Chiral Counter-ions in Asymmetric Synthesis

Many chemical processes involve cationic reagents, intermediates and products. Frequently, cationic intermediates react with nucleophiles to afford desired products. Interaction of these cations with chiral, unreactive anions may be considered as the employment of a remote asymmetric auxiliary. There are a wide range of chiral counter-ions available:

Chiral anion moieties have found use in a wide range of applications, from NMR enantiodifferentiation of chiral cations (and measurement of enantiomeric purity), to resolution of chiral cations, synthesis of chiral ionic liquids (CILs), and asymmetric synthesis.¹

Applications

- NMR enantiodifferentiation:
  Prochiral heptamethine cyanine dye 8 was enantio-differentiated by treatment with the hexacoordinate phosphate anion TRISPHAT, with two sets of signals observed for the olefinic protons.²

- Resolution:
  Along with separation of the diasteromeric complexes formed via solubility differences and chromatography, one interesting method available for some complexes with chiral counterions is the use of asymmetric extraction. Use of a lipophilic anion results in a salt with high affinity for organic solvent, which can be separated from the other enantiomer, if it shows low binding to the anion.³

- Chiral Ionic Liquids:
  Use of chiral ionic liquids as solvents has been utilised in a variety of enantioselective processes, such as the Baylis-Hillman reaction of aromatic imines.⁴
A similar approach has also been taken in the dihydroxylation of prochiral olefins, yielding the corresponding diols in excellent yields and very high ee.\textsuperscript{5}

Asymmetric Synthesis

The use of chiral anions in asymmetric synthesis was essentially unused in synthetic organic chemistry until relatively recently, as a result of rather disappointing enantioselectivities observed in many initial reports:

- **Cyclopropanation:**
  ArndtSEN et al. achieved enantioselective cyclopropanations of prochiral olefins with a catalytic $[\text{Cu(MeCN)}_4][\text{B(OR*)}_4]$ species, with moderate to good yields, but moderate at best enantioselectivities.\textsuperscript{6}

- **Reactions of prochiral nitrogen-containing intermediates:**
  Nelson et al. attempted the induction of asymmetry using borate anion 4, in both the Mannich and nucleophilic ring-opening of meso-aziridinium cations.\textsuperscript{7}

- **Breakthrough** – transfer hydrogenation and epoxidation of $\alpha,\beta$-unsaturated aldehydes:
  List et al. demonstrated that TRIP anion (5, $\text{Ar} = 2,4,6-\text{C}_6\text{H}_2(\text{Pr}_3)$) was effective at inducing enantioselectivity in the organocatalytic transfer hydrogenation of $\alpha,\beta$-unsaturated aldehydes.\textsuperscript{8}
This work was also extended to the epoxidation of these substrates, but it was found that a bis(3,5-bis(trifluoromethyl)benzyl)ammonium salt afforded higher enantioselectivity than the previously employed morpholinium salt.

**Breakthrough** – Au-catalysed hydroalkoxylation of allenes:

In 2007, Toste *et al.* published the Au-catalysed enantioselective hydroalkoxylation and hydroamination of allenes 25 in *Science*. It was found that just use of a chiral ligand resulted in enantioselectivities of <10 %, but when Ag5 was used, and the reaction conducted in benzene, up to 99 % ee could be achieved.

This strategy was even extended to the hydrocarboxylation of allenes 27, although a strategy of chiral anion and chiral ligand had to be employed, with neither chiral component efficient on its own. A clear matching and mis-matching effect was observed, resulting in enantioselectivities of up to 82%, 44% higher than by just chiral ligand alone:

**Chiral Brønsted acid catalysis:**

In what Lacour refers to as the “fraternal” field of chiral Brønsted acid catalysis, chiral phosphoric acids of type 5 are used to induce enantioselectivity in acid catalysed processes, usually *via* the formation of an H-bonded “charge assisted supramolecular entity” (as they are known by pure-blooded chiral counterionists!).

- Mannich-type reaction: 11
A totally different approach to the use of chiral counterions in asymmetry synthesis was devised by Jacobsen et al. and involves the use of thioureas to bind halide anions in a variety of synthetic processes, from Pictet-Spengler reactions, to enantioselective addition to oxocarbenium ions.

Summary

- Chiral anions are available in a wide range of different structures, incorporating a number of different functional groups.
- They may be used for a wide array of functions, such as enantiodifferentiation and resolution of chiral cationic species, by creation of diastereomeric ion pairs.
- They also have a burgeoning utility in asymmetric synthesis, either via the use of chiral ionic liquids (CILs) as solvent, or the use of a catalytic additive, either of a salt, or the conjugate acid, in order to induce enantioselectivity in a reaction.

References

1) Chem. Comm., 2009, 7073
5) Chem. Comm., 2006, 2371
6) Tet. Asymm., 2003, 1789
10) Science, 2007, 496