This highlight focuses on the developments in ionic-liquid (IL)-tagged proline-based organocatalysts. An overview of catalyst structure and application to asymmetric transformations is provided, and a representative synthesis of an IL-tagged organocatalyst is also discussed.

A Snapshot of Ionic-Liquid-Tagged Proline-Based Organocatalysts


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Introduction

Organocatalysis has become recognised over the past decade as a legitimate means of installing chirality into complex organic systems. The exponential growth within this field, first developed by List and Barbas et al. in 2000, and popularised by MacMillan and Jørgenson, has led to organocatalysis being considered the ‘third pillar’ of asymmetric synthesis.[1–3] Most organocatalysts which operate by an enamine intermediate are based around a proline motif. A range of structural elaborations of the l-proline unit have been undertaken to decrease catalyst loadings and improve stereoinduction. These aspects of organocatalysis have been extensively reviewed elsewhere.[4–9] Concurrent with the increasing structural complexity of such catalysts is the growing need to recycle and reuse them in a cost efficient manner. To this end there have been reports of organocatalysts supported on polymers,[10] mesoporous silica,[11] and gold nanoparticles.[12]

Discussion

Conducting organocatalysed reactions within IL reaction media has seen some success for the reuse of catalysts, although reports of catalyst leaching (loss of the catalyst during product extraction or IL purification) has hampered progress.[13,14] Throughout the past five years several groups have gone to further lengths to facilitate efficient reuse of their catalysts by incorporating an IL-tag(s) directly onto organocatalyst scaffolds. A question to be asked is: ‘what advantages do ionic liquid organocatalysts possess over other, more established, organocatalysts?’ One answer lies in that this approach offers a robust alternative to traditional solid-support strategies. This is due to the pendant IL groups offering an opportunity to customise properties such as solubility, melting point, and catalytic activity, while still providing the mechanistic and kinetic advantages of a homogenous catalytic system. The ability to tailor the aqueous versus organic solubility (or even selective solubility in organic solvents) of IL-tagged organocatalysts makes them highly suitable for recovery and reuse. From a mechanistic standpoint, Zlotin has stated that ‘they [IL-tagged organocatalysts] create the hydrophobic environment of the enamine-type transition state, which resembles a hydrophobic pocket of aldolases, which is essential for efficient reaction stereocntrol’.[15]

The first report of an IL-tagged organocatalyst based on the proline scaffold was by Miao and Chan in May 2006,[16] although there was a near concurrent report of a pyrrolidine-based organocatalyst reported by Luo et al.[17] in April of the same year. The catalyst design adopted by Chan (1, Fig. 1) incorporated an imidazolium group (a typical IL moiety) at the 4 position on trans-4-hydroxy-L-proline, leaving the α-amino acid portion of the scaffold intact. The approach of using the 4-hydroxy moiety as a handle to install the IL-tag has become a mainstay within this field, with most compounds conforming to the general structure 2 (Fig. 1).

Since that initial work, there have been several reports of this class of catalyst, although major contributions to this field have emerged primarily from the groups of Zlotin,[15,18–22] Lombardo,[23,24] and Liebscher.[14,25,26] Organocatalyst 3 (Fig. 2), synthesised by Lombardo et al.[23] was used in an array of asymmetric aldol reactions. In each case a small amount of

Fig. 1. First reported ionic-liquid-tagged organocatalyst 1 and the general structure of ionic-liquid-tagged organocatalysts 2 (ee: enantiomeric excess).
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1. Introduction

The development of organocatalysts has led to significant advancements in asymmetric transformations, particularly in the Michael addition and aldol reaction. Ionic-liquid-tagged organocatalysts, as explored by Lombardo et al., offer an innovative approach by integrating the advantages of ionic liquids with the specificity of organocatalysis. This integration is exemplified by the synthesis and application of catalysts 3, 5a, and 5b, as depicted in Scheme 1.

2. Results and Discussion

- **Catalyst 3**: Developed by Zlotin and co-workers, this catalyst is notable for its water solubility, which facilitates easy separation from the reaction mixture. It forms aqueous emulsions upon reaction, which are then reusable by the addition of more water. This feature is crucial for industrial applications, as it reduces the environmental footprint and enhances operational efficiency.

- **Catalysts 5a and 5b**: Synthesised by Zlotin and co-workers, these catalysts were employed in an aqueous aldol reaction with high catalyst loading (30 mol-%). They demonstrated the ability to form aqueous emulsions and the desired aldol products in very high yield and enantiomeric excess, highlighting their versatility and robustness.

3. Conclusion

The use of ionic-liquid-tagged organocatalysts in Michael additions and aldol reactions represents a significant breakthrough. The advantages of water solubility, ease of separation, and reusability make these catalysts highly promising for both academic and industrial applications. Further research is anticipated to explore the full potential of these catalysts in various asymmetric transformations.
performed better than 7 in the aldol reaction, typically giving yields, diastereomeric excess (de), and ee values over 90 % for several cyclohexanone/benzaldehyde combinations. Unfortunately, application of 7 to the Michael addition of ketones to nitrostyrenes afforded products in low enantiopurity (typically <30 % ee). Attempts to reuse 7, by selective solubilisation, resulted in substantial losses in ee with each successive reuse.

Catalyst 8 (Fig. 2) is the most structurally complex IL-tagged catalyst to date[23] and draws on recent catalyst design strategies to develop scaffolds which bear more than one ‘catalytic unit’.[25–33] In that study, a 10 mol-% catalyst loading in the presence of water (100 equivalents with respect to the aldehyde) furnished aldol products in excellent enantioselectivity and very high yield (96 % ee, 95 : 5 anti : syn, 99 % yield).[21] The proposed role of water in the emulsion was to reinforce important hydrophobic effects which enhance stereoselectivity within the transition state, although removal of water from the reaction mixture had a minor influence on the diastereomeric ratio (dr) (89 : 11 anti : syn) only. Despite this inconsistency, under the optimal conditions 8 was a suitable catalyst for cyclic ketones paired with activated aldehydes although it did not perform well when employing electron rich aldehydes as the electrophile, or when any aldehyde was employed as the nucleophile.[12] Catalyst 8 was recycled 15 times using a cyclohexanone/4-nitrobenzaldehyde aldol reaction, with a negligible change observed for the dr, ee, and yield after the 15th reuse.

As with most molecules a plethora of potential syntheses are possible, several of which have been successfully employed to install IL moieties onto the proline scaffold, and so an exhaustive analysis of these syntheses cannot be provided here. Through examination of several published synthetic strategies, several common features become apparent and as such will be discussed in the context of the scheme provided (Scheme 1). The synthesis illustrated in Scheme 1 shows a method employed by Lombardo et al.[23] to access imidazolium-tagged organocatalyst 3. A common starting point for the installation of IL tags is the esterification of the 4-hydroxy group with a halogenated carboxylic acid. A Mitsunobu reaction is then employed to install the desired cis-stereochemistry in order to exploit the previously discussed ‘cis-effect’. This same transformation can also be done using common coupling agents (N,N′-dicyclohexylcarbodimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl) carbodimide (EDCI), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), etc.) to retain the preinstalled trans-stereochemistry.

The installation of the pendant imidazolium group is undertaken by reaction of 10 (bearing the primary alkyl halide) with an N-alkylimidazole reagent. The alkylation depicted in Scheme 1 employs N-methyl imidazole, but variations of this moiety are often used to tailor the solubility and activity of the final catalyst. An example of this is provided by Zlotin and co-workers whereby N-dodecyl imidazole was introduced in order to increase the lipophilicity of the corresponding organocatalyst.[22]

Anion metathesis is most commonly carried out before the nucleophilic nitrogen is deprotected, affording 12 in high yield and purity. This process is typically performed by dissolving the imidazolium salt (in this case 11) in water followed by the addition of an excess of an organic soluble salt such as KPF₆ or NaBF₄, followed by extraction into an organic solvent. A common means of ensuring complete halogen anion removal is by the addition of silver salts such as AgBF₄ which cause the precipitation of AgX salts.

The nucleophilic nitrogen is, to the best of our knowledge, always revealed by catalytic hydrolysis of either a benzyl or carboxybenzyl (Cbz) protecting group. The universal reliance on these two similar protecting groups presumably arises due to the mild conditions and the heterogeneous catalyst used in the deprotection procedure. In the case of tert-butoxycarbarnates, the standard removal conditions (20 % trifluoroacetic acid (TFA) in CH₂Cl₂) would invariably result in anion scrambling to some extent.

The representative synthesis described in Scheme 1 concerns IL-tagged organocatalysts based on the l-proline structure that forms the basis of this highlight. Proline-derived organocatalysts are just one class of the many organocatalytic scaffolds that have been successfully elaborated with IL moieties, examples of other IL-tagged organocatalysts are highlighted in Fig. 3.

Conclusion

The evolution of IL-tagged organocatalysts has already begun with ionic functionalities becoming an increasingly prevalent feature of organocatalyst design. So far, IL-tagged organocatalysts have been applied only to routine chiral transformations (e.g. aldol, Mannich, Michael reactions, etc.), although they show great promise as a reusable means to install asymmetry within organic molecules. Future directions for this field would be the application of IL-tagged catalysts to cascade and domino processes with the intent of accessing increasingly sophisticated chiral scaffolds. Current preliminary results from this field so far are furnishing catalysts which possess ever greater recyclability and the potential to catalyse a growing pool of asymmetric transformations.

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References


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