I. Case Studies in Catalysis

Unfortunately, the rational design of catalysts is largely elusive and the process is based mostly on luck. The development of new catalysts is an iterative process. Metal ligand complexes are formed and screened to determine their enantioselectivity and efficiency. Upon identification of trends, newer generations of ligands and catalysts are prepared and screened again.

Because the success of catalyst development is dependent on the ability to quickly and easily prepare diverse libraries of chiral catalysts/ligands, the realization of this is the greatest challenge. 


1.1 Isicom, a drug for the treatment of Parkinson’s disease, is a drug combination of L-dopa and L-carbidopa

A group of researchers led by William S. Knowles at Monsanto realized that the chiral amine could be prepared by hydrogenation with a chiral catalyst.

1.2 Chiral Phosphane Ligands

Wilkinson’s catalyst had been commonly applied in the hydrogenation of alkenes.


Knowles recognized that the replacement of the (Ph)₃P ligands with chiral phosphines would produce a chiral catalyst. Around the same time, new methods for the resolution of tertiary phosphines were also developed.
The researchers prepared a chiral phosphine and incorporated this into a catalyst of the structure \( \text{RhClL}_3 \) where the \( L = (R)\)- or \( (S)\)-methyl propyl phenyl phosphine. They used this first catalyst to catalyze the hydrogenation of \( \alpha \)-phenylacrylic acid. The 15 % e.e. obtained proved the hypothesis that such asymmetric hydrogenations were possible.

\[
\begin{align*}
\text{RhClL}_3 & \quad \text{H}_2 \\
\rightarrow & \quad \text{OH} \\
\end{align*}
\]

\[ L = \text{P}-\text{CH}_3 \quad \text{C}_6\text{H}_5 \]

1.3 Ligand Screening and Optimization

The researchers conducted a mechanistic study that revealed that only two ligands would be needed on the catalyst. The catalyst was generated in situ by mixing a a Rhodium(I)-diene complex of the type \([\text{Rh}(1,5\text{-hexadiene})\text{Cl}_2] \) with two chiral ligands and prehydrogenating for 5 min at 1 atm hydrogen.

A number of new catalysts were thus prepared. Chirality on the alkyl side chains of the phosphorous showed undetectable changes to the e.e of the products so chiral phosphines rather than a chiral backbone were prepared. A model screening process was established with a simple phenylalanine derivative as the test reaction. In order to obtain the ee, they compared the optical rotation of the total mixture to that of a blank made with the authentic acylated amino acid in order to factor for the workup enrichment.

The researchers then changed the aromatic group to an anisyl group, a possible hydrogen bonding site as well as a more hindered group. Toggling the position of the methoxy functionality eventually yielded a high e.e. of 88 % after optimizing the reaction conditions. The most active catalyst was named CAMP. The reaction conditions and substrates were optimized.
1.4 L-Dopa Synthesis
After the discovery of CAMP, the focus moved from catalyst screening to the development of a commercial synthesis of L-Dopa using this methodology. At the time, CAMP was a state of the art ligand. An improved synthesis was developed.

Soon after this synthesis was commercialized and optimized, a newer type of ligand called DIOP was discovered by Kagan et al.


- This chelating bisphosphane ligand with chirality on the backbone of the gave similar results to CAMP disproving the previous hypothesis that chirality had to reside on the phosphorous in order to effect an asymmetric hydrogenation. As a result, a new chelating ligand called DIPAMP was prepared that worked in 95 % ee on the L-Dopa system.
- The synthesis of DIPAMP, a stable solid, is simpler than CAMP, but still requires a multistep route and is quite expensive. This ligand was therefore applied to the commercial synthesis of the drug.

1.5 Conclusion
The development of chiral phosphine ligands and their application to the asymmetric hydrogenation of enamides was developed through a ligand screening and optimization process. The researchers were able to optimize their results from 28 % ee to 88 % ee, and later to 95 % ee. William S. Knowles would later be awarded the Nobel Prize in chemistry in 2001, along with Ryoji Noyori and K. Barry Sharpless for the development of catalytic asymmetric synthesis.

Knowles Chem. Commun., 1972, 10

2. Case Study II – Merck Synthesis of Januvia
2.1 Sitagliptin/Januvia is Merck’s popular drug for the treatment of type 2 diabetes. It generated 1.9 billion dollars in sales in 2009.

Hansen JACS 2009 131, 8798
The efficient synthesis of Januvia begins with a three step sequence to an enamine intermediate.

The final crucial step is the asymmetric hydrogenation of this intermediate utilizing a rhodium based chiral catalyst. Only the hydrogenation of N-acyl enamines had been documented in the literature. It was necessary to design and screen new ligands for an efficient hydrogenation of this enamine.

2.2 Catalyst Screen

Round I

The study began with a small focused screen of commercially available chiral bisphosphines. Ir, Ru and Rh metal precursors were used because of their efficiency in other asymmetric hydrogenations. A high catalyst loading was used for the initial screen before optimization. The trends observed in the screen are shown.

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2.3 Catalyst Screen Round II

A larger comprehensive screen of ligands was conducted. Cheaper Rh(COD)Cl₂ dimer was used as a precursor instead of [Rh(COD)_2]OTf. Several ligand classes catalyze the reaction with good yield and enantioselectivity. Ultimately, the researchers chose [Rh(COD)Cl₂-tBu-JOSIPHOS as their model after a comparison of the yields, enantioselectivity and rate of the other systems. The ligand and metal precursor are air-stable solids that can be stored for prolonged periods. The active catalyst is generated in situ by mixing the two solids in degassed reaction solvent.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>ee (%)</th>
<th>Ligand</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPh₂</td>
<td>97 %ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPh₂</td>
<td></td>
<td>Fe</td>
<td>98% ee</td>
</tr>
<tr>
<td>PPh₂</td>
<td></td>
<td>PtBu₂</td>
<td>95% ee</td>
</tr>
<tr>
<td>PCy₂</td>
<td>97 %ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pr(p-tol)₂</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(Ph)₃</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.4 Optimization of Reaction Conditions

Catalyst performance was still below standards of practical utility. A hydrogenation with deuterium was conducted to understand the reaction mechanism.

A number of reaction parameters were changed.

**Solvent:** A kinetic study was conducted using in situ FT-IR technology to optimize the reaction rate by minimizing the effects of product inhibition over time. The reaction was thus conducted as a slurry in MeOH, in which the starting material is more soluble.

**Additive:** Consistent ee and conversion rate were realized upon the addition of 0.15-0.3 mol % of NH₄Cl.

**Temperature:** At 50 °C ee is. At 70 °C the ee is decreased to 90 % and side reactions such as elimination of ammonia.

**Catalyst loading:** Decreased from 0.3 mol % to 0.15 mol %.

**Pressure:** Increased to 250 psig
2.5 Conclusion
A robust and cost effective asymmetric hydrogenation was developed on a manufacturing scale. The reaction proceeds in the presence of NH$_4$Cl (0.15 mol %), catalyzed by [Rh(COD)Cl]$\text{$_2$}$ (0.15 mol %), and tBu JOSIPHOS (0.155 mol %) in MeOH under 250 psig of hydrogen at 50 °C for 16-18 h in 98 % and 95 % ee.

Merck Synthesis of Januvia using Transaminases
Transaminases are a type of enzyme that have been known to catalyze the hydrogenation of enamines. Researchers at Merck developed a system to synthesize Januvia using reactions of this class. 11 rounds of evolution conducted yielded an active transaminase enzyme with high activity, tolerance and >99.9% e.e. Final catalyst contained 27 mutations, 10 of which were predicted by computational studies to be required. Converted 200g/L of prositagliptin ketone to sitagliptin of >99.95% e.e. with 53 % higher productivity and 19 % less waste than the original conditions.

II. General Methods of Catalyst Screening and Optimization
In screening and optimizing reactions for practical utility the enantiomeric excess, yield, rate, catalyst turnover frequency (TOF), turn over number (TON), cost effectiveness and environmental impact are considered. Optimal reaction conditions are determined in order to ensure that the screen reflects the best results possible.

1. Catalyst Optimization

1.1 Temperature
Reaction temperature, enantiomeric ratio and enantiomeric excess are related. $\Delta\Delta G^\ddagger=RT\ln(k_{rel})$ where $k_{rel}$ is the enantiomeric ratio and $\Delta\Delta G^\ddagger$ is the difference in transition state energies. Energy difference in diastereomeric pathways allows changes in temperature to be used to increase the ee.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>92%</td>
</tr>
<tr>
<td>0</td>
<td>93%</td>
</tr>
<tr>
<td>-20</td>
<td>95%</td>
</tr>
<tr>
<td>-50</td>
<td>97%</td>
</tr>
<tr>
<td>-78</td>
<td>99%</td>
</tr>
</tbody>
</table>

Evans JACS 1999 121, 686

1.2.2 Solvent
Solvents have the potential to behave as ligands, participate in hydrogen bonding, shuttle reactive intermediates and therefore change the ee. As there are no general rules, a solvent screen must be conducted.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>81</td>
<td>0</td>
</tr>
<tr>
<td>CH$_3$NO$_2$</td>
<td>94</td>
<td>88</td>
</tr>
</tbody>
</table>

Jaquith Organometallics 1995, 14, 1079
1.2 Concentration and Pressure
The concentration does not usually drastically affect the enantioselectivity of a reaction, although sometimes lower concentrations may reduce the enantioinduction through competition with background reactions. For practical utility, it is best to optimize for higher concentrations. There is no general relationship between pressure and enantioinduction.

2. Catalyst Screening Methods
Rapid determination of ee is frequently hampered by the availability of a suitable chiral assay. Relatively few general methods for high-throughput screening of catalysts have been devised. Ideal screening methods should require little to no workup of the reaction, a systematic method of assaying effectiveness.

2.1 Chromatography
Chromatographic methods such as HPLC, SFC, GC are commonly used in catalyst screening processes. A disadvantage is the laborious development of chiral HPLC and GC assays.

For example, a library of chiral triazolium organocatalysts was screened in a γ-lactam forming reaction. The ee, relative d.r and relative conversion were directly assayed by injecting reaction mixtures onto a chiral column on supercritical fluid chromatography.

2.2 Capillary Electrophoresis
Electrophoresis can separate charged enantiomers under the influence of an external electric field. This is possible through the use of a chiral polymer or appropriate chiral selectors as part of the electrolyte. In capillary array electro-phoresis a high number of capillaries are operated in a parallel manner so that separations can be performed automatically with high-throughput.

Reetz ACIE 2000, 39, 3891

2.3 Fluorescent Probes
Assays can be developed with chromogenic or fluorogenic substrates. The assay couples product formation to the release of a fluorescent signal. Pronounced differences in color enable rapid identification and determination of absolute configuration. HELIXOL, for example, is a fluorescent sensor for chiral amines and amino alcohols that is selectively quenched by a single enantiomer.


2.4 IR
Infrared Thermography has been used to screen substrate specificity of enzyme catalyzed reactions. Thermal imaging of a reaction measured the enantioselectivity due to the differential heat generated by the R or S enantiomers. The method is not yet been widely applied.

Mahmoudian OPRD, 2002, 6, 463

2.5 Optical Rotation
In the Monsanto synthesis of L-Dopa, the enantioselectivity of each reaction mixture were directly assayed by dilution and measurement of optical rotation.

Knowles Chem. Commun. 1968, 1445
2.6 Chiral Shift NMR
If a transient diastereomeric complex is formed in solution it can be used to detect and quantify chiral molecules.

2.7 Mass Spectrometry
Assay is based on the use of isotopically labeled substrates in the form of pseudo-enantiomers or pseudo-prochiral compounds.

Pfaltz Angew Chem Int Ed 2004, 43, 2496; Chen Angew Chem Int Ed 2003, 42, 2832

The power of this method lies in the simultaneous screening of various catalysts and the direct analysis of the catalyst intermediates by means of their different m/z values.

2.8 Circuar Dichroism.
Chiral catalysts can be screened on a nonchiral HPLC column using a detection system based on circular dichroism (CD). Continuous monitoring of stationary phases allows the simultaneous monitoring of the CD signal, $\Delta \varepsilon$. Where $\varepsilon$ is the absorption

Disymmetry Factor, $g = \frac{\Delta \varepsilon}{\varepsilon}$

$g$ is independent of concentration and linearly related to ee. So, ee of products can be determined within minutes without separation of the enantiomeric products.
The method has been applied to the screen of asymmetric activation of chiral diol-zinc catalysts by chiral nitrogen activators for the enantioselective addition of diethylzinc to aldehydes.

Mikami *ACIE*, 1999, 38, 497

2.9. Computational Methods.

Because catalyst efficiency is governed by the subtle interplay of steric and electronic effects, it is hard to predict computationally. However, there are examples of computational predictions aiding in the discovery of new catalysts. Sigman et. al have used three dimensional free energy relationships to correlate steric and electronic effects of varying the functionality in a given ligand and therefore derive a mathematical model. They have been able to design and optimize a ligand class which was screened for enantioselectivity in a Nozaki-Hiyama-Kishi propargylation of ketones.

Sigman *Science* 2011, 333, 605

III Various Ligand Classes

For catalysts, the choice of ligands and metals are both important. To achieve good selectivity and reactivity, a wide range of ligands needs to be screened. However, complicated ligand structures usually require multiple synthetic steps, and it greatly limits their application. Therefore, the idea of ligand design is to have structures that can be easily synthesized and modified.

1. BINOL

In these catalytic reactions the racemic substrates have different binding affinities to the enatio-resolved catalyst. Theoretically, two different diastereomeric transition states can be formed. In order to achieve good selectivity, only one of them is greatly preferred. However, because of the flexible nature of the catalyst, more conformational isomers are usually generated which complicate the final results (*Chem. Rev.* 2005, 105, 857) BINOL is the best known ligand possessing a C2 symmetry.

The high energy barrier of substituted binaphthyl ranges from 24 kcal/mol to 46 kcal/mol

*JOC, 2003, 68, 5677*
1.1 Synthesis

Synthesis of BINOL by oxidative coupling of 2-naphthol is well known.

\[
\text{FeCl}_3 \rightarrow \begin{array}{c}
\text{2-naphthol} \\
\text{BINOL}
\end{array}
\]

Toda JOC 1989, 54, 3007

Two major approaches for chiral BINOL:

(a) Enzymatic resolution

\[
\text{C. sinensis cell culture, pH 5.4} \rightarrow \begin{array}{c}
\text{2-naphthol} \\
\text{BINOL, 47% yield, 59% ee}
\end{array}
\]

Takemoto TL 2002, 43, 8499

(b) Chemical resolution

\[
\begin{array}{c}
\text{precipitate, 95% yield, >99.8 ee} \\
\text{Solution, 99% yield, 99% ee}
\end{array}
\]

Cai TL, 1995, 36, 7991

A direct way to obtain enantiopure BINOL is the oxidative coupling of 2-naphthol with chiral catalysts.

\[
\text{Cu(II)(NO}_3)_2 \cdot \text{H}_2 \text{O, MeOH, 20°C, NH}_2 \text{Me, H}_2 \text{O, 8 equiv.} \rightarrow \begin{array}{c}
\text{BINOL, 94% yield, 96% ee}
\end{array}
\]

Nuss Tetrahedron 1985, 41, 3313

1.2 Substituted BINOLs

The 3,3'-substituted BINOL ligand substituted with both Lewis acid and base moieties creating a bifunctional catalyst.

1.3 Heterobimetallic compounds

Heterobimetallic asymmetric catalysts mimic the behavior of metal-ion co-catalysis in enzymes. They attain their selectivity with synergistic cooperation between two different metals and chiral templates.
Application in total synthesis of Epothilone A

2. Phosphoramidites

The confined structures of bidentate ligand catalysts allow facile prediction of stereochemical outcomes easier. Therefore they prevalent asymmetric catalysis for a long time. However, a new class of monodentate phosphorus ligands has emerged and complemented this area.

Feringa ACIE, 2010, 49, 2486

Three new classes of chiral monodentate phosphorus ligands

2.1 Synthesis

2.2 Catalyst screening

The simple synthesis of phosphoramidites makes it possible to use combinatorial method to generate a
2.3 Mixtures of monodentate ligands

Instead of single ligand, one could mix two different ligands that would provide a different chemical environment for the substrates.

<table>
<thead>
<tr>
<th>Number of ligands (n)</th>
<th>(\frac{(n(n+1))}{2}) Heterocombinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>190</td>
</tr>
<tr>
<td>50</td>
<td>1225</td>
</tr>
<tr>
<td>100</td>
<td>4950</td>
</tr>
<tr>
<td>150</td>
<td>11175</td>
</tr>
<tr>
<td>200</td>
<td>19900</td>
</tr>
<tr>
<td>500</td>
<td>124750</td>
</tr>
</tbody>
</table>

An example of a dramatic selectivity improvement by mixing ligands

\[
\text{(R)-1}/(R)-1: 76.6\% \text{ ee} \\
\text{(R)-2}/(R)-2: 13.2\% \text{ ee} \\
\text{(R)-1}/(R)-2: 96.1\% \text{ ee}
\]

3 Nonsymmetrical P,N-ligands

Although C₂ symmetry ligands are in wide use, there is no fundamental theory that C₂ symmetry ligands work better than the corresponding nonsymmetrical ones.
Further desymmetrization of the ligands, e.g. using a P,N-ligand with both $\pi$-acceptor and $\sigma$-donor characteristics provides more diversity. Pfaltz, Helmchen, and Williams independently introduced the phosphinooxazoline (PHOX) ligands.

Enantioselective hydrogenation of tri-substituted unfunctionalized olefins is one application of PHOX ligands.

3.1 Synthesis

Their straightforward synthesis and modular structural nature make PHOX ligands useful in screenings.

4. Peptide

Scientists are amazed by the extraordinary stereoselectivity and substrate selectivity by enzymatic reactions in nature. The tertiary enzyme structure generates a delicate chiral environment. Specific amino acid residues are brought close in space to achieve catalysis. However, the size of a protein makes their de novo chemical synthesis nearly impossible. In contrast, peptides are also constituted by amino acids and are much smaller than proteins. Easy synthesis from cheap starting materials make peptides good catalysts.

4.1 Rational design

Miller’s group uses the strategy of incorporating one of the reactants into the peptide catalyst. The functionalities on the peptide catalyst can interact with other reactants and direct the reaction selectivity.

Below two diastereromeric transition states are shown. To achieve good selectivity, one of them should be strongly favored over the other.
4.2 Synthesis

Small peptides are synthesized by a well-established solid phase peptide synthesis. Nowadays, automated synthesis quickens the process. Because of the modular nature of peptides, it is very easy to fine-tune the reactivity and selectivity by simply replacing specific amino acid residues.

A rational design of a high throughput peptide catalyst library:
Instead of synthesizing all possible 8000 compounds (Schiff base, amino acid 1 and amino acid 2), only 60 of them necessary to be generated to obtain good selectivity.

A similar approach is by Jacobsen, JACS, 1998, 120, 4901

4.3 On-bead high throughput screening method

Polymer-supported catalysts provide a lot of operational advantage. The Wennemers group has developed a method to quickly identify the active polymer-supported catalyst.

Wennemers ACIE, 2003, 42, 1722 & OL, 2005, 7, 1101

4.4 Secondary structure

For highly functional substrates, it is difficult to achieve site-specific chemical transformation. However, in nature enzyme reactions are usually highly regio- and stereoselective. The secondary structure of the enzyme plays an important role in their extremely high selectivity, but it also means that their substrate scope is very limited. Peptides with only a few amino acids also adopt a secondary structure and their ability to be modified with ease make them ideal in this case.
Erythromycin A, a challenging target for site-selective functionalization was explored by the Miller group.

Miller *ACIE*, 2006, 45, 5616

5. Salen ligands
5.1 Salen ligands are class of schiff base ligand that is synthetically accessible from the condensation of salicylaldehyde and amine. The reaction often proceeds in quantitative yield. The ligands form complexes with first row and second row transition metals and main group metals.

5.2 Metal salen complexes form privileged chiral catalysts and catalyze several reactions well, including epoxidations and epoxide ring openings, carbonyl additions, imine cyanations, conjugate additions, cycloadditions and kinetic resolutions. The most common structures of typical salen complexes are:

5.3 Examples of salen complex catalyzed reactions:
Kinetic Resolution/ Epoxide and Asymmetric Epoxidation

Jacobsen *Topics Organomet Chem* 2004, 6, 123
6. Bisoxazoline (BOX) ligands

6.1 BOX ligands are chiral ligands based on a bis-oxazoline core. They were originally inspired by the ligand framework of vitamin B12. The C2 symmetric axis in the ligands minimizes the number of possible transition states in a reaction, constraining the metal chelate and increasing the enantioselectivity of the reactions.

![PyBOX](image1)

PhBOX : $R=Ph, R'=H, R''=Me$

$tBuBOX: R=tBu, R'=H, R''=Me$

$R=Ph, R'=Ph, R''=Me$

$R=Ph, R'_1=H, R''=Me$

$R=CH_2Ph, R'_1=H, R''=Me$

$R=Pr, R'_1=H, R''=Me$

$R=CH_2OH, R'_1=H, R''=Me$

Jorgensen *Chem. Rev.* 2006 106, 3561

6.2 Synthesis

Many BOX ligands are commercially available, but a number of syntheses of are outlined below. The chiral centers of the ligands can be derived from commercially available chiral amino acids or amino alcohols.

![Chemical structures](image2)

Nishiyama *Organometallics* 1991, 10, 500 & Davies *JOC*, 1996, 61, 9629


It is useful to begin with malonitrile where constrained ligands are being prepared.

![Chemical structures](image3)

Davies, *TL*, 1996, 37, 813
Should the spacer between the oxazoline rings require more than methyl groups, a dianion may be formed with two equivalents of NaH or BuLi and substituted nucleophilically with the desired alkyl halide. The chiral groups on the oxazoline rings may be manipulated to introduce heteroatoms that increase coordination of the BOX ligand, or be used to graft the ligand onto a solid surface.

6.3 These ligands either react with metals in situ or form complexes prior to utilization as catalysts by reaction with the metal salt. Monomeric and dimeric complexes may be formed. The metal chelate ring size also changes the outcome of the reaction. BOX- metal complexes have been applied for catalytic asymmetric aldol reactions, mannich reactions, olefin aziridination, cyclopropanation, allylic substitution, allylic oxidation, free radical addition and diels alder reactions, mannich reactions, carbonyl additions and conjugate addition reactions.

6.4 Examples of BOX complex catalyzed reactions:

Evans TL, 1997, 38, 57; Evans JACS, 1997 119, 10859; Ma JACS, 2007 129, 9300; Nishiyama JOC 1992, 57, 4306
7. N-heterocyclic carbenes

7.1 N-heterocyclic carbenes (NHCs) such as imidazolylidenes, imidazolinylidenes, benzimidazolylidenes, triazolinylidines, and related carbenes readily complex with high and low oxidation state metals. NHCs are both sigma donor ligands with little back-bonding character but they form stronger bonds with metals (stable complexes). The order of electron donating power goes as follows: benzimidazole< imidazole< imidazoline. Although they are electron rich, these ligands are neutral.

7.2 Synthesis

Imidazole derived carbenes are prepared in a one pot from glyoxal, primary amine and formaldehyde

\[
\text{H}_2\text{CO} + \text{R-NH}_2 + \text{O} + \text{H} \rightarrow \text{R} = \text{N} = \text{NR} + \text{X}^-. \]

Herrmann *Organometallics* 1997, 16, 2472 Arduengo *Tetrahedron* 1999, 55, 14523

Unsymmetrical imidazolium salts can either be prepared from a variation of the previous method:

\[
\text{HN}_2\text{N} \rightarrow \text{K}^+ + \text{K} -1/2 \text{H}_2 \rightarrow \text{HN} = \text{NR} \rightarrow \text{R} = \text{N} = \text{NR}^+ + \text{X}^- \]

Herrmann *CEJ*, 1996, 2, 1627

This newer synthetic route was developed to allow new substitutions, see Furster *Chem. Comm.*, 2006, 2176

Another route, suitable for aryl substituted imidazoliums, involves the conversion of 1,2-diamines by reaction with an orthoformate. The starting materials are easily accessible from Pd-catalyzed amination.

Cyclic thiourea derivatives can be prepared and desulfurized to form such imidazolium salts. The conditions are harsh but work well for specific examples such as benzimidazolin-2- ylidenes.

Carbenes can be prepared in good yields from the vacuum thermolysis of methoxy derivatives, although fewer carbenes are stable to air.

1,4-disubstituted and 1,3,4-trisubstituted triazolium salts are prepared from an alkyl, aryl or acyl hydrazine and a mixed hydrazine to form a bisformyl hydrazine. Upon treatment of this with acid, a cyclization occurs to
7.3 Azolium salts can be converted to metal complexes by adding base and transition metal precursor, or by treating the of the azolium salt with a complex containing basic ligands. Due to their inherent instability, the carbenes are normally formed in situ.

7.4 Some of the several reactions employing NHC’s as ligands are the olefin metathesis and methathesis cross couplings, alkyne coupling, Heck, Suzuki, Sonogashira, Kumada, Stille couplings, C-H activation reactions, hydrogenation and hydroformylations. Examples of NHC-metal catalyzed processes:

8. Chiral P,N-ligands

8.1 The P,N ligands are a successful class. QUINAP and PINAP shown below display unique reactivity and selectivity.

8.2 Synthesis
The challenge in the synthesis of QUINAP is the final resolution of the ligands.
The preparation and resolution of PINAP is much easier.

8.3. P,N-ligands catalyze reactions such as hydroboration, alkyne addition, diboration and azomethine cycloaddition.


Carreira *ACIE*, 2004 43, 5971

Carreira *ACIE*, 2004 43, 5971


Morken *OL*, 2004, 6, 131