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Asymmetric Michael Addition Mediated by Chiral Ionic Liquids

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Abstract: Chiral ionic liquids with a focus on their applications in asymmetric Michael additions and related reactions were reviewed. The examples were classified on the basis of the mode of asymmetric induction (*e.g.*, external induction/non-covalent interaction or internal induction/covalent bond formation), the roles in reactions (as a solvent or catalyst), and their structural features (*e.g.*, imidazolium-based chiral cations, other chiral oniums; proline derivatives). Most of the reactions with high chiral induction are Michael addition of ketones or aldehydes to chalcones or nitrostyrenes where proline-derived chiral ionic liquids catalyze the reaction through enamine/iminium formation. Many reports demonstrate the recyclability of ionic liquid-tagged pyrrolidines.

Keywords: Michael addition, imidazole ionic liquid, Chiral ionic liquid, asymmetric reaction, chiral solvent, catalysts.

1. INTRODUCTION

In 1999, Seddon's group reported the first example of a chiral ionic liquid, 1-butyl-3-methylimidazolium lactate [1]. Since then, the syntheses of various chiral ionic liquids and their applications to organic synthesis have been reported [2-6]. Unlike the first example where chirality was induced by the lactate anion, most of the chiral ionic liquids reported thus far consist of chiral cations and achiral anions. Many of the reported chiral ionic liquids have been used as chiral agents for asymmetric organic synthesis, *e.g.*, aldol reaction, Baylis-Hillman reaction, and Michael addition [2-8]. This review provides an overview of the asymmetric Michael addition mediated by chiral ionic liquids. Michael addition is one of the most powerful, efficient methods for the formation of carbon-carbon bonds, and its asymmetric version is beneficial in organic synthesis. In the following sections, chiral ionic liquids and their applications in Michael addition were classified based on the structural features of the ionic liquids and the manner in which they cause asymmetric induction.

2. EXTERNAL ASYMMETRIC INDUCTION BY CHIRAL CATIONS THROUGH NON-COVALENT INTERACTIONS

2.1. Chiral Ionic Liquids as Solvents

Bao and co-workers have reported the application of imidazolium-based chiral ionic liquids to the enantioselective Michael addition (Scheme 1) [9]. A majority of the chiral ionic liquids reported in previous studies other than Bao's study, especially those from the chiral pool, contain positive

ly charged atoms adjacent to chiral centers, possibly causing the racemization of the chiral ionic liquids [10]. In view of this drawback, Bao and co-workers synthesized chiral ionic liquids with "better configurational stability" compared to natural acid derivatives. Imidazolium salts **1a**, and **2a** are synthesized from L-(+)-diethyl tartrate or ethyl (*S*)-lactate in five steps, and the anion exchange affords hexafluorophosphates **1b**, **2b**, and tetrafluoroborate **2c**. Chiral imidazoliums **1b**, **2a-c** was applied to the enantioselective Michael addition of diethyl malonate to chalcone as the chiral reaction media. Co-solvents were used to ensure that the reaction mixture could be stirred smoothly, because low temperature was required to enhance the chiral induction and the melting points of **1b**, **2a-c** were greater than 40 °C. In the reaction using **2c**, better enantioselectivity (24% ee) is obtained in toluene compared to DMSO (17% ee) and DMF (16% ee). The chiral ionic liquid with C₂ symmetry **1b** exhibits lower asymmetric induction than **2a-c**. Enantioselectivity was possibly induced by molecular interactions, *e.g.*, electrostatic attractions between the imidazolium and malonate anion. *N*-heterocyclic carbenes are expected to be produced from ionic liquids under basic conditions to mediate the reaction. However, that is unlikely considering that the reported pK_a values of the imidazolium salts range from 19.7 to 24 in DMSO [11-13] and from 19.8 to 25.4 in water [14, 15], whereas a pK_a value of the conjugate acid of potassium carbonate is ca. ~10.

In addition, Ou and Huang have reported the same type of enantioselective Michael reaction using imidazolium-based chiral ionic liquids prepared from L-amino alcohols and 1-(2,4-dinitrophenyl)-3-methylimidazolium chloride in one or two steps (Scheme 2) [16] using acetonitrile as the co-solvent. In the presence of potassium carbonate, the addition of diethyl malonate to chalcone proceeds in moderate-to-good yields. A majority of their chiral ionic liquids exhibited enantioselectivity up to 15% ee.

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Scheme 1.

Scheme 2.

Suzuki's group has reported the synthesis of four structural types of chiral ionic liquids and their applications (Scheme 3) [17]: monoimidazolium salts bearing an asymmetric carbon atom α to the nitrogen atom on a *N*-substituent (**6**); monoimidazolium salts bearing an asymmetric carbon atom β to the nitrogen atom on an *N*-substituent (**2a**) (for structure, see Scheme 1); *C*₂-symmetric bisimidazolium salts bearing asymmetric carbon atoms α to the nitrogen atoms of imidazoles (**7**); and *C*₂-symmetric bisimidazolium salts bearing asymmetric carbon atoms β to the nitrogen atoms of imidazoles (**8**, **9**). They also performed Michael addition between chalcone derivatives and malonates using them as solvents to evaluate their chiral induction abilities. Bisimidazoliums **7–9** exerted subtle, but steady, induction effects.

2.2. Chiral Ionic Liquids as Catalysts

Vo-Thanh and Trung have synthesized chiral ionic liquids **10–13** in two or three steps from (–)-ephedrine and applied them for the asymmetric Michael addition of diethyl acetylaminomalonate to chalcone derivatives (Scheme 4) [18]. A solvent-free microwave-assisted methodology was utilized to prepare **10–13**. The Michael addition proceeded in moderate-to-good yields and enantioselectivities (up to 80% yield and 70% ee, respectively). Particularly, the best ee values are obtained using **10a** and **11a**. Besides the steric effect, one possible explanation for the higher selectivity of this reaction compared with that observed for the above-mentioned examples in Scheme 1 (Section 1.1) and the present and following examples in this section is the hydrogen bonding between the catalysts and substrates. The substrate

diethyl acetylaminomalonate comprises a hydrogen-bond donor, *i.e.*, amide hydrogen. Particularly, the pyridine moieties of **10**, and **11** can act as hydrogen-bond acceptors.

Scheme 4.

Gortor and co-workers have synthesized optically active ionic liquids **14** derived from cyclohexenone and imidazole by lipase-catalyzed kinetic resolution and applied them to organocatalysis (Scheme 5) [19]. Eighteen optically active salts with (1*R*,3*R*)-*trans*, (1*R*,3*S*)-*cis*, or (1*S*,3*R*)-*cis* configuration were used as asymmetric phase-transfer catalysts in the reaction between chalcone and diethyl malonate. The catalyst with the octyl group exhibits higher catalytic activity than those comprising benzyl or butyl groups. (*R*)- and (*S*)-products were preferentially produced using *cis* and *trans* catalysts, respectively, albeit with low selectivities.

Scheme 5.

As another example, chiral ionic liquid **15** (Fig. 1) was synthesized from chiral bicycle [3.3.1] nonane-2,6-dione in three steps, which was used in the reaction between chalcone and diethyl malonate [20]. The reaction was carried out at room temperature for 12 h using potassium carbonate as the base, affording the (*S*)-adduct with 57% ee.

Fig. (1). Imidazole ionic liquid from Chiral bicyclo[3.3.1]nonane-2,6-dione.

Zlotin and co-workers have recently reported tertiary amine-derived ionic liquid-supported squaramides **16**, **17a,b** and *ent*-**17a** (enantiomer of **17a**) as organocatalysts for asymmetric Michael additions of β -dicarbonyl compounds to nitroolefins (Scheme 6) [21]. The catalysts were prepared *via* chiral tertiary amines as key precursors, which were derived from CBz-protected cyclohexane-1,2-diamine. Both **16** and **17a** perform well as catalysts at ambient temperature in various organic solvents, affording the adduct (Scheme 6, R = Ph) with the (*R*)-configuration in high yields. The enantiomeric enrichment of the product is higher (up to 96% ee in organic solvent) with **17a**, especially when pure water is used as solvent (98% ee). Catalyst **16** exhibits inferior activity and stereoselectivity under aqueous conditions. In contrast to hydrophobic hexafluorophosphate **17a**, water-soluble bromide **17b** affords nearly racemic product in the same reaction. The catalyst loading of **17a** can be reduced to 0.1 mol%, however, longer reaction time is required and a slightly lower enantioselectivity is observed. In addition, **17a** is readily recoverable and reusable at least 30 times without a significant decrease of catalytic activity and enantioselectivity. It is suggested that in the presence of water, the amphiphilic catalyst **17a** is located in the frontier zone between the organic phase and aqueous phase, which accelerates the catalytic transformation through a hydrophobic solvation effect.

Scheme 6.

3. INTERNAL ASYMMETRIC INDUCTION VIA ENAMINE OR IMINIUM FORMATION BY CHIRAL CATIONS

3.1. Imidazole Ionic Liquids Bearing a 2-Pyrrolidinyl-Methyl Group as a *N*-Substituent

Cheng's group has reported asymmetric organocatalysts **18-21** for the Michael addition to nitroolefins, which have a proline-derived chiral pyrrolidine unit covalently tethered to

the imidazolium moiety (Scheme 7) [22]. The pyrrolidine unit was designed as the catalytic site, and the imidazolium moiety served as the phase tag and chiral-induction group.

Scheme 7.

Fig. (2). Various Michael addition products produced in the presence of **19a** and **19b**.

The chiral ionic-liquid-catalyzed Michael addition of cyclohexanone to nitrostyrene was conducted in neat mixtures using TFA as the co-catalyst. Most of the catalysts exhibit higher activity than those reported previously for chiral pyrrolidine catalysis in ionic liquids [23]. Amongst these catalysts, bromide **19a** and tetrafluoroborate **19b** are the best chiral catalysts, with nearly quantitative yields and high diastereoselectivity (*syn/anti* = 99:1) and enantioselectivity (98% ee), whereas 40 mol% of L-proline is required to perform the same reaction in ionic liquids for 60 h with a 75% yield (d.r. = 95:5 and 75% ee for the *syn* diastereomer) [23]. The catalysts with the imidazolium core are superior to those with the 2-methylimidazolium core, and the protic group in

the side chain of the cation (as in **21a,b**) decreases the catalytic activity and selectivity. Catalysts **19a,b** were also applied to the Michael addition between other acceptors (nitroolefins) and donors (aldehydes and ketones) to afford the products shown in Fig. (2).

The catalysts are easily recycled by precipitation with diethyl ether. Recycled **19b** is used in the second run of the reaction between cyclohexanone and nitrostyrene, with identical activities and slightly decreased selectivities. The loss of activity is observed in the third and fourth reuse, but excellent yields and ee values are achieved with a long reaction time.

The high diastereo- and enantioselectivities can be explained by the concept of an acyclic synclinal transition state [24]. That is, the ionic-liquid moiety would shield the *Si* face of the double bond of the enamine formed from the pyrrolidine and ketone, and the reaction would proceed through a *Re-Re* approach (Fig. 3). Zhang's group has conducted a theoretical investigation to elucidate the stereoselectivity of the Michael addition to olefins catalyzed by this type of pyrrolidine-based imidazolium ionic liquids [25, 26].

Fig. (3). Proposed transition state for the reaction between cyclohexanones and nitroolefins.

Luo, Cheng, and their co-workers have applied the chiral ionic-liquid-catalyzed Michael addition to the desymmetrization of prochiral ketones (Scheme 8) [27]. During the screening of **19d**, **21-25** for their catalytic activities in the reaction between 4-methylcyclohexanones and nitrostyrene, benzimidazolium **22** is found as the optimal catalyst. Thiazolidine-containing cation **23** and bis-cation **24** are inactive in the reaction. In addition, the effects of side chains of the imidazole core are observed. Specifically, a protic group (**21a**) and longer chain (**25**) lead to decreased product yields.

Among several Brønsted acids (*e.g.*, acetic acid, benzoic acid, chloroacetic acid, salicylic acid, trifluoroacetic acid (TFA), trifluoromethanesulfonic acid) screened as additives, salicylic acid affords optimal results in terms of both activity and stereoselectivity. Using **22** and salicylic acid, the Michael addition of other 4-substituted cyclohexanones and nitrostyrene derivatives was examined. The reaction of 4-ethyl, 4-*t*-butyl, 4-phenyl, 4-azido, and 4-acetylmercaptocyclohexanone affords the Michael adducts in 61-99% yields with excellent enantioselectivities (93-99% ee) and diastereoselectivities ranging from 4:1 to 12:1. In contrast, the reaction does not proceed with the use of 4-hydroxy, 4-bromo, and 4-cyanocyclohexanone.

Ionic liquid **22** is recycled by precipitation with diethyl ether and reused four times with a similar degree of stereoselectivities. However, decreased activity (prolonged reaction time and decreased yield) is observed in the third and fourth reuse.

The Michael addition of cyclohexanone to nitrostyrene catalyzed by the same class of chiral ionic liquids **26a-g**,

comprising either/both alternative side chains on the imidazolium core and/or bis(trifluoromethylsulfonyl)imide as the counter anion, has also been reported by another group (Fig. 4) [28]. There are also reports on a similar type of pyrrolidine-based chiral imidazolium ionic liquids with higher reusability, *i.e.*, polymer-immobilized chiral ionic liquids **27a-c** and silica-gel-supported chiral ionic liquids **28, 29** (Fig. 4). Both ionic liquids are simply recovered by filtration. For the asymmetric Michael addition to nitrostyrenes, **27a** can be recycled up to eight times without the loss of activity and enantioselectivity [29]. Silica-gel-supported chiral ionic liquids **28, 29** can be recycled at least five times [30].

Scheme 8.

Fig. (4). Other imidazole ionic liquids bearing a 2-pyrrolidinylmethyl group.

3.2. Imidazole Ionic Liquids Tethered to a Pyrrolidinyl-methyltriazole Moiety

Chiral ionic liquids **30**, and **31** (Fig. 5) containing a triazole moiety between the imidazole core and pyrrolidine were synthesized by “click chemistry,” and they were applied to the enanti-

oselective Michael addition of ketones to nitroolefins [31, 32]. In the reaction using **30**, the addition of TFA significantly enhances the reaction rate and enantioselectivity. Catalyst **30** is easily recycled by precipitation *via* the addition of diethyl ether into the reaction mixture, and reused without additional TFA four times with no significant decrease in yields and enantioselectivities [31]. Ionic liquid **31a** could be recycled in a similar manner by precipitation and reused at least eight times without the loss of its catalytic activity [32].

Fig. (5). Imidazole ionic liquids tethered to a pyrrolidinylmethyltriazole moiety.

3.3. Imidazole Ionic Liquids Bearing a *N*-(Pyrrolidin-2-ylmethyl)sulfonamide Moiety

Headley and co-workers have developed a series of pyrrolidine-based chiral imidazolium ionic liquids containing a sulfonamide moiety as a protic functionality (Fig. 6) [33–35]. They first reported imidazolium **32** as a recyclable organocatalyst for the asymmetric Michael addition of aldehydes and cyclohexanone to nitrostyrenes (Scheme 9 and 10) [33]. The acidic N-H plays an important role in the selectivity of the reaction *via* the formation of hydrogen bonds to the nitrostyrene substrate. In the addition of aldehyde, C–C bond formation would occur by the preferential addition of the enamine to the less hindered *Si*-face of nitrostyrene, affording a product with *2R,3S* configuration (Fig. 7A) [34]. In contrast to cyclohexanone, the ketone-derived enamine attacks nitrostyrene from the less hindered *Re*-face, affording a product with the *2S,3R* configuration (Fig. 7B).

Fig. (6). Imidazole ionic liquids bearing a *n*-(pyrrolidin-2-ylmethyl)sulfonamide moiety.

Considering the stabilization effect of the acidic N-H on the transition state *via* a hydrogen bond, ionic liquids with a shorter methylene chain between the sulfonyl group and imidazolium unit than that of **32** are designed as a more efficient catalyst [34]. Ionic liquid **33** contains a more acidic N-H and sterically bulky groups near the catalytic site. In combination with TFA, **33** has been reported to be more effective than **32** for the Michael addition of α,α -disubstituted aldehydes (Scheme 9, R¹ = R²) and nitrostyrenes, enantioselectively affording the Michael adducts with one quaternary carbon center. In contrast, **32** produces superior enantioselectivities for reactions involving α -monosubstituted aldehydes

(R¹ = H, R² = alkyl), whereas **33** is more reactive, affording products in a higher yield. Catalysts **32** and **33** are recovered by precipitation with ether and are reused five times without any significant loss in activity.

Scheme 9.

Scheme 10.

Fig. (7). Mechanism for Michael addition in the presence of imidazole ionic liquid bearing a *N*-(pyrrolidin-2-ylmethyl)sulfonamide moiety.

To increase the N-H acidity for the formation of the strong hydrogen bonds in the transition state, a new type of a pyrrolidine sulfonamide catalyst **34** was designed (Fig. 6) [35]. Catalyst **34** contains a sulfonyl group directly connected to the electronegative C-2 position of the imidazolium cation, which serves as the electron-withdrawing group. In addition, improved stereoselectivity was expected because of the close proximity of the imidazole core to the catalytic center.

Even with a lower catalyst loading (10 mol%) of **34**, the Michael addition of six-membered cyclic ketones and *i*-butylaldehydes to nitroolefins afforded the products in good yields at room temperature with high stereoselectivities (ee up to 99%; *syn/anti* up to 99/1) (Scheme 11). In contrast, the reaction of cyclopentanone to nitrostyrene using **34** affords the product in low yield, and the reaction of acetone with nitrostyrene affords low enantioselectivity. The catalyst is readily recovered and reused at least five times without any significant loss of catalytic activity and stereoselectivity.

The Michael addition of cyclohexanone to styrenes catalyzed by a similar pyrrolidine-based chiral imidazolium ionic liquid **35** containing a sulfonamide moiety has also been reported by another research group Fig. (8) [36].

Scheme 11.

Fig. (8). Imidazole ionic liquid bearing a (N-(pyrrolidin-2-ylmethyl)sulfamoyl)benzyl Group.

3.4. Imidazole and Triazole Ionic Liquids Tethered to a Prolinol Moiety

A series of chiral imidazolium ionic liquids bearing an α,α -diphenylprolinol unit have been developed as recoverable organocatalysts **36 a-d**, **37-40** for the asymmetric Michael addition by Zlotin and co-workers (Fig. 9) [37-41].

Proline-derived compounds **36a-c** were used in the reaction between *trans*-cinnamaldehydes and malonates (Scheme 12) [37]. The reactions with 10 mol% of **36a** proceed under mild conditions (4 °C) in high yield (up to 98%) with high enantioselectivities (up to 96% ee), whereas the presence of the free hydroxyl groups in **36b,c** decreases the conversion (less than or equal to 26%). Catalyst **36a** could be used four times without any decrease in the activity and enantioselectivity.

Fig. (9). Ionic liquids tethered to a prolinol moiety.

The catalysts with the *S* configuration at position 5 of the pyrrolidine (**36 a,b,d**) and their diastereomers with the *R* configuration (**39 a,b**) were used in a reaction between α,β -enals and nitromethane derivatives (Scheme 13, Scheme 14)

[38]. *O*-trimethylsilylated compounds **36a,39a** exhibit high catalytic performance with various substrates. In contrast, *O*-triethylsilylated analog **36d** is nearly inactive. Compounds with a free hydroxyl group **36b,39b** exhibit lower selectivity than their *O*-trimethylsilylated counterparts **36a,39a**. (Scheme 13) Although **36 a,b** and **39 a,b** are not enantiomers, the reactions with **36a,b** and with **39a,b** afford (*S*)-products and (*R*)-products, respectively. The existence of water in the reaction medium is favorable. That is, the reaction conversion in the presence of catalyst **36b** was >99% in 96% MeOH, whereas it was 66% in dry MeOH. Although the catalytic activity decreases after the third use, catalyst **36a, b** and **39a** could be used five times without any decrease in the product yield and ee values.

Scheme 12.

Scheme 13.

Scheme 14.

The Michael addition of acetaldehyde derivatives with nitroolefins catalyzed by the same class of chiral ionic liquid **36e**, which affords functionalized 4-nitrobutanals, has also been reported (Scheme 15) [42].

Scheme 15.

The domino reaction between α,β -enals and hydroxylamines in the presence of the chiral imidazolium ionic liquids has also been reported by Zlotin's research group (Fig. 9,

Scheme 16) [39–41]. The products of this domino reaction are chiral 3-aryl-5-hydroxyisoxazolidines, which are formed by the Michael addition followed by spontaneous intramolecular acetalization. Catalyst **36a** exhibits activity greater than those of **36b**, **37**, **38**, and **40** in the reaction between *trans*-cinnamaldehyde and *N*-benzyloxycarbonyl-protected hydroxylamine, selectively affording (*S*)-product [40]. In contrast, **39a** preferentially affords the (*R*)-product.

Scheme 16.

3.5. Imidazole Ionic Liquids Tethered to a Chiral Primary Amine

Zlotin's research group has reported chiral primary amine-derived ionic liquids **41**, **42** as reusable organocatalysts for the asymmetric Michael addition reactions (Scheme 17) [41, 43]. The catalytic properties of **41** and **42** were evaluated in the reaction of 4-hydroxycoumarin with benzylideneacetone at room temperature using THF as the solvent. With 20 mol% of **41**, the (*R*)-enantiomer-enriched product (10% ee) is obtained in 60% yield, whereas the reaction with **42** preferentially affords the (*S*)-enantiomer in 73% yield with 68% ee. The addition of acetic acid to this reaction using **42** leads to improved product yield (up to 80%) and enantioselectivity (up to 80% ee). The reactions of 4-hydroxycoumarin and its sulfur-containing analog with various benzylideneacetones or cyclohexenone in the presence of **42** also affords (*S*)-adducts in up to 77% ee. The catalytic efficacy of **42** progressively declines after the third cycle plausibly because of its deactivation by the irreversible reaction with the Michael adduct. To suppress this Brønsted-acid-sensitive undesired off-cycle reaction, structurally-modified catalyst **43** was designed [44]. In the presence of **43**, the Michael adducts are obtained in high yields (up to 97%) and enantioselectivities (up to 90% ee). The catalyst can be recycled five times with minor decreases in yield and enantioselectivity.

3.6. Pyridinium and Ammonium Ionic Liquids Bearing a 2-Pyrrolidinylmethyl Group as the *N*-Substituent

Studies related to the synthesis of proline-derived chiral ionic liquids with onium moieties other than imidazolium and their use in asymmetric Michael addition reactions have been published. 1-(Pyrrolidin-2-ylmethyl)pyridinium ionic liquid **44** has been reported by Headley and his co-workers (Scheme 18) [45], and alkyl ammonium ionic liquids bearing *N*-pyrrolidin-2-ylmethyl group **45** and **46** have been reported by Wang's group (Scheme 19) [46] and Chen's group (Scheme 20) [47], respectively.

Scheme 17.

All these ionic liquids were used in the Michael addition of ketones and aldehydes to nitroolefins as organocatalysts. In general, the reaction of cyclic ketones (except for cycloheptanone) using **44–46** afforded the adducts in good yields with high diastereo- and enantioselectivities. Similar to the examples of proline-derived imidazolium ionic liquids in Scheme 6 and Fig. 2 (Section 2.1), and in Schemes 8–10 (Section 2.3), (*3R*)-adducts are selectively obtained in the reaction of ketones, and (*3S*)-products are preferentially generated in the reaction of aldehydes. Catalyst **44b** could be recycled two times with a slightly decreased yield, with decreased selectivity in the third cycle (Scheme 18). Among catalyst **45a–c**, catalyst **45b** is considered as the catalyst of choice, and the optimal reaction solvent is [Bmim][BF₄] (Scheme 19). The catalyst remains in the solvent after the reaction. Thus, the catalyst and solvent are easily recovered in greater than 90% yield, and it can be reused at least six times without any loss of stereoselectivity and a slightly decreased activity. A good performance is observed for catalyst **46a–f**, but a longer time is required in the third cycle of the reaction, *i.e.*, 480 h for a product yield of 70%, whereas in the first cycle, the product yield is 80% after a 72-h reaction (Scheme 20).

Scheme 18.

Scheme 19.

Scheme 20.

Hirose and co-workers have used chiral ammonium ionic liquids containing a prolinamide moiety as the catalytic site in the asymmetric Michael addition of aldehydes to nitroolefins (Scheme 21) [48]. Catalyst **47** was synthesized from commercially available (+)-*cis*-2-benzamidocyclohexanecarboxylic acid and *N*-protected proline. Chiral ammonium ionic liquid **47b** with a longer alkyl group is found to be a catalyst superior to **47a** in the reaction between aldehydes and nitroolefins. Recyclability was tested for both catalysts. Although fairly constant enantioselectivities are observed, the catalytic activities decrease in the third run.

Scheme 21.

4. ASYMMETRIC INDUCTION BY L-PROLINATE AND L-PROLINIUM

Ohno's research group has reported the synthesis and the properties of ionic liquids containing natural amino-acid-derived anions [49]. Twenty chiral ionic liquids are prepared

by the neutralization of 1-ethyl-3-methylimidazolium hydroxide with a series of natural amino acids. Wang's research group has used one of these amino acid ionic liquids, imidazolium *L*-prolinate **48**, as the catalyst for the asymmetric Michael addition of cyclohexanone to chalcones (Scheme 22) [50]. In the reactions catalyzed by **48**, the solvent-dependent inversion of the enantioselectivity is observed. In particular, the reaction in methanol, ethanol, toluene, THF, dichloromethane, or in ionic liquids afforded (2*S*,3*R*)-enantiomer-enriched products. In contrast, the reaction in DMSO preferentially afforded (2*R*, 3*S*)-products.

Scheme 22.

Pernak and co-workers synthesized ammonium *L*-prolinate **49** and applied it to the asymmetric Michael addition of cyclohexanone to nitrostyrene (Scheme 23) [51]. They concluded that the catalytic activity and selectivity of **49** are better than those of *L*-proline in [bmim]BF₄ [22] and worse than functionalized ionic liquid **17b** (Scheme 6 in Section 2.1).

Scheme 23.

Scheme 24.

Yadav's group has reported stereocontrolled multicomponent reactions using a chiral ionic liquid, *L*-prolinium sulfate **50** [52], as both solvent and catalyst to obtain mercapto-

pyranothiazoles [53] (Scheme 24). In the postulated reaction mechanism, the products are obtained by the Michael addition to arylidenes, which are generated as intermediates. In general, high yields (up to 90%) and good selectivity (up to 95% ee) are achieved.

CONCLUSION

Examples of the asymmetric Michael addition reaction using chiral ionic liquids as solvents or catalysts were reviewed. A majority of the reported chiral ionic liquids applied in the Michael addition are pyrrolidine-based salts originating from proline. In addition, most of the chiral ionic liquids, which afforded products with high yields and high selectivities in the asymmetric Michael addition, were derived from proline, and these catalysts were developed as recyclable catalysts using the pyrrolidinyl groups as the catalytic sites and the cationic moieties as functionalities for immobilization.

Ionic liquids are widely used as reaction solvents in organic synthesis. Although successful syntheses through asymmetric induction by chiral solvents are rare, chiral ionic liquids demonstrate potential as viable chiral solvents for effectively transferring their chiralities to reaction products because of their recyclability, ease of synthesis, and high degree of organization.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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