Chapter 1 – Introduction

Chirality

The left and the right human hand, converse twisting snake houses or corkstrew stairs appear to be similar to the general audience. But when attempting to superimpose such objects, they cannot be brought into congruence. They are called chiral, an expression that stems from the greek word "χέιρ" (cheir) = hand. The same principle applies in chemistry. Molecules which look the same but are mirror images of each other are called enantiomers (greek: "ενάντιος" (enantios) = opposite). Enantiomers exhibit the same physical properties except their optical rotation which is of opposite orientation. Furthermore, they operate in different ways in a chiral environment, such as the human body and thus exhibit different physiological properties. Many examples of enantiomers with different physiological properties are known and some are shown in Figure 1. An every-day example is the monoterpene carvone (**1**) found in many essential oils. While the (*S*)-enantiomer smells like caraway, the (*R*)-enantiomer tastes like spearmint. Another example is aspargine (**2**), a common amino acid. Whereas the (*S*)-enantiomer tastes bitter, the (*R*)-enantiomer is tastes sweet.[1] More dramatic examples can be found in medicine. The first incident that emphazised the importance of enantiomerically pure drugs was Contergan (Thalidomid) (**3**), where the (*R*)-enantiomer acts as a sedative but the (*S*)-enantiomer is highly teratogenic.

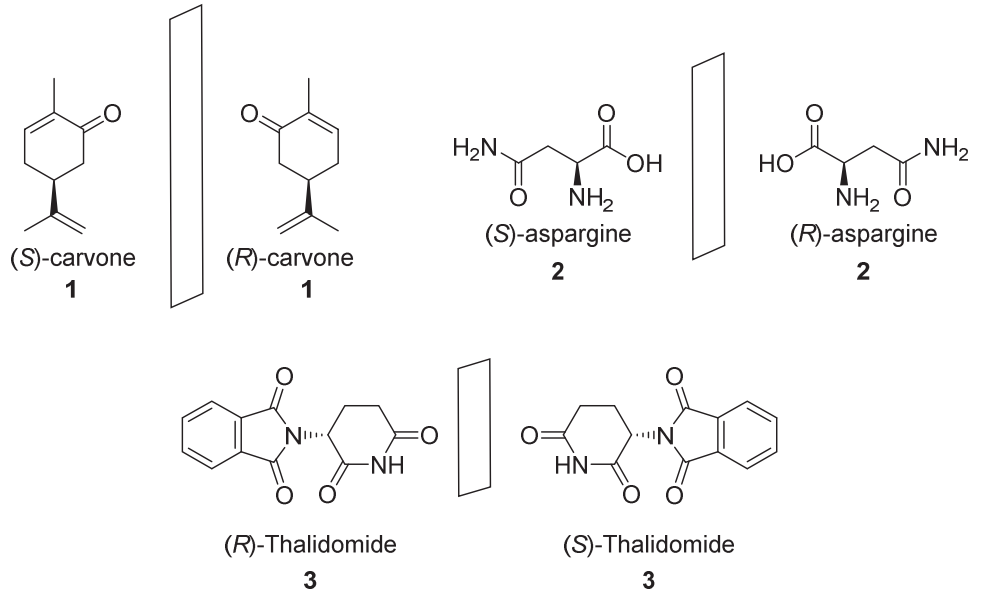


Figure 1: Enantiomers of commonly encountered every-day chemicals

These examples highlight the need for selective preparation of drugs. Therefore chemists have a strong and long-standing interest in the stereoselective synthesis of drugs. Several methods can be used to obtain enantiomerically pure material. Four different approaches have been developed to date:

First of all, application of enantiomerically pure substances isolated from natural resources, which are summarized as the "chiral pool". Examples include amino acids, monosaccharides, terpenes or alkaloids;

Secondly, resolution (racemate separation), which is achieved by addition of an enantiomerically enriched material to afford crystallisation of diastereomerically pure salts or applying separation techniques such as chromatography with chiral stationary phase to afford enantiomer separation. This method can only deliver a maximum of 50% yield.

Thirdly, to overcome the loss of 50% of the material, variations of resolution such as dynamic kinetic resolution, where interconversion of the racemic starting materials is faster than subsequent separation by derivatisation of the material, have been developed. Such procedures are also called DYKAT (dynamic kinetic asymmetric transformation);

Fourthly, enzymatic or microbiological transformations; these are highly selective and efficient processes but often display limited substrate scope. A famous example is the lipase *Candida antarctica* which has been applied in numerous industrial processes;[2]

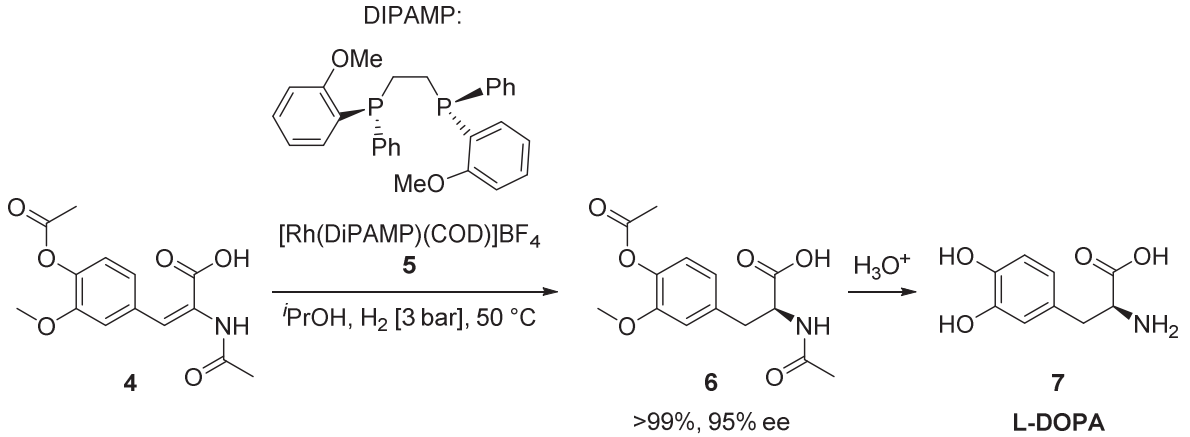
Ultimately, asymmetric synthesis and catalysis; while a reagent based approach has been the main focus in the early days of investigating stereoselective synthesis, in the last three to four decades the use of chiral catalysts has emerged as a very powerful tool for the preparation of enantiomerically pure building blocks.[3]

Asymmetric Synthesis and Catalysis

Asymmetric catalysis can often out-compete other approaches by a number of factors. Artificial catalysts offer a large substrate scope and can also be used in organic solvents in contrary to enzymatic or microbiological catalytic processes. In asymmetric synthesis, auxiliaries need to be removed and disposed of and therefore often require elaborate or cumbersome purification processes. Furthermore, the generation of large amounts of waste displays a major drawback. On the other hand, artificial catalysts can circumvent these issues both in economic as well as ecological terms. As an example, asymmetric hydrogenation offers a number of highly desirable advantages. Perfect atom economy, in that all the atoms the molecules applied in the reaction (hydrogen gas and substrate) are incorporated in the product. Usually, high conversions and high selectivities are obtained with low catalyst loadings, while reactions are conducted under mild conditions, thus offering a large functional group tolerance.

The importance of asymmetric hydrogenation had been rewarded, together with asymmetric oxidation of organic molecules, with the Nobel prize in chemistry in 2001 given to *Knowles*, *Noyori* and *Sharpless*.[1]

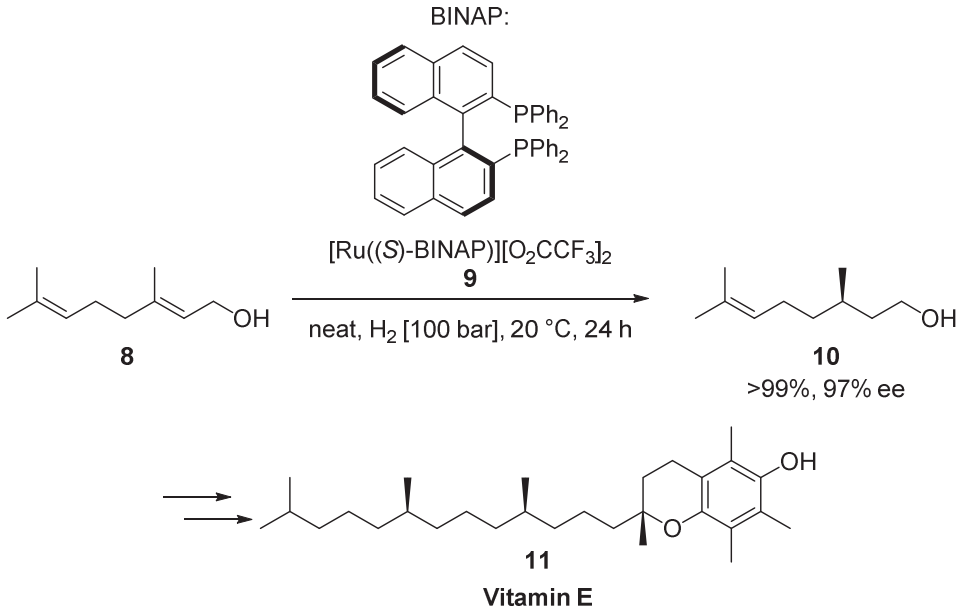
Famous examples of industrial asymmetric hydrogenation processes include L-DOPA (**7**) which has been produced on a one ton scale per year (Scheme 1).[4],[5]



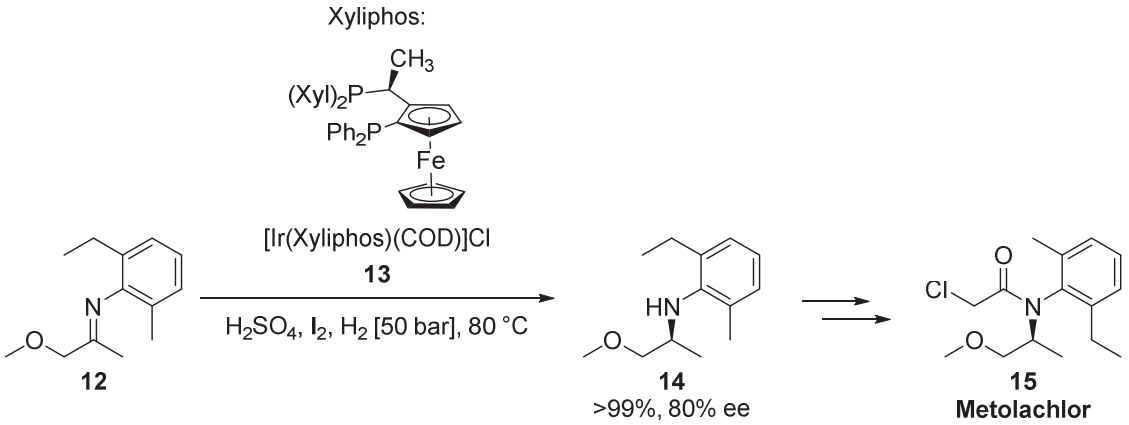
Scheme 1: Industrial rhodium-catalysed asymmetric hydrogenation of enamine **4** in the L-DOPA process

Vitamin E (**11**) (Scheme 2)[6] and Metolachlor (**15**) (Scheme 3)[7] are produced on much larger scale (300 to >10'000 tons per year) and highlight the importance of asymmetric hydrogenation for the chemical industry.

[1] http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2001/press.html

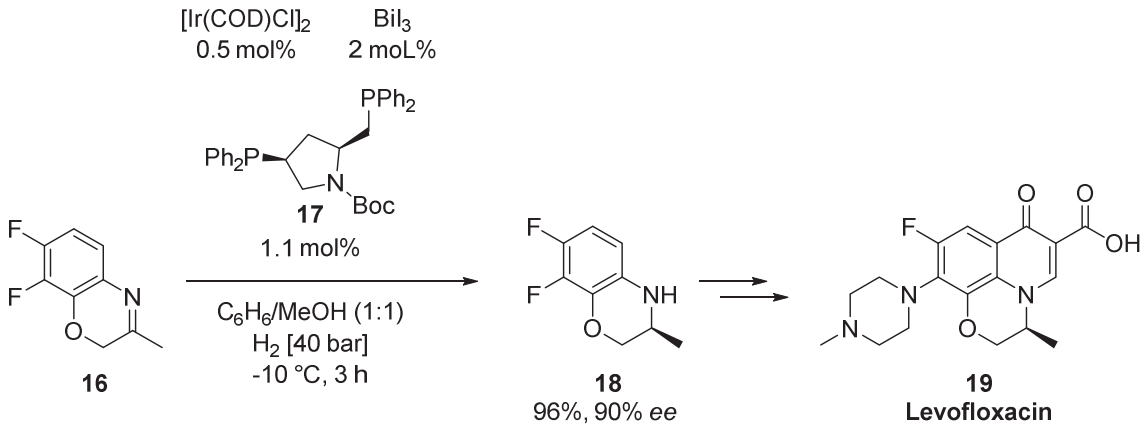


Scheme 2: Industrial ruthenium-catalysed asymmetric hydrogenation of allylic alcohol **8** by *BASF*

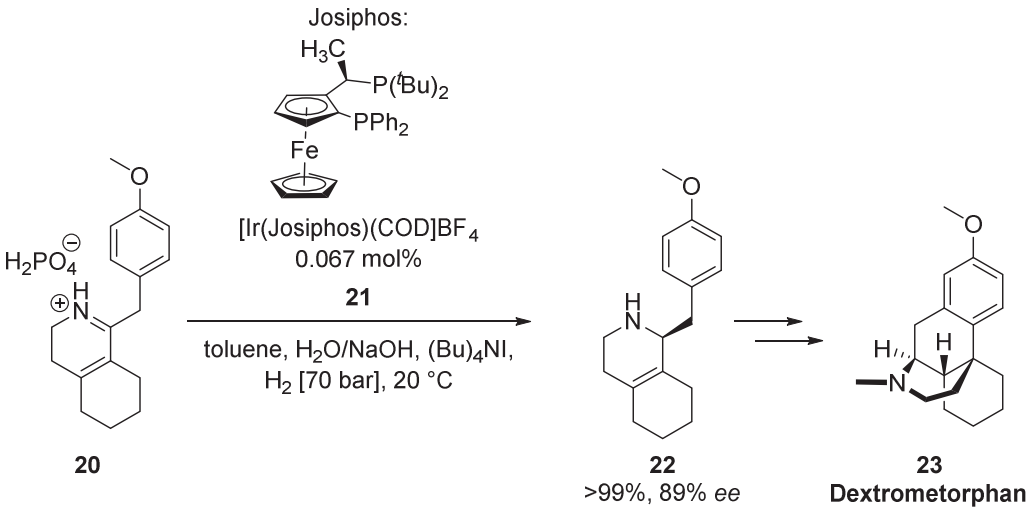


Scheme 3: Industrial iridium-cataysed asymmetric hydrogenation of imine **12** by *Syngenta*

Large scale test reactions have also been conducted in the pharmaceutical industry, such as on levofloxacin[8] (**19**) (Scheme 4) or dextrometorphan[9] (Scheme 5).



Scheme 4: Industrial iridium-catalysed asymmetric hydrogenation of imine **16** by *Daichi Pharmaceuticals*



Scheme 5: Industrial iridium-catalysed asymmetric hydrogenation of imine **20** by *Lonza*

Chiral amines

Chiral amines are ubiquitous in nature. They are found in many natural products as well as in synthetic targets, both drug candidates and agrochemical agents. A selection is given in Figure 2 and Figure 3. Chiral amines can be prepared by plethora of synthetic methods. Before the development of stereoselective synthesis, the only method to isolate enantiomerically pure amines was by recrystallisation with enantiopure carboxylic acids such as tartaric acid or malic acid. A representative example for an industrial synthesis evolving from resolution to asymmetric synthesis is given in the case of Tamsulosin (**27**).[10],[11]

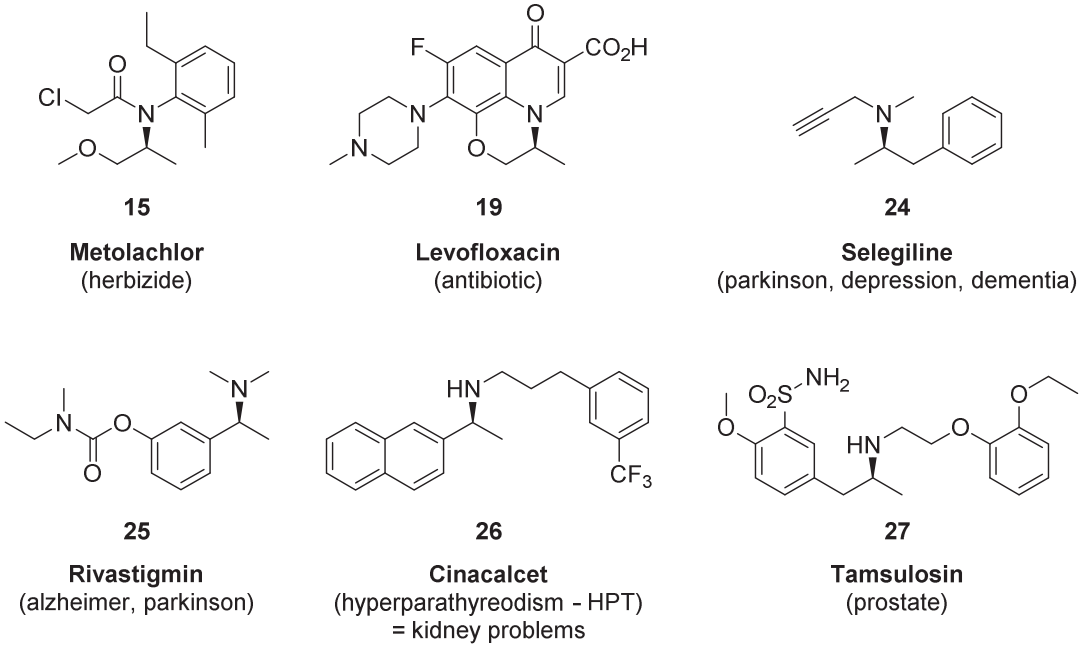


Figure 2: Pharmaceuticals, drug candidates and agrochemicals containing chiral amines

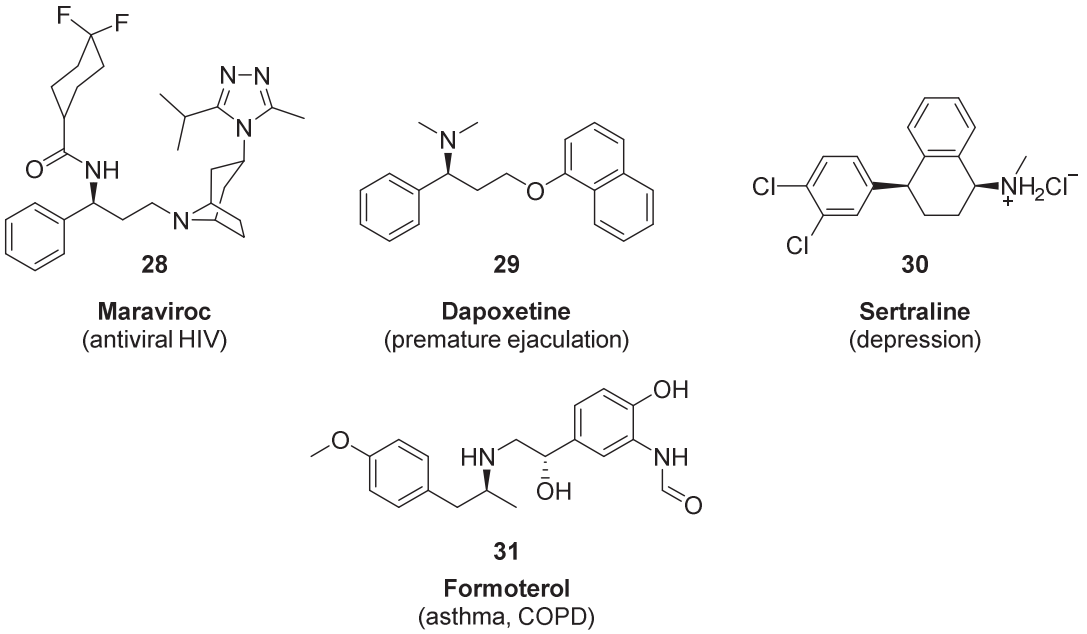
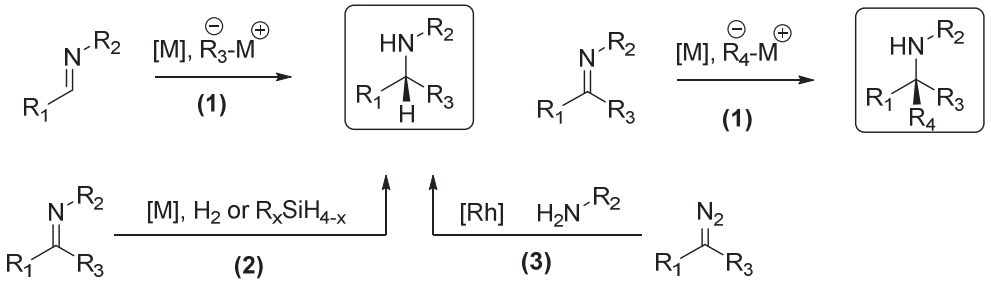


Figure 3: Pharmaceuticals, drug candidates and agrochemicals containing chiral amines

Over the years three main synthetic approaches for the preparation of chiral amines have evolved (Scheme 6). (1) Formation of a carbon-carbon bond by nucleophilic addition of an organometallic reagent to an aldimine or ketimine. (2) Reduction of prochiral imines with a chiral catalyst and a hydrogen source. (3) carbon-nitrogen bond formation by carbene insertion into a N-H bond.



Scheme 6: Synthetic procedures to prepare chiral amines

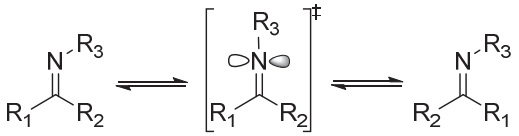
Enantioselective hydrogenation of imines represents the most efficient method out of the three to prepare enantiomerically enriched chiral amines (except for the preparation of quaternary stereogenic centres alpha to an amine). Nevertheless, imine hydrogenation bears a number of challenges:

- C=N double bonds are intrinsically not very reactive and require a Lewis acid to promote nucleophilic attack.
- C=N double bonds are sensitive to hydrolysis, especially under Lewis acidic conditions.
- They exist as anti/syn isomers, as aminals in the presence of amines and as hemiaminals in the presence of alcohols. Imines with an alkyl substituent at the iminoyl carbon can also undergo imine-enamine tautomerisation. Such species interconvert under the reaction conditons.
- The reactivity of a C=N double bond is highly dependent on the nitrogen substituent and thus sometimes limits the substrate scope.
- The product amines are strong ligands and thus may poison and deactivate the catalyst.

The C=N double bond – isomerisation and other phenomena

Many difficulties with reducing imine double bonds are associated with their existence as *E/Z* isomers, imine/enamine tautomerism as well as *E*/*Z* interconversion in solution.

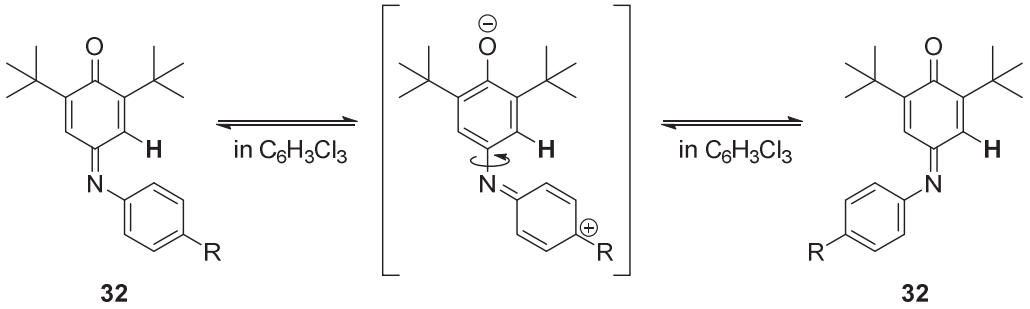
McCarthy and co-workers have investigated the uncatalysed *syn-anti* interconversion of *N*-aryl and *N*-alkyl imines (Scheme 7).[12] For aldimines, energy barriers between 14-20 kcal mol^{-1} were determined for uncatalysed isomerisation in solution (CCl_4). The low barriers were explained by the "lateral shift mechanism", also described as in-plane inversion. This isomerisation mechanism involves a linear transition state, where the nitrogen is adopting an sp-configuration. All the π-bonds in the aromatic system remain intact and the unshared electron pair is occupying the *p*-orbital of the nitrogen in the transition state.



Scheme 7: "Lateral shift mechanism" in the *E/Z* isomerisation of imines

Kessler and co-workers have studied the influence of substituents at the *N*-aryl ring in the thermal isomerisation of chinonaniles **32** (Scheme 8).[13] By determining the coalescence temperature of the proton in capital letter by NMR studies, a clear trend towards facilitated isomerisation by electron-poor chinonaniles was observed (

Table 1). However, the substituent in *para*-position (*e.g.* methoxy) facilitates a rotational mechanism by electron pair migration to a phenoxide zwitterionic structure.



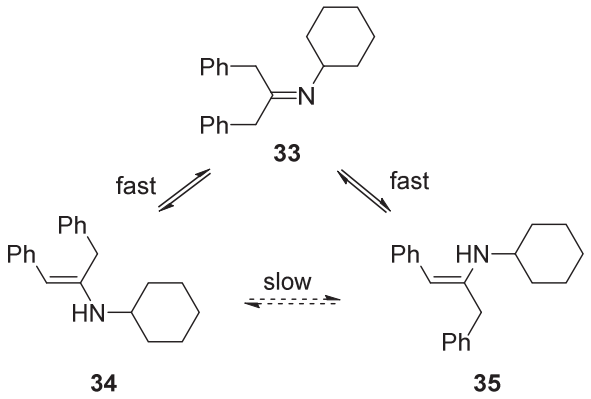
32 **32**

Scheme 8: Thermic isomerisation of chinonaniles **32**

Table 1: Coalescence temperatures of different chinonaniles **32** with electron-withdrawing and –donating substituents

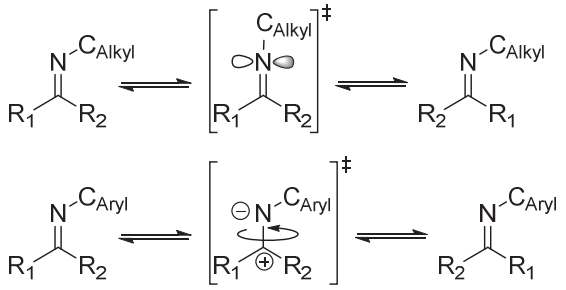
Coalescence T [°C]	152	146	144	144	140	134	125	125	96	90	68
R	OMe	^{t}Bu	$N(Me)_2$	F	H	SMe	Br	I	CO_2Et	C(=O)Me	NO_2

Clark and *Parker* reported on a thermodynamic study of imine-enamine tautomerisation in different solvents (Scheme 9).[14] A clear trend of polar solvents favouring enamine **34** and **35** formation was observed. However, only poor solvent dependence on the *cis*-/*trans*-isomerisation of the enamine tautomers **34** and **35** was observed. This suggested that isomerisation would predominantly proceed *via* the imine tautomer **33**. Studies were conducted in d_6-DMSO, where imine-enamine tautomerisation is clearly favoured over *E*/*Z* interconversion.



Scheme 9: Enamine interconversion of **34** and **35** *via* **33**

Jennings and *Boyd* investigated thermal interconversion on a series of *N*-alkyl ketimines by ^{1}H-NMR coalescence experiments in apolar solution (biphenyl, m.p. 69 °C) (Scheme 10).[15] The ΔG values observed were insensitive to the nature of the iminoyl carbon substituents (e.g. aryl, alkyl or hydrogen). They concluded that thermal *E/Z* interconversion occurred by a mechanism close to pure nitrogen inversion. For an *N*-aryl substituent, the energy of the dipolar (or diradical) transition state to result in rotation around the C=N double bond, would be considerably lowered. This interconversion mechanism was called out-of-plane rotation.



Scheme 10: Imine interconversion processes of nitrogen inversion (C_{Alkyl}) and out-of-plane rotation (C_{Aryl})

Furthermore, a strong solvent dependence on the interconversion mechanism was observed. While *E/Z* interconversion of **36** in diphenyl solution was fast at 200 °C, imine-enamine tautomerisation was slow. However, when **36** was dissolved in trichlorobenzene, *E/Z* interconversion was observed already at 140 °C by coalescence. Additionally the imine and enamine signals collapsed at 200 °C consistent with rapid imine-enamine tautomerisation. A more illustrative example is the rapid imine-enamine tautomerisation of **37** in deuterated methanol. Imine **37** can be crystallized in pure *Z* isomeric form. Once dissolved, the *C*-methyl protons rapidly show concomitant deuterium incorporation. This example demonstrated the dominance of imine/enamine tautomerism over *E/Z* isomerisation in methanol.

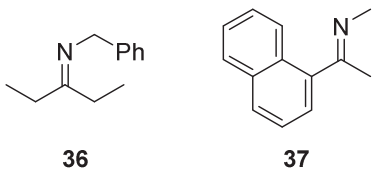
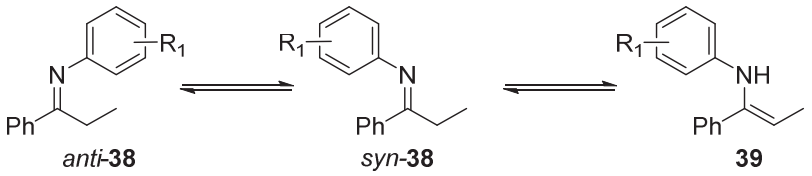


Figure 4: Imines **36** and **37**

Fischer and *Albrecht* investigated *E/Z* imine-enamine equilibria of several *N*-aryl propiophenone-derived imines **38** by NMR spectroscopy with regards to *N*-aryl substituent effects (Scheme 11, Table 2).[16] Only substituents in the *meta*-position of the *N*-aryl ring displayed a clear Hammet dependence. Substituents in the *para*-position of the *N*-aryl ring result in additional stabilizing and destabilizing effects which could not be correlated or described with Hammet coefficients.



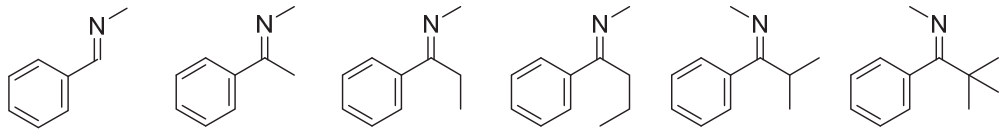
anti-**38** *syn*-**38** **39**

Scheme 11: Imine-enamine tautomerism of **38** to **39**

Table 2: Percentage of enamine **39** observed by ^{1}H-NMR with different substituents at the *N*-Aryl ring on **38**

R_1	% enamine
4-NMe_2	0
4-OPh	2.2
4-OMe	1.6
4-Me	3.0
4-F	2.4
4-Br	5.3
4-Cl	5.7
4-CN	27.5
4-NO_2	38.9
3-Me	4.0
3-OMe	4.1
3-F	7.4
3-Br	7.0
3-NO_2	10.7
H	3.9

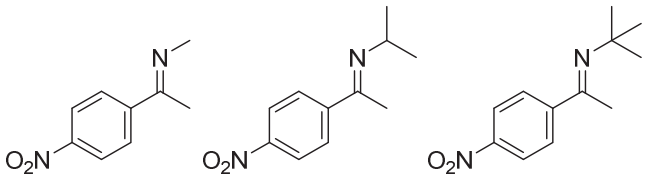
The studies on *E/Z* ketimine isomers by *Jennings* and *Boyd* were extended to investigations of the equilibrium distribution of acyclic *N*-alkyl imines **40** to **45** (Figure 5).[17] Steric factors were investigated by increasing the size of the C_{Alkyl}-substituent and it appeared that the larger the C_{Alkyl}-substituent, the *E*-isomer became more destabilized due to steric repulsion. This also concluded that the steric bulk exhibited by a phenyl group lies in the range of a *n*-propyl and *iso*-propyl group.



40	**41**	**42**	**43**	**44**	**45**
E/Z	*E/Z*	*E/Z*	*E/Z*	*E/Z*	*E/Z*
100:0	93:7	74:26	70:30	5:95	0:100

Figure 5: Investigation of imine-enamine ratio with regards to the C_{Alkyl}-substituent at the iminoyl carbon in **40** to **45**

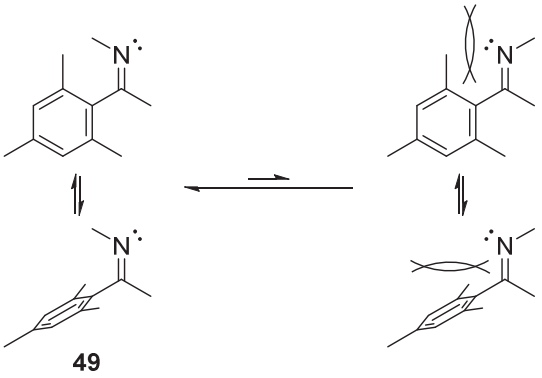
On the other hand, electronic effects appeared to overrule steric repulsion. Three examples of increasing steric bulk around the *N*-alkyl substituent in **46** to **48** did not change the ratio of *E/Z* isomers significantly (Figure 6). The ratio of *E/Z* isomers did not change significantly over a large solvent range either: $CDCl_3$, CCl_4, C_6D_6, $C_6H_3Cl_3$, CD_3CN, $(CD_3)_2CO$ and ^{t}BuOH.



46	**47**	**48**
E/Z	*E/Z*	*E/Z*
97:3	95:5	98:2

Figure 6: Unaffected *E/Z* ratio of imines **46** to **48** with increasing size of the *N*-substituent

Steric repulsion between *ortho*-substituents of imine **49** resulted in formation of the of the *Z* isomer. While steric clash could be prevented by a rotation of the phenyl substitent out of the plane of delocalization, also a destabilizing repulsive interaction between the nitrogen lone pair and the aromatic π-electrons was discussed (Scheme 12).



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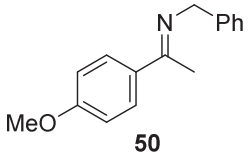
Scheme 12: Favoured formation of the *Z* isomer in **49** due to electronic repulsion of the aryl ring and the nitrogen atom lone pair

James and co-workers investigated the rate of isomerisation of **50** in benzene/MeOH 1:1 at ambient temperature (Figure 7).[18] Isomerisation rates of *Z*=>*E* of 155 h^{-1} and *E*=>*Z* of 11 h^{-1} were determined by EXSY NMR experiments. These values have been obtained with large mixing times of 1.8 seconds. Thus, they need to be considered with care, since accurate numbers can only be obtained with much shorter mixing times. They also investigated the asymmetric hydrogenation of imine **50**. The TOF of their catalyst was determined to be between 14 to 66 h^{-1}. Since the *E/Z* isomer ratio and the rate of isomerisation did not affect the *ee*, it was concluded that the rate of the reaction entirely depended on the diffusion of hydrogen into the solution and not isomerisation. Isomerisation processes catalysed or promoted by the transition metal have not been discussed but may well be considered in such an example.



50

Figure 7: Imine **50**

Kocovsky and co-workers have analysed a number of *N*-aryl imines with aromatic, heteroaromatic and alkyl substituents at both carbons adjacent to iminoyl funtionality (Figure 8). The main configuration of the imine double bond was observed to be *E* with *E/Z* ratios between 10:1 and 7:1. This only holds true as long as one substituent is large (e.g. aryl) and one is small (e.g. methyl) as in **51**. Mixtures are observed when both substituents are sterically demanding, especially in the case of an aryl and a large alkyl substituent as in **52**. Enamines have been observed predominantly in substrates bearing electron withdrawing substituents such CH_2COOEt as in **53**. They postulated the enamine form to be more stable due to a stabilizing hydrogen-

bonding between the N-H proton and the electron-withdrawing group. Equilibration of imines was observed in $CDCl_3$ solution in the case of β-enamino nitriles as **54**. Also, traces of Brønsted acids were shown to facilitate isomerisation.

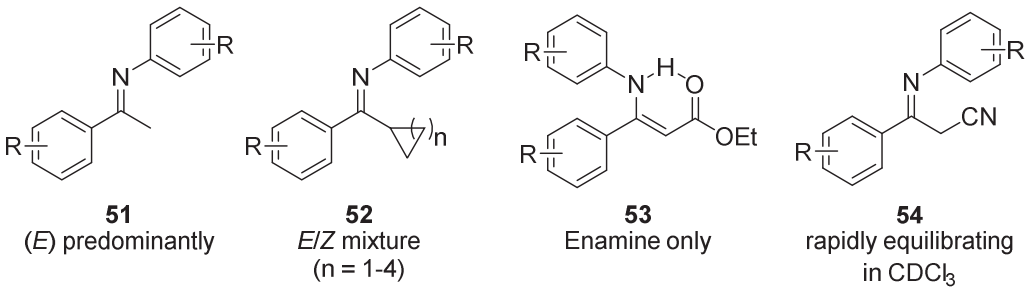
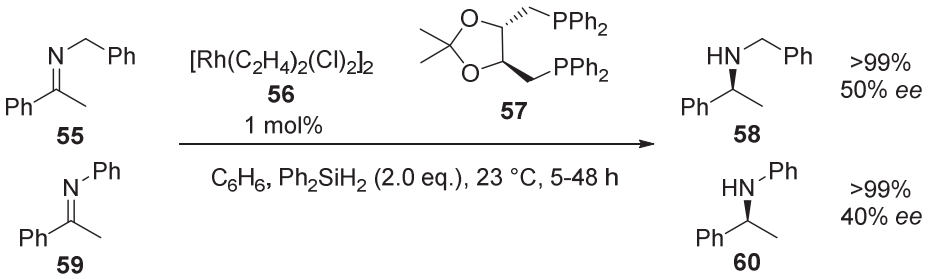


Figure 8: Predominant imine or enamine tautomer of **51** to **54** observed in solution, depending on the substrate structure and substituent

Facilitated isomerisation by Brønsted acids is particularly interesting since iridium hydride species have been demonstrated to be Brønsted acidic. Therefore, *E/Z* ratio of *N*-aryl imines in solution can possibly be ignored due to rapid interconversion in case where *E/Z* isomerisation is faster than hydrogenation, e.g. catalysed by metal coordination or Brønsted acidic hydrides.

Asymmetric Imine Hydrogenation

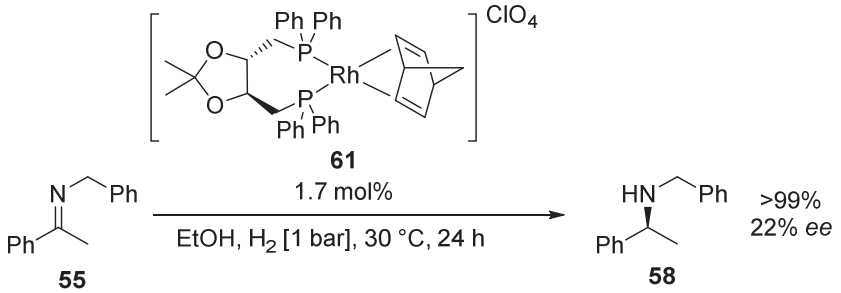
The first approach for the preparation of enantiomerically enriched chiral amines was reported by *Kagan* and co-workers. They developed a hydrosilylation reaction catalysed by rhodium catalyst **56** with ligand **57** and subsequent hydrolysis to afford the chiral amines **58** and **60** (Scheme 13).[19] Rhodium-catalysed hydrosilylation had been developed independently by *Ojima* and co-workers[20] using *Wilkinson's* catalyst and Ph_2SiH_2.[2]



Scheme 13: Asymmetric rhodium-catalysed imine hydrosilylation of **55** and **59**

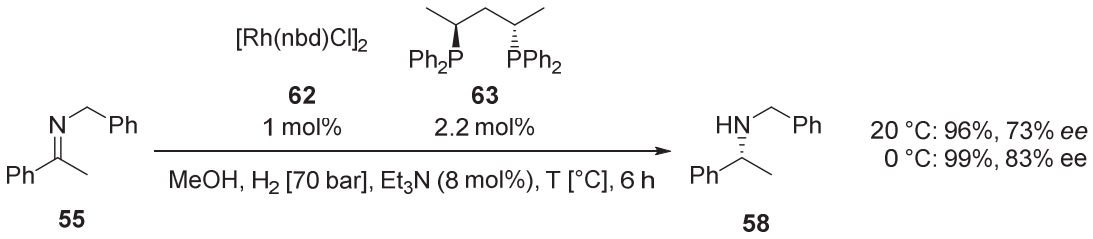
This newly developed protocol for imine hydrosilylation also paved the way for the development of enantioselective hydrogenation of imines. While homogeneous hydrogenation of imines had already been reported by *McQuillin* and co-workers employing a rhodium catalyst $[(Py)_3RhCl_3]$ and sodium borohydride in the presence of hydrogen gas,[21] *Scorrano* and co-workers reported the first example of an asymmetric hydrogenation of an imine (Scheme 14).[22] They generated a rhodium catalyst **61** very similar to the one *Kagan* used in the hydrosilylation of imines.

[2] *Kagan* and co-workers were not aware of this discovery when submitting their work.



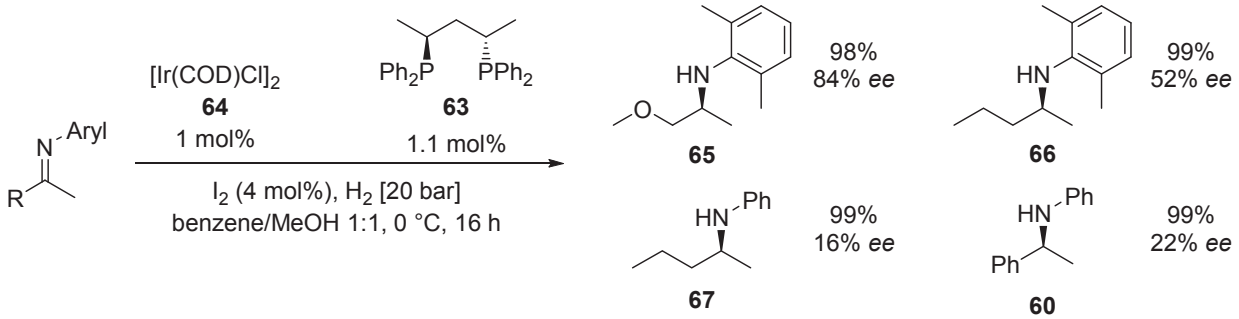
Scheme 14: Asymmetric rhodium-catalysed imine hydrogenation of **55** using **61**

During the next decade, with the development of new chiral phopshorus ligands such as **63**, higher enantioselectivities were achieved. Furthermore, a temperature dependence was noted. Conducting reactions at lower temperature provided higher enantioselectivities while maintaining reactivity. A selected example is given in Scheme 15.[23],[24]



Scheme 15: Improved *ee* in the asymmetric rhodium-catalysed hydrogenation of imine **55** at lower temperature

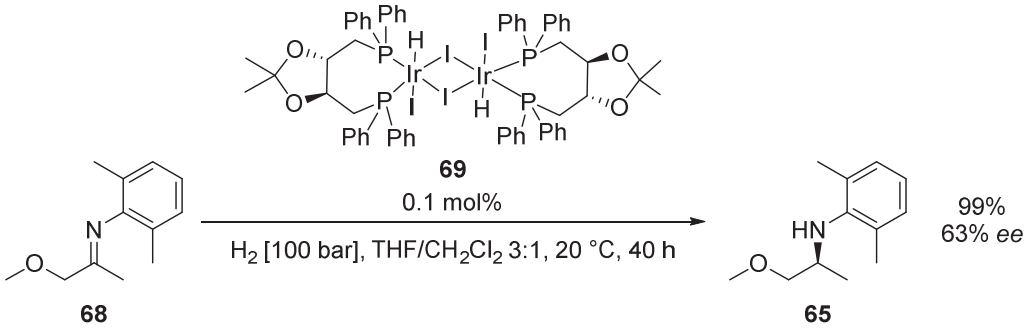
By the time of the late 1980's, asymmetric hydrogenation had been established on C=C, C=O and C=N double bonds with rhodium and ruthenium catalysts. Industrial asymmetric hydrogenations were dominated by rhodium and ruthenium catalysts due to their high efficiencies and extensive studies in the literature. This drastically changed in 1990 when an industrial team of researchers led by *Blaser* and co-workers reported on the first enantioselective hydrogenation of imines using iridium complexes generated from **64** and chiral phosphorus ligands such as **63**. Efforts were devoted to structural analogues **65** and **66** of the potent herbicide Metolachlor (Scheme 16).[25] Further studies led to the currently applied protocol using Xyliphos ligands (Scheme 3).



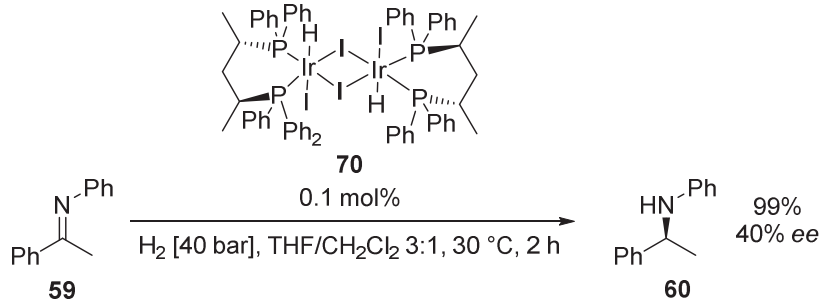
Scheme 16: First example of iridium-catalysed asymmetric imine hydrogenation

Shortly after the discovery of *Blaser*, *Osborn* and co-workers reported similar results on the asymmetric hydrogenation of imines by iridium(III) hydride complexes such as **69** or **70**. Very low catalyst loadings up to 0.1 mol% showed highly efficient asymmetric reduction of imine **68** (Scheme 17) and **59** (Scheme 18) albeit with low to moderate enantioselectivities. The catalyst was optimized for each substrate. The role of iodine was demonstrated to be of critical importance. The complexes were prepared by refluxing $[Ir(I)(P'P)(COD)]BF_4$ in the presence of LiI. The oxidation was postulated to occur due to the presence of

water by an unknown mechanism.[26] Such an oxidation thus probably also occurs *in situ* in the system reported by *Blaser*.[3,27]

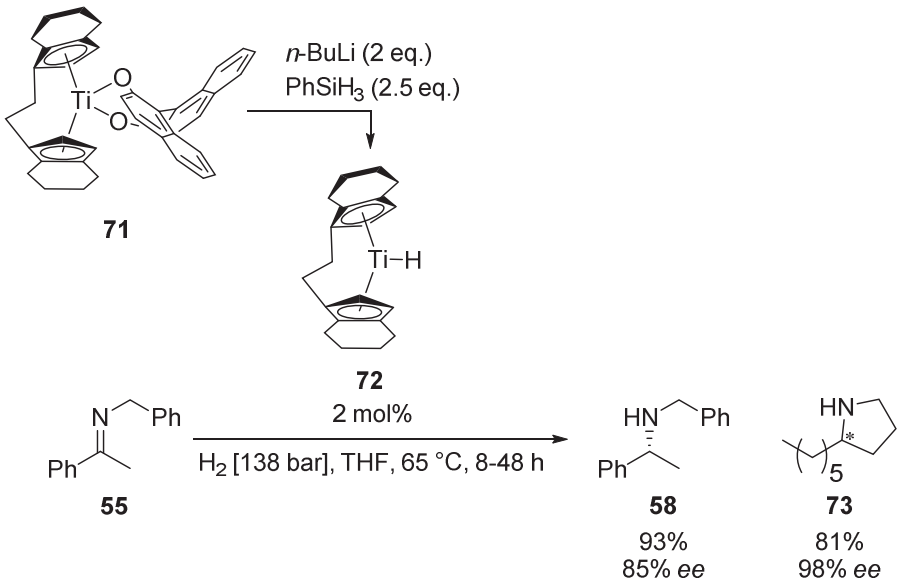


Scheme 17: Asymmetric hydrogenation of imine **68** by iridium(III) hydride iodo-bridged trimer **69**



Scheme 18: Asymmetric hydrogenation of imine **70** by iridium(III) hydride iodo-bridged trimer **70**

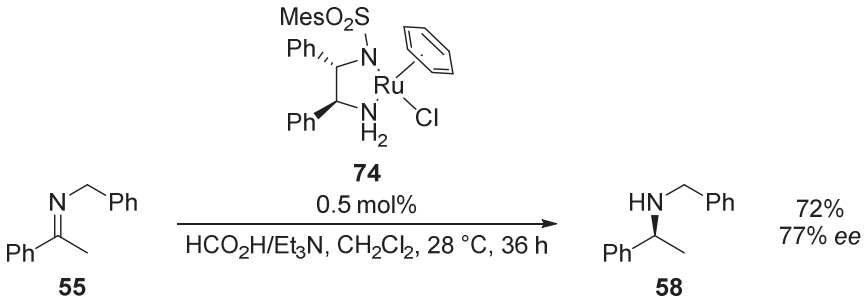
In 1992, *Buchwald* and co-workers developed a titanocene complex **72** and employed it in asymmetric hydrogenation of imines. While excellent enantioselectivites were obtained for cyclic amines such as **73**, moderate to high enantioselectivities were observed with acyclic imines such as **55** (Scheme 19). Very high hydrogen gas pressure, elevated reaction temperature, long reaction times and an impractical preparation of the catalyst from complex **71** with *n*-butyl lithium represented major drawbacks of this methodology. Furthermore, the *E/Z* ratio of the imine could be well correlated to the enantiomeric excess observed for each substrate and therefore limited the possibilities towards optimisation.[28]



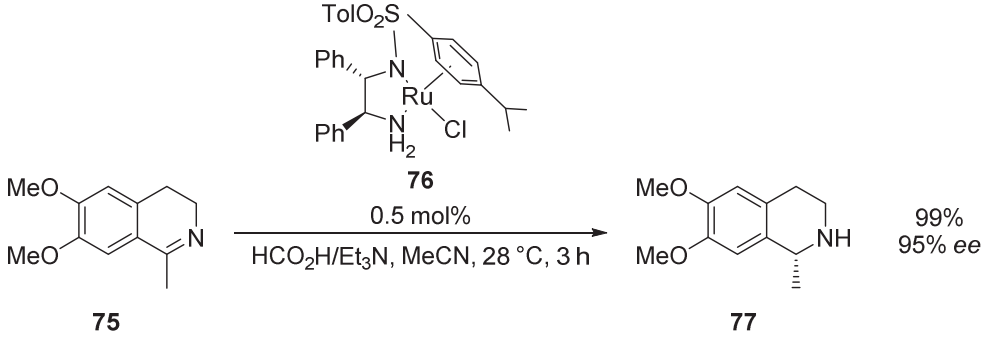
Scheme 19: Titanocene **72** catalysed asymmetric hydrogenation of imine **55**

[3] details are given in the mechanistic section

In 1996, *Noyori* and co-workers showed high *ee*'s in the asymmetric transfer hydrogenation of imines employing a ruthenium-diamine complex **74** and **75**. While excellent enantioselectivities and very fast reactions were obtained for cyclic substrates such as tetrahydroquinoline **75** (Scheme 21), moderate to good enantioselectivities with very long reaction times were observed for acyclic imine **55** (Scheme 20).[29]

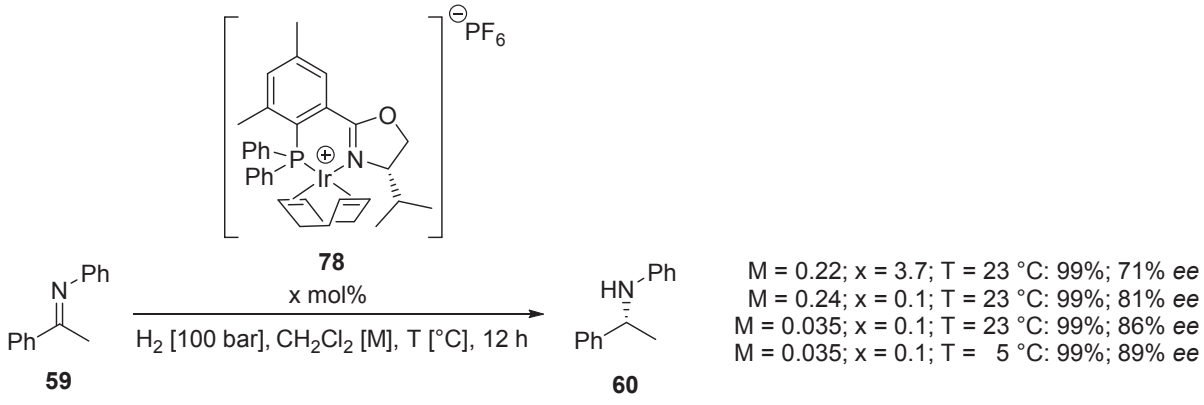


Scheme 20: Asymmetric hydrogenation of imine **55** by ruthenium catalyst **74**



Scheme 21: Asymmetric hydrogenation of tetrahydroquinoline **75** by ruthenium catalyst **76**

In 1997, *Pfaltz* and co-workers[30] developed iridium catalyst **78** with a phosphine-oxazoline ligand and used it in the asymmetric hydrogenation of imines (Scheme 22). The isopropyl substituent on the oxazoline was demonstrated to be optimal for imine hydrogenation. Full conversion with moderate to high enantioselectivities was observed for a number of substrates. A remarkable concentration effect was observed in the case of imine **59**: decreasing the substrate and catalyst concentration improved the enantioselectivity of the hydrogenation significantly. Such high enantioselectivites marked a significant improvement of iridium catalysts in asymmetric imine hydrogenation.



Scheme 22: Asymmetric hydrogenation of imine **59** with iridium-PHOX catalyst **78**

A careful study of the different substituents at the imine was conducted (Scheme 23).