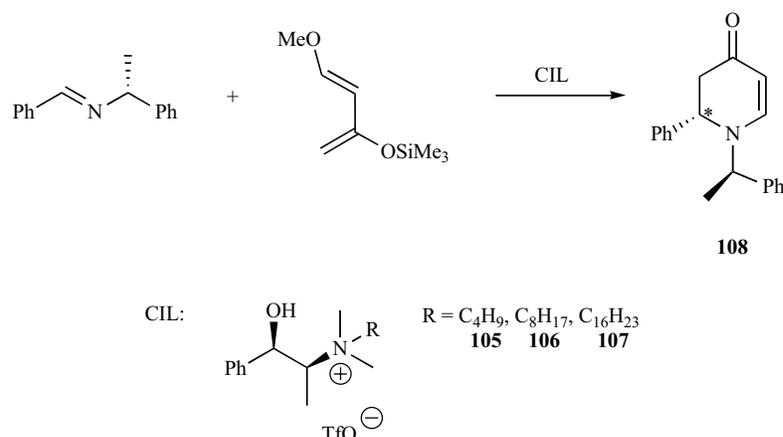
Scheme 23. Asymmetric aza-Diels-Alder reaction of Danishefsky´s diene in CIL as source of chirality (72% de) [57].
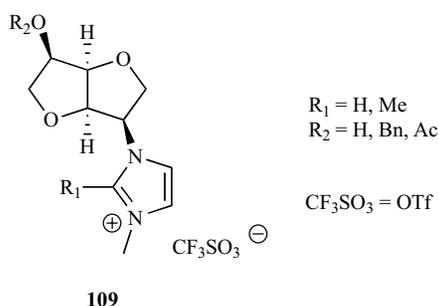
Fig. (2). Suitable CIL for Asymmetric aza Diels–Alder reaction (Scheme **23**) [58].

loss of activity in recycling reactions. Other CILs for diastereoselective Diels-Alder reaction are camphor-based CILs [60].

7. SUMMARY, CONCLUSIONS, OUTLOOK AND PERSPECTIVES

In summary, the presented outstanding publications about asymmetric induction with chiral ionic liquids as single source of chiral information show similar conclusions in most cases concerning the question of chirality-transfer in CILs. Effective chirality transfer is based on strong electrostatic interaction, respectively ion-pairing effects and hydrogen bonding between the CILs and the reactants and/or catalysts. The activity and enantioselectivity is enhanced in presence of hydrogen bond donor groups such as hydroxy groups and the anion has in general a strong influence onto the chirality transfer. In certain cases using ion pairing effects, the concentration of the CIL in the co-solvent plays important role, where highest *ee*'s are obtained with concentrations leading to the lowest degree of dissociation. Typical organocatalysts, such as proline-based systems, are immobilized in an alkyl side-chain or act as chiral counterion, usually anion. The potential for immobilized organocatalysts in CILs is very high, as it is reflected in most publications of that field since 2006. The advantage lies in the potential for recycling these ionic organocatalysts. Using CILs with organometallic catalysts is more difficult, and in this case, the CIL act as a chiral ligand for the organometallic precursor. Here, the enantioselectivity is assumably based on *chiral poisoning,* where one complex diastereomer is more stable (less reactive) than the other, thus an enantiomeric excess is reached. The disadvantage is, that the valuable CIL is used in large excess to induce chiral information. Presumably, this attempt will be rethought in future works, focusing more on well-defined chiral organometallic complexes incorporating (chiral) ionophilic ligands for the immobilization in ionic liquid media. Diels-Alder type reactions, represents the most challenging reactions using CILs as single source for asymmetric inductions. In such reaction (cyclo-additions, En-reaction, etc.) the CILs act as solvents and the asymmetric information is induced from the chiral solvent-environment of the *3D* IL-network (chiral folders, chiral pockets, etc.) onto the substrates (transition-state), giving diastereomeric excess in the corresponding products. Indeed, theses reactions can really be called *solvent-induced* asymmetric reactions. The first examples with solid state catalysts for heterogeneous catalysis assumed that the asymmetric induction relays on ion-pairing effects between the chiral anion and the cation (substrate). However, one can not exclude that the solid catalyst material serves as a reservoir for molecular complex species incorporating the chiral ion as ligand.

Without any doubt in the near future a full range of catalytic systems and more mechanistic details will be find in the literature about chiral ionic liquids for asymmetric catalysis. Until now, the transfer of chirality in ionic liquids is not clearly understood. The works in this review article, represents pioneering research in a quite young area, as many others, several decades ago, performed the first generation of classical homogeneous asymmetric catalysis with chiral ligand systems obtaining the first remarkable and high enantiomeric excesses [61].

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