Catalytic Asymmetric Synthesis

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7 lectures

Recommended texts:
"Catalytic Asymmetric Synthesis, 2nd edition", ed. I Ojima, Wiley-VCH, 2000
(or 1st ed., 1993, which contains most of the lecture material)
"Asymmetric Synthesis", G Procter, Oxford, 1996

Aims of course: To give students an understanding of the basic principles of asymmetric catalysis, and to demonstrate these in the context of state-of-the-art catalytic asymmetric processes for C-C bond formation and redox processes.

Course objectives: At the end of this course you should be able to:

- Recognise the types of functional groups which can be prepared by catalytic asymmetric methods discussed in the course;
- Use this knowledge in planning the synthesis of enantiomerically enriched compounds from given prochiral starting materials;
- Outline the scope and limitations of any methods you propose, with respect to parameters such as turnover, substrate and functional group tolerance, availability of catalysts and/or ligands *etc*

Course content (by lecture, approximately):

1. Introduction and general principles of asymmetric catalysis.
   Oxidation of functionalised olefins: asymmetric epoxidation of allylic alcohols and enones

2. Oxidation of unfunctionalised olefins: epoxidation, dihydroxylation and aminohydroxylation.

3. Reduction of olefins: asymmetric hydrogenation.

4. Reduction of ketones and imines

5. Asymmetric C-C bond formation: nucleophilic attack on carbonyls, imines and enones

6. Asymmetric transition metal catalysis in C-C bond forming reactions (cross-couplings, Heck reactions, allylic substitution, carbenoid reactions)

7. Chiral Lewis acid catalysis (aldol reactions, cycloadditions, Mannich reactions, allylations)

Catalytic Asymmetric Synthesis - Lecture 1

Background and general principles

- *Why asymmetric synthesis?*

The need to prepare pharmaceuticals and other fine chemicals as single enantiomers drives the field of asymmetric synthesis. The reasons for preparing compounds as single enantiomers can be due to adverse effects of employing a racemate, undesired properties of enantiomeric molecules or simply economic factors. Whatever the reason, asymmetric synthesis is now big business.

- *Strategies for synthesis of enantiomerically pure molecules*
  1. Resolution (often still used, but wasteful)
  2. "Chiral pool" syntheses (limited in terms of starting materials and available enantiomers)
  3. Asymmetric Synthesis

- *Types of asymmetric synthesis*

  All rely on creating an energy differential between the two 'enantiomeric' transition states, by making them 'diastereomeric':
  1. Chiral solvents (solvation of molecules in chiral environment - little used and expensive!) and chiral additives (solvation of specific parts of reacting system *eg* chiral ligands for organometallic reagents - popular and useful)
  2. Chiral auxiliaries (covalent attachment of chiral group to prochiral educt - now reaction gives rise to diastereomeric products - popular, useful, often predictable. Requires efficient attachment and removal of auxiliary. Problems of separation.) Common example: "Evans" oxazolidinones.
  3. Chiral reagents
  4. Chiral catalysts - the ideal solution! Small amount of chiral material is multiplied to give large amounts of new chiral material.

- *Terminology and definitions for asymmetric synthesis/catalysis*

(The reference bible for stereochemical terminology is "*Stereochemistry of Organic Compounds*" by E.L. Eliel, S.H. Wilen and L.N. Mander, Wiley, 1994.)

Cahn-Ingold-Prelog stereochemical nomenclature rules:

a) List atoms joined directly to the carbon in order of decreasing atomic number
b) Where two or more atoms are the same, the atomic number of the 2nd atom out counts, and so on.
c) Double and triple bonds count as two and three carbon substituents respectively
d) Place lowest priority C-X bond away from you. Count in decreasing order of priority around the remaining three atoms. If the route is clockwise, the stereochemistry is (*R*), if anti-clockwise then it is (*S*)

Re and Si nomenclature for describing enantiotopicity

1. Prioritise substituents according to Cahn-Ingold-Prelog rules above
2. Count around the substituents in decreasing order of priority. If the route is clockwise, the face presented is described as *Re*, if anti-clockwise then it is *Si*

Enantiomeric ratio and enantiomeric excess

Enantiomeric ratio = % ent a : % ent b

Enantiomeric excess = (% ent a) - (% ent b)

Enantiomeric excess is popular because of its (ideally) linear relationship with optical rotation.

Turnover
Ratio of moles of product formed to moles of catalyst used - higher turnover = more efficient catalyst.

Asymmetric Epoxidation

The importance of epoxides in synthesis (both in their own right and, more usefully, as synthons) is unquestionable. The stereochemical fidelity of their reactions means that methods for the asymmetric preparation of epoxides are of great importance. There are catalytic asymmetric approaches to all of the main classes of epoxide synthesis (halohydrin ring closure, Darzens/sulfur ylide chemistry and oxygen delivery), but we'll concentrate on the latter class of reactions, *ie* on the conversion of prochiral, readily available olefins to enantiomerically enriched epoxides.

Epoxidation of allylic alcohols - the Sharpless-Katsuki asymmetric epoxidation

The Sharpless-Katsuki asymmetric epoxidation was really the first reliable and predictable catalytic asymmetric reaction. Its use today (*ca.* 20 years on!) even on industrial scale is witness to its enduring utility.
This reaction sprang out of initial observations by Sharpless on the directing ability of hydroxyl groups in metal catalysed epoxidation reactions of readily available allylic alcohols. The postdoctoral worker (Takahashi Katsuki) was responsible for the key finding that the use of tartrate esters with titanium (IV) isopropoxide gave excellent levels of asymmetric induction. The next key finding several years later (1986) was that the addition of molecular sieves as a drying agent allowed the reaction to proceed with sub-stoichiometric amounts of catalyst. The general scheme for the reaction, mnemonic for stereoselectivity and scope of the reaction are shown on the slides.
The success of the reaction is due to the lability of titanium (IV) alcoholates to ligand exchange. Careful control of stoichiometry is necessary to ensure (a) good levels of enantioselectivity and (b) good rates of reaction. A representation of what is believed to be the active catalyst is shown in the slides.

- *Resolution mode*

The proximity of the allylic centre to the catalyst means that any existing chirality at this centre can affect the rate of reaction - for each enantiomer of the catalyst, one configuration at the allylic centre will result in normal (quick) reaction, while the other will interfere with the alcohol binding and slow the reaction. This discrimination allows one to operate the reaction in resolution mode: in a racemic mixture of allylic alcohols, for a given catalyst, one enantiomer will be consumed quickly, leaving the other enantiomer 'untouched' in an ideal case - in practice running the reaction to *ca.* 60% conversion gives good ee of the remaining allyl

alcohol in most cases. This is still one of the easiest ways to make optically enriched allyl alcohols!

- *Desymmetrisation mode*

In a variation on the above, if a molecule with a *meso*-plane of symmetry has alcohols with two prochiral olefinic groups, then one can be selectively oxidised by the Sharpless reagents; this creates additional asymmetric centre(s) due to the alcohol losing its *meso*- symmetry.

- *Reagent control*

The Sharpless AE is slightly sensitive to chirality in the molecule which is not at the allylic centre, but levels of asymmetric induction (while a little lowered in mismatched cases) is still excellent and useful. The stereochemical outcome of the reaction is said to operate under *reagent control*.
The ultimate application of this work was in Masamune and Sharpless' ground-breaking and efficient catalytic asymmetric synthesis of all 8 hexose sugar isomers.

- *Regiocontrolled functionalisation of glycidols*

One of the most useful facets of the AE reaction is that one can carry out the regiocontrolled ring-opening of the epoxides to access either regioisomeric outcome under appropriate conditions. Thus, nucleophilic organometallics/hydride sources act at the proximal carbon to the alcohol, whilst Lewis acidic neutral reagents react (by prior co-ordination to the epoxide) so as to open at the distal carbon.

Asymmetric epoxidation of enones

The asymmetric epoxidation of α,β-unsaturated carbonyl compounds can be achieved using poly-amino acids, most commonly poly-L-leucine. The strongly basic conditions mean that this works best for compounds with a β-aryl group, but it is synthetically useful nevertheless. The reaction was discovered by Julia and Colonna, but has been popularised by Professor Stan Roberts, now at the University of Liverpool, who advanced the reaction by finding organic-soluble sources of peroxide to allow the reaction to be done in non-aqueous systems - this gives better yields and longer catalyst lifetimes. Other competing systems include the use of phase transfer catalysts for peroxide delivery in biphasic systems and the use of chiral magnesium hydroperoxides.

AA 16/01/2003

Catalytic Asymmetric Synthesis - Lecture 2

Epoxidation of unfunctionalised alkenes - the Jacobsen-Katsuki asymmetric epoxidation

Yes, it's the same Katsuki, now a professor in his own right in Japan!!!! Just to complete the circle, Eric Jacobsen (first at Illinois, now at Harvard) also worked for Sharpless, on the development of the asymmetric dihydroxylation (see later). Chemistry can be a small world sometimes!

An early attempt at the asymmetric epoxidation of unfunctionalised alkenes used molybdenum species and tartrate esters, but gave low levels of asymmetric induction. The inspiration for the new approach outlined here comes from nature. Nature's oxidising agents are manifold, but one class responsible for metal oxo type oxidations are the cytochrome P450 enzymes. These proteins contain iron porphyrins at the active site, and not surprisingly, chemists attempted to recreate these reactions themselves with limited success. Many of the limitations of the porphyrin reactions could, in principle, be overcome by the use of metal salen complexes.

The challenge was taken up simultaneously in the early 1990's by both Jacobsen and Katsuki. For reasons of brevity, the slides show only the optimised system from Jacobsen but this is not to imply that the Katsuki system is inferior - both have merit. The reactions share some commonality in mechanism, and give high ee's for certain classes of olefin (mainly cis- and cyclic olefins - terminal olefins give low ee's and trans-olefins are slow to react - see mechanistic discussion!).

The real attraction of the reaction is that it can be run using sodium hypochlorite (household bleach!) as a cheap co-oxidant. The use of axial co-ordinating ligands such as amine N-oxides also stabilises the catalyst and allows very low catalyst loadings to be used. Thus, the method is of great interest industrially and this is exemplified by the SmithKline Beecham synthesis of the potassium channel activator BRL 55834.

Catalytic Asymmetric Epoxidation using Chiral Dioxiranes

The asymmetric epoxidation of *trans*-disubstituted and trisubstituted olefins is best achieved using dioxiranes, which can be generated *in situ* by the action of the peroxysulfate ion on ketones. The usual source of peroxysulfate is the commercially available triple salt marketed as Oxone®. Use of chiral ketones gives chiral dioxiranes, but beware: not any old ketone can be used! A side reaction of the dioxirane formation is the Baeyer-Villiger reaction, which destroys the catalyst. The best results are therefore obtained with electron poor ketones (reluctant to undergo bond migration). A fructose-derived ketone reported by Shi and co-workers in the US provides very high ee for epoxidation of *trans*-1,2-disubstituted- and trisubstituted alkenes, but relatively high catalyst loadings are needed.

Catalytic asymmetric ring opening of epoxides

Of course, once you've made your chiral epoxide you still have to open it with a nucleophile for it to be useful. An alternative strategy would be to use a chiral catalyst to promote the asymmetric ring opening of either *meso*-epoxides (in desymmetrising mode) or racemic epoxides (in resolution mode). Several catalyst systems have been defined for this. Note that although the resolution pathway seems wasteful, since terminal epoxides are cheap to make (halohydration, elimination) from alpha-olefins which are bulk petrochemical products, this is actually economically viable and is done on large scale. The mechanism with the Jacobsen-type catalysts involves two molecules of catalyst, one to activate the epoxide and one to activate the nucleophile.

Sharpless Asymmetric Dihydroxylation*: Chemical Reviews, 1994,* **94,** ***2483***

We all know of the dihydroxylation of olefins with OsO_4. Even in non-asymmetric mode it's an important process, even on an industrial scale (the Upjohn process). Amine derivatives are known to accelerate the dihydroxylation process, so it was not surprising that the use of chiral amines attracted attention. Early attempts at developing an asymmetric version examined chiral pyridines as ligands, but these gave poor results since their binding to Os is too weak. Chiral diamines, on the other hand, can afford excellent enantioselectivities but have to be used in a stoichiometric system since their high affinity for Os prevents catalytic turnover. The big breakthrough came when Sharpless examined bicyclic amines such as quinuclidines, building upon important early observations of Bill Griffith in this Department. Sharpless used naturally occurring chiral quinuclidine compounds (the *pseudoenantiomeric* compounds dihydroquinine and dihydroquinidine) along with the Upjohn NMO co-oxidant system, and bingo!

However, Sharpless noted a slight (and in some cases drastic) decrease in enantioselectivity on going to the catalytic mode. This was puzzling, until a detailed kinetic investigation showed the presence of a second oxidative pathway which proceeded with the opposite enantioselectivity to the primary pathway - thus the overall ee was eroded. This could be avoided by slow addition of alkene but this is inconvenient – a much better solution came with the use of the biphasic ($^tBuOH/H_2O$) ferricyanide co-oxidant system, where the intermediate osmate ester is in a different phase to the co-oxidant, thus preventing the second catalytic cycle. This improvement, along with the development of dimeric ligands that give higher ee, led to the highly practical Sharpless AD reaction that is one of the most useful and important catalytic asymmetric processes available.

A stereochemical model for the reaction is in place, and gives rise to a mnemonic for the prediction of facial selectivity. It has been followed in every case so far, but requires more rigorous interpretation than that for the AE reaction, since there is no covalent binding to the active complex to anchor conformation. All classes of olefin work, most giving EXCELLENT ee. Cis-disubstituted olefins can be a problem - this is quite easy to understand from the model (distinguishing medium from large groups isn't easy).

The diol products can be converted into epoxides, thus overcoming some of the limitations of the catalytic asymmetric epoxidation reactions we've looked at. They can also be used to make cyclic sulfates which provide an alternative to epoxides.

AA 23/01/2003

Catalytic Asymmetric Synthesis - Lecture 3

Asymmetric Aminohydroxylation

Stoichiometric and catalytic achiral aminohydroxylations were known for many years, so it's hardly a surprise that Sharpless tried his ligand system for asymmetric osmium mediated dihydroxylation out on it! It works, although mixtures of regioisomers are common. The stoichiometric reagent is an N-halosulfonamide or N-halocarbamate salt. The former were first used (chloramine T and chloramine M), the smaller sulfonamide giving superior results. Reactions were however limited to 1,2-disubstituted olefins - monosubstituted olefins appeared not to work well - slightly bizarre since they are the fastest with asymmetric dihydroxylation!!! It turns out that the carbamates, aside from being easier to deprotect, are also superior reagents and give good ee for most classes of olefin, including styrenes. Note that the regiochemical control is still sometimes poor though! The AA of styrenes is a useful route to arylglycines, by oxidation of the alcohol. In an important development, use of an anthraquinone derived ligand allows for the reversal of regioselectivity in the amino hydroxylation of styrenes and cinnamates.

Asymmetric Hydrogenation of Olefins and Derivatives

This is a very appealing reaction to industry - H_2 is CHEAP!!!! Also the substrates are easy to come by - alkenes, enoates, enamides etc are all very readily prepared.
The field of asymmetric hydrogenation dates back to *ca*. 1930! Early attempts focused on the use of chiral stationary phases as supports for palladium or platinum metal in heterogeneous catalysis. By the mid-1950s ee up to 60% had been observed - at the time this was amazing! Not surprisingly however, these reactions were unpredictable in both enantioselectivity and substrate tolerance.
The key breakthrough came in the early 1960s with the discovery of soluble transition metal complexes which could catalyse homogeneous hydrogenation of olefins. One such catalyst is of course Wilkinson's catalyst! These better defined complexes with ligands intimately bound to the metal and involved in the stereochemistry determining step offer opportunities for rational ligand design. By the late 1960s, chiral monodentate phosphines were being used with modest success. The key breakthrough came with the observation/discovery by Knowles at Monsanto and Kagan in France that chelating diphosphines offer much better opportunities for asymmetric induction, since they hold the complexes more rigidly and have fewer degrees of freedom themselves, potentially maximising the effect of the chiral ligands. (It is interesting to note that very recently, attention has turned back to monophosphines, and some of these have found that give very good ee - and they're easier to make than bisphosphines).

Asymmetric hydrogenation of N-acylaminoacrylates
These are of interest since the products are obviously protected amino acids! This is one of the best ways to make amino acids in asymmetric form. Many ligands work for this reduction, with varying degrees of success. The mechanism of hydrogenation of N-acylaminoacrylates was determined for Rh(I)(dipamp). Note that the major enantiomer actually arises through the less stable, minor diastereomeric adduct between N-acylaminoacrylate and the metal - but this is the faster reacting. This has been used in the preparation of the important anti-

Parkinson's drug L-DOPA. BINAP ligands were developed as better (more general) ligands. Note that the sense of asymmetric induction is determined by the olefin geometry.

Development of DuPHOS

*(*See Burk*, Acc. Chem. Res.,* **2000**, *33*, 363.)

This work stems from the early 1990s to the present day and leads to what is probably the most generally efficient and tolerant ligand system to date, although some others run it close. Original efforts by Mark Burk (then at DuPont, later at Duke University, then Chirotech, Cambridge, and now back in the US) focused on the preparation and uses of BPE. These were quite successful in hydrogenation of N-acylaminoacrylates but still fell short of ideal values. When they got an X-ray structure of a COD complex of the ligated Rh, they discovered why - the flexible backbone can exist in two diastereomeric conformations. One of these points the substituents directly at the coordination sites, the other directs them away slightly (opening up the coordination sites). Obviously, the former is what you want but it turns out the latter is more stable. They reasoned that getting rid of the conformational flexibility would achieve this and the DuPHOS ligands were born!

Results for the reduction of simple N-acylaminoacrylates were excellent, and can be readily understood in terms of the ligand approaching so as place the bulkiest group (CO_2Me) in an empty 'quadrant' of the complex. Exceptional ee's are obtained in the reduction of a range of N-acylaminoacrylates. The key improvement with this family of ligands is that the sense of asymmetric induction is NOT affected by olefin geometry, unlike BINAP - useful!!! Other systems can also be reduced by Rh-DuPHOS.

Ruthenium complexes for asymmetric hydrogenation

Ruthenium is much cheaper than rhodium, so a system based on a Ru catalyst would be particularly useful. BINAP-Ru species are good catalysts for the reduction of unsaturated acids and cyclic enamides. Note that the catalytic cycle is different from the Rh one - Ru prefers to form monohydrides, while Rh prefers to form dihydrides. The system can also be used to reduce allylic alcohols.

AA 30/01/2003

Catalytic Asymmetric Synthesis - Lecture 4

Asymmetric Reduction of Ketones and Imines

Oxazaborolidine reductions

These sprang out of observations on some stoichiometric chiral borane mediated reductions. The idea that a chiral activating group could be used in conjunction with stoichiometric achiral reducing agents was first noted by Itsuno, and investigated in detail by Corey. He soon arrived at the oxazaborolidine skeleton based on proline as his system of choice. The reaction is pretty general: most examples are given for aryl substituted ketones, but it works for vinyl, alkynyl and alkyl substituted ketones as well. The mechanism of reaction is really exquisite in terms of assembling the necessary components in close enough proximity to react, and also in a chiral environment. The ability to distinguish substituents on electronic rather than steric grounds is both useful and impressive! The applications of the reaction in synthesis are widespread (see the excellent recent review by Corey in Angewandte Chemie, 1998, p1987), but a limiting factor is that the catalyst loadings are relatively high compared to *eg* hydrogenation methods, making this quite an expensive process.

Asymmetric hydrogenation

Rhodium and (more commonly) ruthenium based systems for the reduction of ketones are well developed. One limitation is that, as in the reduction of olefins, there is a general need for a coordinating group additional to the ketone to ensure good enantioselectivity. There are many examples of the reduction of substituted ketones with Ru[(*S*)-BINAP]X_2 complexes; note that ketoesters are selectively reduced to the hydroxyesters, and that even o-bromophenyl groups are good enough coordinating groups to facilitate the hydrogenation!
The reduction of β-diketones gives mainly C_2 symmetric 1,3-diols. These reactions are highly enantioselective because of an effective 'resolution' step in the second reduction: the 'wrong' enantiomer from the first step is mostly converted to the achiral meso compound, thus enhancing the ee.
The reduction of racemic β-ketoesters is a nice demonstration of dynamic kinetic resolution: the readily enolisable proton means that the two enantiomeric starting materials are constantly equilibrating. Thus, provided that the hydrogenation discriminates between the two enantiomers of the starting material, we can get not only asymmetric induction in the reduction of the ketone, but also selection of one of the enantiomers of the starting material - two chiral centres for the price of one!
The reduction of simple ketones has latterly been addressed by Noyori, particularly with respect to his mixed amine/phosphine ligand systems - a very elegant demonstration of the principles of ligand accelerated catalysis.
Some success has been enjoyed with the reduction of imines, best under normal hydrogenation conditions - indeed this is a commercial reaction in the synthesis of the herbicide metolachlor.

Transfer hydrogenation
This is another useful technique for ketone reduction. Alkoxides or formate act as the hydride donor. Noyori observed significant ligand accelerated catalysis using amino alcohols and monotosylated diamines. Amino alcohols work well in many cases, but they have to be used with ^{i}PrOH as the hydride donor - they are not compatible with formate. So electron rich

alkylaryl ketones can sometimes give low ee due to reversibility of the reaction. Monotosylated diamines are tolerant of the irreversible formic acid system, and so give better results in these cases.

Asymmetric hydrosilylation

Yet again our starting point is Wilkinson's catalyst! Most early success in this arena came from chiral phosphines used in conjunction with Rh(I) species. A significant advance has been the finding that sp^2 nitrogen donor ligands (imines or oxazolines and pyridines) are good ligands with rhodium. Pyridylmono-oxazolines (Pymox) ligands give good ee's when used in large excess (10 fold with respect to the metal). Interestingly, this is due to the binding of TWO ligands to the rhodium -one bidentate and the other monodentate. Increasing the steric requirements of the Pymox ligand by substitution at the 6-position of the pyridine precludes this type of assembly, with only one ligand being bound in bidentate fashion. Thus, less ligand is required - unfortunately the ee's don't really hold up. The best class of ligand is the terdentate pyridine-2,6-bisoxazolines or Pybox ligands.
The species must be cationic on rhodium and is usually prepared by chloride abstraction from the rhodium with silver salts.
Buchwald has developed a chiral titanocene catalyst which is used along with (cheap!) poly(methylhydrosiloxane) for ketone reduction. Imines are pretty poor substrates for normal hydrosilylations, but give good ee with Buchwald's system.

AA 7/2/2002

Catalytic Asymmetric Synthesis - Lecture 5

Asymmetric Addition of Carbon Nucleophiles to Carbonyls, Imines and Enones

(a) Asymmetric Addition to Aldehydes

(i) Asymmetric organozinc additions to carbonyls

This was one of the first areas of non-transition metal asymmetric catalysis. Organozincs generally are too unreactive to add to carbonyl compounds. (They're not, however, 'unreactive' per se - as anyone who has ever handled diethylzinc will confirm!). However, they are activated in the presence of amino alcohols, which form oxaza-zinc species which can catalyse the addition through a Lewis acid/Lewis base mechanism resembling the oxazaborolidine reduction of carbonyls we talked about last time. Good yields and ee's are reported, particularly with aromatic aldehydes. Noyori discovered a remarkable non-linear effect, which means that product of high enantiomeric purity can be obtained even if the catalyst is of low ee!

One limitation is the number of commercially available dialkylzincs (there is more 1-phenylpropan-1-ol about than you would ever need to make!). Knochel has been highly active in developing routes to more highly functionalised organozinc compounds and has succeeded, although again there are limitations on scale-up. Knochel's asymmetric additions work by trans-metallation to a chiral titanium species.

(ii) In situ generation of acetylide nucleophiles

Most methods for adding carbon nucleophiles to aldehydes involve separate preparation of the nucleophile (*e.g.* organozincs, Grignards etc.) It would be nice if we could take stable, non-activated compounds which require no special handling precautions and use these. Carreira has developed just such a system based around zinc acetylides. Its well known that copper acetylides can be generated in situ from alkynes and copper salts with weak amine bases. This appears to be contrathermodynamic (pK_a of acetylene is about 25, pK_a of triethylammonium is about 10) but the reaction proceeds by activation of the π-system, followed by deprotonation at the now-activated site. Unfortunately copper acetylides are highly stable and therefore unreactive, but through screening Carreira found that zinc acetylides could be generated in situ and that further, these could add to carbonyls and nitrones asymmetrically in the presence of chiral amino alcohol ligands in a catalytic sense. The great thing about this chemistry is that it is apparently insensitive to oxygen or trace amounts of water - you can just use reagent grade solvent off the shelf in the open air! Trying this approach with some of the other reagents above is NOT recommended……

Early reports required stoichiometric amounts of Zn salt and chiral amino alcohol. Attempts to make it catalytic by including various additives or altering the solvent were not successful. However, very recently (*J. Am. Chem. Soc.*, **2001**, *123*, 9687), Carreira has reported addition of terminal alkynes to aldehydes that is sub-stoichiometric in both metal (20 mol% $Zn(OTf)_2$) and amino alcohol (50 mol%). The trick is simply to heat the reaction to 60ºC in toluene as solvent; fortunately, excellent ee values are still obtained even at this higher temperature. Some of the reactions can be run neat (*i.e.* no solvent required).

(b) Asymmetric Strecker reactions

Conceptually one of the simplest asymmetric approaches to amino acids, the Strecker reaction involves the addition of HCN and an amine to an aldehyde to give α-amino nitriles. Amazingly, it is only recently that catalytic asymmetric variants of this reaction have become available. Lipton was the first to demonstrate that catalysis was possible with an interesting use of a cyclic dipeptide containing a guanidine function. Although Lipton never postulated a mechanism (in print at least), recent work by Corey using a simple cyclic guanidine suggests a bifunctional catalysis of the reaction.

Two groups have chosen this reaction as a testing ground for the combinatorial discovery of new catalysts. Snapper and Hoveyda used Schiff-base peptides as ligands for metal salts and found that titanium (IV) promoted efficient reactions with good asymmetric induction. In a closely related contemporary study, Jacobsen found that in fact related compounds could act as good catalysts WITHOUT the metal! He developed reasonably efficient catalysts after three rounds of iterations from a simple starting material screening around 200 catalysts in all. Although the catalysts work well on the solid support (as a recyclable, heterogeneous catalyst) they work even better in solution for a range of aldehydes. These include enolisable aliphatic imines and this was the first example of an efficient asymmetric Strecker catalyst for these particular substrates. Other developments include Shibasaki's dual Lewis acid/Lewis base catalyst (although this may just be a more complicated version of the simple organic catalysts, with LA/LB interactions replacing H-bond donors and acceptors). Kobyashi has developed a zirconium BINOL based catalyst which will promote one-pot reactions, negating the need for separate imine formation steps. However, this is limited in the range of amine components.

(c) Asymmetric conjugate additions

Extensive work has gone into development of asymmetric versions of the well-known conjugate addition of copper-based nucleophiles to unsaturated carbonyl systems. Progress is summarised in a recent review (Alexakis, *Eur. J. Org. Chem.* **2002**, 3221): "there is as yet no ligand of general applicability". Again, one of the best systems uses organozinc compounds which do not react with enones/enoates at any appreciable rate alone. Upon transmetallation to copper, however, they become active and if chiral ligands are used on the copper, then asymmetric induction results. The chiral phosphoramidites developed by Feringa seem to have the best compromise of activity and selectivity across a range of substrates.

Promising results across a range of substrates have been achieved using rhodium catalysed addition of boronic acids across enones. Given the huge range of commercially available boronic acids (prepared for use in Suzuki couplings) and the fact that this seems to work on acyclic and cyclic ketones and esters, this is an important development.

AA 13/02/2003

Catalytic Asymmetric Synthesis - Lecture 6

Transition metal catalysed asymmetric C-C Bond Forming Reactions

(a) Asymmetric π-Allyl metal complex substitutions

The basic reaction involves oxidative addition of zero-valent palladium (or less commonly, nickel) to an allylic halide or sulfonate, liberating the leaving group and generating cationic π-allyl metal (II) complexes. Attack of a nucleophile (organometallics, enolates, heteroatoms) regenerates the zero-valent metal together with the substituted allyl system. The reaction has useful stereochemical imperatives: initial displacement of the leaving group occurs with inversion of configuration, and subsequent nucleophilic attack on the π-allyl palladium complex can occur with either inversion (soft nucleophiles; generally those whose conjugate acid has pK_a 15-20) or retention of configuration (hard nucleophiles). The former are the most useful from the point of view of asymmetric synthesis.

Because the nucleophile approaches the π-allyl complex from the *exo*-face, away from the palladium (and hence ligands), not surprisingly only limited success is observed when chiral phosphine ligands are used – they just can't reach far enough to be an effective influence. Three strategies have been used to overcome this. Firstly, ligands have been synthesised which incorporate long, flexible, heteroatom containing arms which can reach to the *exo*-face of the π-allyl complex and guide the incoming nucleophile. A second, more elegant solution is to use electronically different coordinating groups in a single bidentate ligand. Thus, mixed phosphorus/nitrogen ligands are of use, since the nucleophile always attacks the carbon *trans* to the π-accepting phosphorus group: the control of stereochemistry then comes down to controlling the 'up' and 'down' conformations of the coordinated π-allyl ligands. Thirdly, ligands with large bite angles (which move the substituents on phosphorus closer to the π-allyl complex) can be effective sterically demanding ligands. These are the ligands of choice certainly for cyclic systems.

These reactions are very practical and much used in the preparation of building blocks for pharmaceuticals and natural products, largely because the ligands are simple and cheap to make and the reactions are very reliable and robust.

(b) Asymmetric Heck reactions

Heck reactions involve the addition of R-Pd-X (formed by oxidative addition of Pd(0) into R-X where R is aromatic or vinyl and X is halide or triflate) across an olefin, followed by reductive *syn*-elimination of H-Pd-X to regenerate an olefin. This can give rise to asymmetric centres when the addition is performed to cyclic olefins or so as to form quaternary centres - in both cases the lack of a *syn*-hydrogen forces olefin formation away from the site of reaction. Pd-BINAP and Pd-phosphinyloxazoline complexes have been used effectively in this context - note that the choice of X-function and reaction conditions are both critical to the sense of asymmetric induction!

(c) Asymmetric olefin metathesis

Olefin metathesis is one of THE reactions of contemporary times. Just open a journal and see if you can find one without a metathesis paper or step in it! Asymmetric variants of the catalyst have been introduced and the reactions can be run in resolution or desymmetrisation mode. Most interesting of all are tandem ring-opening/ring-closing or tandem cross/ring-opening/ring-closing reactions - these can give rise to huge increases in molecular complexity in a single step. The original chiral catalysts were quite sensitive to air/moisture and can be tricky to prepare, but recent progress has been made in the development of air stable, more "user friendly" catalysts.

AA 20/02/03

Catalytic Asymmetric Synthesis - Lecture 7

Asymmetric Catalysis by Lewis Acids and Amines

(a) Lewis acid catalysis

Lewis acids are electron deficient species which can accept a lone pair from a suitable donor (Lewis base), thereby imparting a positive charge to the Lewis base. Therefore this is going to accelerate any reaction requiring electron deficient species as electrophiles, or species with low lying LUMOs. There are many many types of reaction that can be catalysed by Lewis acids (*e.g.* important C-C bond forming processes like Diels-Alder cycloadditions, aldol reactions, ene reactions.)

For high selectivity, it is necessary to control the orientation of the Lewis acid relative to the carbonyl it is activating. One of the most generally successful strategies is to use substrates capable of bidentate coordination, along with Lewis acids derived from chiral bisoxazoline copper (II) complexes. We will see examples of this approach used in Diels-Alder, hetero-Diels-Alder, and ene reactions.

Many Lewis acid catalysed reactions without bidentate coordination are remarkably selective. Corey has recently put forward a rationale for some of them in terms of another organising principle: the H-bonding interactions between the formyl C-H and heteroatoms on the Lewis acid.

(b) Amine catalysed reactions

Although examples of amine-catalysed asymmetric reactions have been known for some time (*e.g.* catalysis of the aldol reaction by proline), dramatic advances have been made in this area in very recent years. Most notably, MacMillan has reported the use of novel amine catalysts which effect "LUMO lowering", mimicking the effect of Lewis acids. They work by reversible formation of iminium intermediates. This strategy has allowed effective asymmetric Diels-Alder reactions. These D-A reactions take place at ambient temperature in aqueous solution - in contrast to the low temps and strictly anhydrous conditions needed with most Lewis acids. The use of organic catalysts can also have advantages in terms of product purification (potentially toxic metals are absent).

Interestingly, reactions that are not amenable to Lewis acid catalysis can be accomplished using this approach - for example, 1,3-dipolar cycloaddition of nitrones to unsaturated carbonyl compounds is retarded by Lewis acids due to competing complexation of the Lewis acid to the nitrone. Using the amine-catalysed approach, this reaction can be performed successfully.

Benzylic stereocentres are present in many important natural products and drug candidates. Recently, MacMillan has shown that the same type of amine catalyst will promote Friedel-Crafts alkylation of pyrroles as well as anilines. In the latter reaction, the amino group of the aniline ring can be removed, allowing anilines to act as benzene surrogates.

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