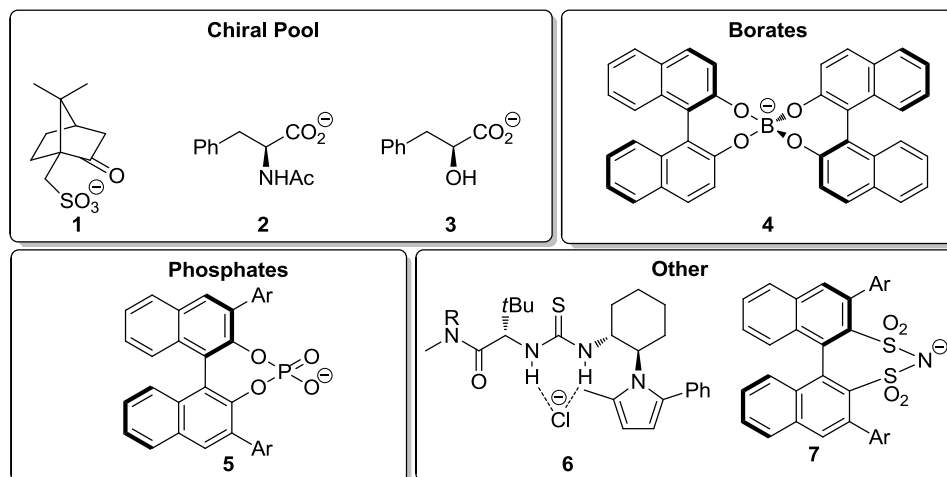


Chiral Counter-ions in Asymmetric Synthesis

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:

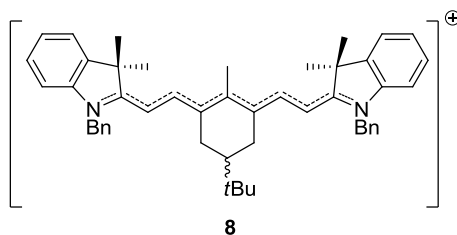


Chiral anion moieties have found use in a wide range of applications, from NMR enantiodifferentiation of chiral cations (and measurement of enantiomeric purity), to resolution of chiral cations, synthesis of chiral ionic liquids (CILs), and asymmetric synthesis.¹

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

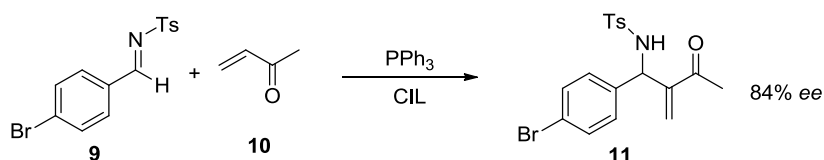


- Resolution:

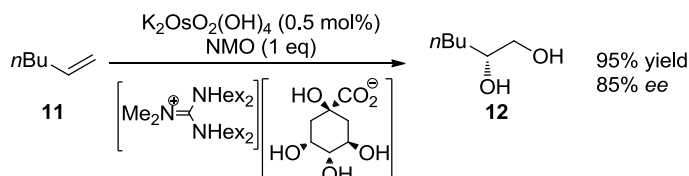
Along with separation of the diastomeric complexes formed *via* solubility differences and chromatography, one interesting method available for some complexes with chiral counterions is the use of asymmetric extraction. Use of a lipophilic anion results in a salt with high affinity for organic solvent, 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*.⁵

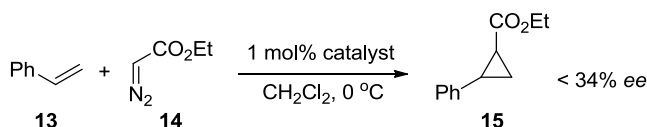


Asymmetric Synthesis

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:

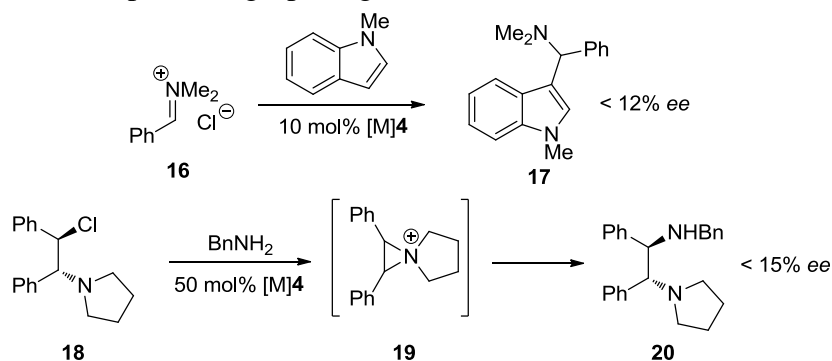
- Cyclopropanation:

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



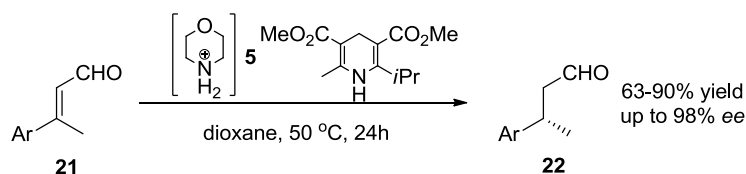
- Reactions of prochiral nitrogen-containing intermediates:

Nelson *et al.* attempted the induction of asymmetry using borate anion **4**, in both the Mannich and nucleophilic ring-opening of *meso*-aziridinium cations.⁷

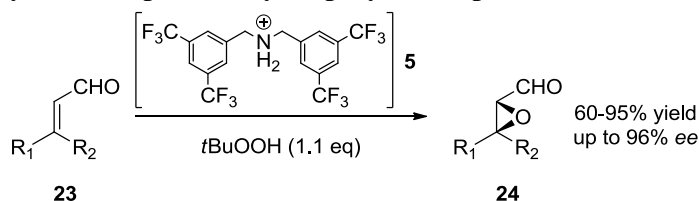


- **Breakthrough** – transfer hydrogenation and epoxidation of α,β -unsaturated aldehydes:

List *et al.* demonstrated that TRIP anion (**5**, $\text{Ar} = 2,4,6\text{-C}_6\text{H}_2i\text{Pr}_3$) was effective at inducing enantioselectivity in the organocatalytic transfer hydrogenation of α,β -unsaturated aldehydes.⁸

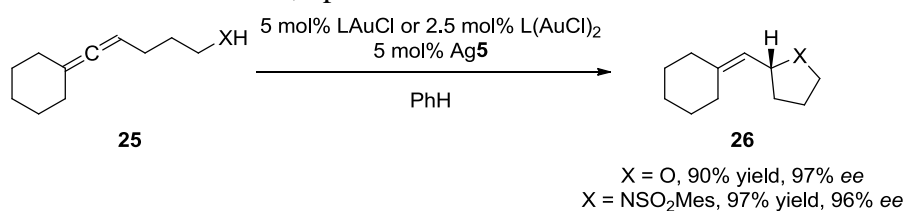


This work was also extended to the epoxidation of these substrates, but it was found that a bis(3,5-bis(trifluoromethyl)benzyl)ammonium salt afforded higher enantioselectivity than the previously employed morpholinium salt.⁹

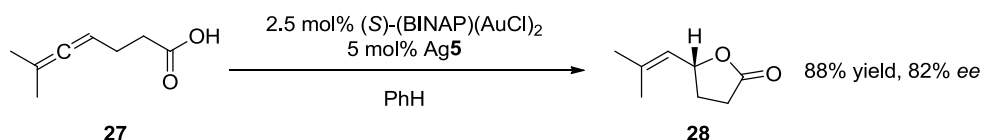


- **Breakthrough** – Au-catalysed hydroalkoxylation of allenes:

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 Ag**5** was used, and the reaction conducted in benzene, up to 99 % ee could be achieved.¹⁰



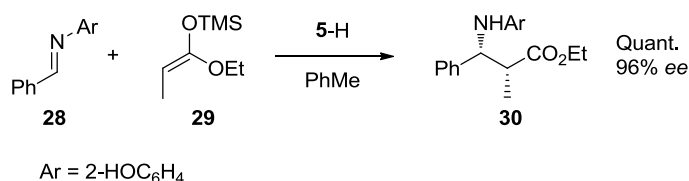
This strategy was even extended to the hydrocarboxylation of allenes **27**, although a strategy of chiral anion and chiral ligand had to be employed, with neither chiral component efficient on its own. A clear matching and mis-matching effect was observed, resulting in enantioselectivities of up to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



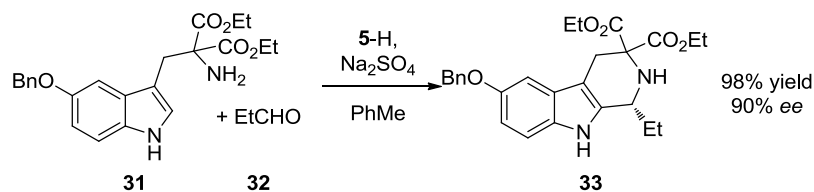
- Chiral Brønsted acid catalysis:

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

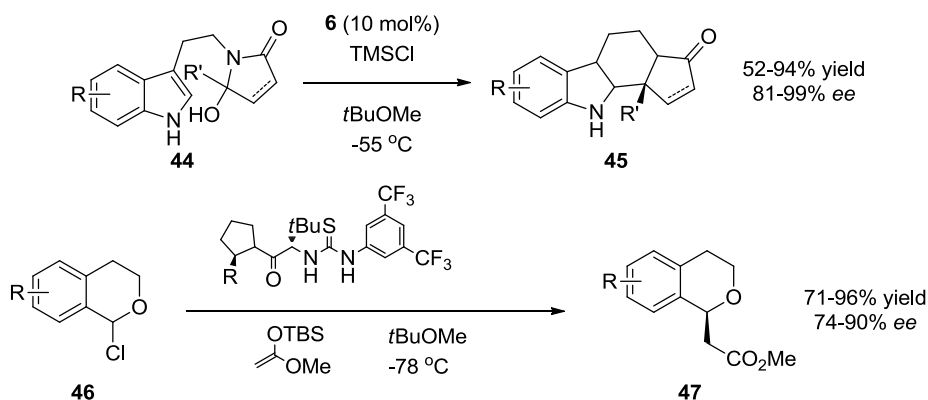


○ Pictet-Spengler reaction:¹²



● Thiourea anion-binding:¹³

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 diastomeric 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

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