A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

Scope of Enantioselective Reduction of Imines with Trichlorosilane

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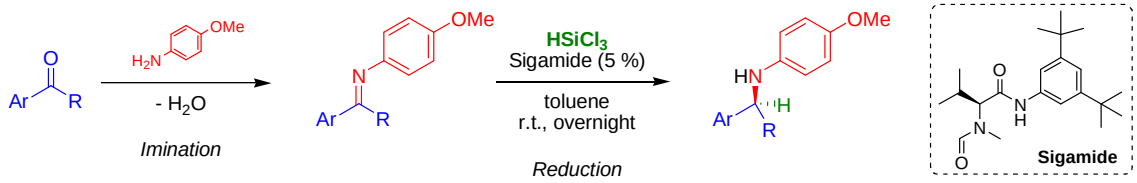
Abstract

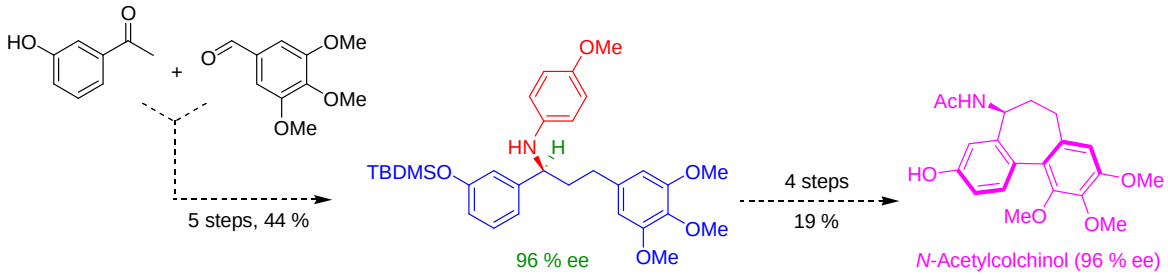
Herein, we report the results of research continuing previous success[I] in the field of enantioselective organocatalytic reduction of imines with trichlorosilane. Syntheses of various precursors (ketones) and substrates (imines) for the reduction reaction and their reduction following the protocol (Scheme A1) are described in this thesis.



Scheme A1. Enantioselective Reduction of Imines with Trichlorosilane and Sigamide Organocatalyst

1. **Aromatic heterocycles containing nitrogen** – good yields of the reduced product (68-85 %), the enantioselectivity depended on steric bulk in proximity to the nitrogen, steric bulk improved the enantioselectivity (up to 78 % ee), probably due to thwarting the coordination of the nitrogen to $HSiCl_3$.
2. **Aromatic heterocycles containing sulfur** – sulfur in the ring was tolerated well (89 % ee).
3. **Aromatic heterocycles containing oxygen** – generally good yields (62-90 %), dependence on position isomer was observed: furan-2-yl-derived substrates were reduced in moderate enantioselectivity (45-85 % ee), possibly due to the problem of coordination; in contrast, furan-3-yl derivatives were reduced in good enantioselectivity (77-91 % ee).
4. **Non-heterocyclic aromatic or aliphatic** – good yields (62-98 %) but varied enantiomeric excess (10-97 %). The high enantioselectivity values (76-97 % ee) were for substrates with significant *contrast of the steric hindrance* of the groups next to the reaction centre.

Furthermore, an example of practical utilisation of the method is presented. Naturally occurring alkaloid ***N*-acetylcolchinol** was synthesised in 9 steps and overall 8 % yield (Scheme A2). The stereogenic centre was introduced using our method and afforded the desired enantioenriched amine in 96 % ee.



Scheme A2. Synthesis of *N*-Acetylcolchinol Applying the Method

I. (a) Malkov, A. V.; Mariani, A.; MacDougall, K. N.; Kočovský, P. *Org. Lett.* **2004**, *6*, 2253; (b) Malkov, A. V.; Stončius, S.; MacDougall, K. N.; Mariani, A.; McGeoch, G. D.; Kočovský, P. *Tetrahedron* **2006**, *62*, 264; (c) Malkov, A. V.; Stončius, S.; Kočovský, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 3722; (d) Malkov, A. V.; Figlus, M; Stončius, S. Kočovský, P. *J. Org. Chem.* **2007**, *72*, 1315.

Acknowledgement

First of all, I wish to thank to my supervisors Prof. Pavel Kočovský and Prof. Andrei V. Malkov for the interesting research topic, for the many new ideas, inspiring notes and time they offered to me.

Furthermore, I would like to thank to departmental staff members who created pleasant working conditions: Dr. David Adam, Mr Jim Tweedie, Mr Alex Burns and Mr Tony Ritchie.

Many thanks also belong to all my colleagues for the spectacular spirit in the lab, in particular to Joanna, Claire and Louise (the chatting classes), Sigitas (the chemistry lead) and Frédéric (his support).

And of course, I cannot omit all other friends and my parents (for their encouragement despite the distance from home).

Author's Declaration

This thesis represents the original work of Kvetoslava Vranková unless explicitly stated otherwise in the text. The research was carried out at the University of Glasgow under the supervision of Prof. Pavel Kočovský and Prof. Andrei V. Malkov during the period of October 2006 to September 2009. The major part of the work described herein has been published as listed below:

Malkov. A. V.; Stončius, S.; Vranková, K.; Arndt, M.; Kočovský, P. *Chem. Eur. J.* **2008**, *14*, 8082.

Malkov. A. V.; Vranková, K.; Stončius, S.; Kočovský, P. *J. Org. Chem.* **2009**, *74*, 5839.

Malkov. A. V.; Vranková, K.; Sigerson, R. C.; Stončius, S.; Kočovský, P. *Tetrahedron* **2009**, *65*, 9481.

Malkov. A. V.; Vranková, K.; Černý, M; Kočovský, P. *J. Org. Chem.* **2009**, *74*, 8425.

Abbreviations and Acronyms

Ac	Acetyl
ACh	Acetylcholine
AcOH	Acetic acid
BAr_F^-	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Bn	Benzyl
Bs	Besyl, benzenesulfonyl
Bu	Butyl
CAN	Cerium(IV)-ammonium nitrate
Cat, cat*	Catalyst, chiral catalyst
CIP	Cahn-Ingold-Prelog (for nomenclature purposes)
Cy	Cyclohexyl
DDQ	2,3-Dichloro-5,6-dicyanobezoquinone
de	Diastereomeric excess
DET	Diethyl tartrate
DKR	Dynamic kinetic resolution
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPP	Diphenyl phosphate
E°	Standard reduction potential [V]
EDG	Electron donating group
ee	Enantiomeric excess
Et	Ethyl
EWG	Electron withdrawing group
Glf	Glucofuranose
Hex	Hexyl
HMPA	Hexamethylphosphoramide
HSD	Hydroxysteroid dehydrogenase
i-, *iso-*	Isomeric (branched alkyl chain)
L, L*	Ligand, chiral ligand
LA, LA*	Lewis acid, chiral Lewis acid
LB, LB*	Lewis base, chiral Lewis base
Leu	Leucine
M	Metal
Me	Methyl
MeCN	Acetonitrile
mes	Mesityl; 2,4,6-trimethylphenyl
n, *n**	nonbonding occupied orbital (electron pair), nonbonding vacant orbital
n-	Normal (linear alkyl chain)
NAC	*N*-Acetylcolchinol

Napht	Naphthyl
Nu	Nucleophile
OAB	Oxazaborolidine
[ox]	Oxidising agent, oxidation, oxidative conditions
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Pent	Pentyl
Ph	Phenyl
pH	Negative logarithm of the hydrogen cation activity in aqueous solutions
PIDA	Phenyliodonium diacetate
PIFA	Phenyliodonium bis(trifluoroacetate)
pK_a	Negative logarithm of the acid dissociation constant K_a
PMP	*p*-Methoxyphenyl
PNP	*p*-Nitrophenyl
PTMP	*p*-Trifluoromethylphenyl
Pr	Propyl
Pro	Proline
π, π^*	pi bonding orbital, pi antibonding orbital (multiple bond)
[red]	Reducing agent, reduction, reductive conditions
s-, *sec*-	Secondary (branched alkyl chain)
σ, σ^*	sigma bonding orbital, sigma antibonding orbital (single bond)
TBHP	*tert*-Butyl hydroperoxide
t-, *tert*-	Tertiary (branched alkyl chain)
TBDMS	*tert*-Butyldimetylsilyl
TCCA	Trichlorocyanuric acid
TFA	Trifluoroacetic acid
TFAA	Trifluororacetic acid anhydride
TFAc	Trifluoroacetyl
TfOH	Trifluoromethanesulfonic acid
Tf_2O	Trifluoromethanesulfonic acid anhydride
THP	Tetrahydropapaverine (note the unusual use of the acronym)
TIPS	Tri(*iso*-propyl)silyl
TMS	Trimethylsilyl
TOF	Turn-over frequency [s^{-1}] (number of moles of formed product per mole of catalyst per unit of time)
p-Tol	*p*-Toluyl, *p*-methylphenyl
TON	Turn-over number (number of moles of formed product per mole of catalyst before becoming inactive)
Tr	Trityl, triphenylmethyl
TS	Transition state, transition structure

Table of Contents

Part A:

Literature Background of the Method

1. Introduction

1.1. Development of Asymmetric Synthesis

1.1.1. Chirality

The roots of the term *chirality* go back to the nineteenth century when *stereochemistry* acquired serious scientific base after several exquisite discoveries. The pioneer in stereochemistry was certainly the French microbiologist and chemist **L. Pasteur**[1] who had done an extensive research on tartaric acid, both isolated from wine lees and prepared synthetically and he noticed that the latter one did not rotate the plane of polarised light as the natural did. He microscopically examined the crystals of sodium-ammonium tartrate and observed that it was a mixture of two types of crystals, in all aspects identical except that they were mirror images of each other. He used the terms *desymmetrisation* or *asymmetric* for this and similar phenomena. In **1848**, he separated the crystals manually and recorded that the polarisation of each type is the same but of opposite orientation and apparently, equal amount of both of them (one being natural) would give overall zero polarisation effect. His experiments in this field continued: **1853** – first separation of a racemate by diastereomeric crystallisation, **1858** – first racemate separation by fermentation (*Penicillium glaucum*).

The year **1874** brought the real breakthrough in understanding the stereo-arrangements on saturated carbon. Two chemists – a Dutch **J. H. van't Hoff**[2] and a French **J. A. Le Bel**[3] – postulated independently that the four groups bonded to the central carbon atom point into the corners of a regular tetrahedron. This discovery was highly controversial, because it could *so simply* visualise the relation between optical activity and the structure!

Chiral objects which are mirror images of each other are called *enantiomorphic* and they are a part of our everyday life [e.g. hands, screws, scissors, cars or roads; Greek *cheir* (χειρ) means *hand*]. The fact that they cannot be superimposed onto their mirror images provides sufficient definition for what is a chiral object or molecule. The adjective *chiral* only refers to the property of the molecule having a *stereogenic element*. If a compound has more than one stereogenic element, it can exist as either of *enantiomers* or one of *diastereoisomers* (these are no longer mirror images to each other). The number of possible

diastereomers is given by 2^n, where *n* is the number of stereogenic centres in the molecule. A molecule it is said to be *prochiral* if it can be converted into a chiral molecule in one step – typically, an sp^2-hybridised carbon bearing three different substituents that is transformed to an sp^3-centre or an sp^3-carbon with two identical substituents where a change to one of these substituents leads to a chiral compound.

1.1.2. Milestones in Asymmetric Synthesis

From the time when alchemy evolved into an accredited science of chemistry, synthetic methods were focused mostly on **building** simple or more complex structures. When these synthetic tools together with structure elucidation methods improved enough, the accumulated synthetic and stereochemical knowledge of 19th century brought up one of the greatest questions in chemistry – how to **set up a stereogenic centre** in the target molecule, and how to **control this process**. The human desire to exploit contemporary understanding and specialise for more delicate traits has led to the development of several synthetic methods for obtaining a stereocentre in the molecule.

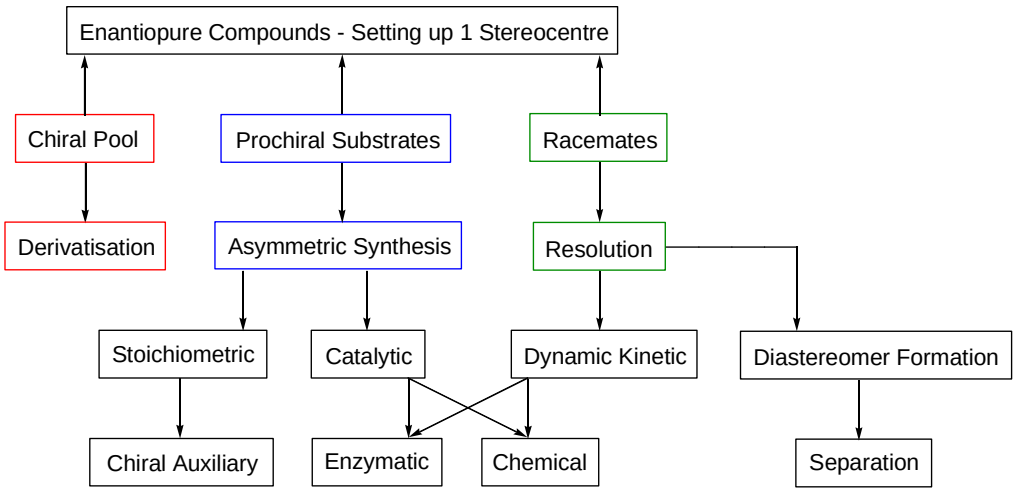


Figure 1.1. Possible ways of Setting-up One Stereocentre

There are three main approaches (Figure 1.1) yielding chiral compounds, by using:

- chiral pool, usually common natural products as amino acids or sugars,
- prochiral substrates used in *asymmetric* or *stereogenic* reactions,[4]
- optical resolution of racemic mixtures.

Nowadays, most of the reactions yielding chiral material are either manipulations of chiral pool or planning the synthesis enantioselectively.[4] Use of chiral pool is the simplest way how to acquire a chiral centre as it already present in the starting material and only **stereochemically unambiguous conversions** are suitable to transform it:

1. *Mechanism controlled reactions* – unambiguous reaction mechanisms:
   - S_N2 displacements,
   - S_N2' displacements,
   - S_E2' displacements,
   - Wagner-Meerwein type [1,2]-migrations,
   - sigmatropic rearrangements ([3,3]-Claisen, Cope, [2,3]-Wittig, etc.).

2. *Substrate controlled reactions* – in general, rigid cyclic substrates exhibit better controlling properties:
   - active via non-covalent interactions on one of the diastereotopic faces,
   - passive via steric shielding of one of the diastereotopic faces,
   - enhanced via cyclic TS.

Reactions of two prochiral starting materials afford two (enantiomeric) pairs of diastereomers in a reaction-specific ratio, no enantiocontrol can be achieved:

3. *Substrate and reagent controlled reactions* – two stereogenic centres are formed from prochiral (sp^2) starting material:
   - simple diastereoselectivity (aldol-type reactions, allylations of carbonyls),
   - endo/exo diastereoselectivity (cycloadditions).

The stereocontrol of reactions can become even more complicated if the starting material already contains a chiral centre due to the combination of their stereodirecting effects called *double differentiation*. The overall selectivity can be increased when the individual effects are **matched** or decreased when **mismatched**:

4. *Auxiliary controlled reactions*:
   - persistent auxiliary (recovered after the stereodifferentiating step),
   - restorable auxiliary (removed at work-up, but restored by simple operations),

- self-immolate auxiliary.

5. *Catalyst controlled reactions* – distinguished *chiraphor* (the chiral ligand bearing the chiral information) and *catalaphor* (the reactive site of the metal complex).

The development of methods of asymmetric synthesis (*vide supra*, sub-group 4. and 5.) dates back to beginning of the 20th century, needless to say, starting with modifying the existing synthetic methods by using natural products as the source of chirality:[4]

1908/1912 Hydrocyanation of benzaldehyde, in the presence of emulsine or quinine/ quinidine, respectively (Rosenthaler, Bredig) – first organocatalysis,

1939 Cinchonine-modified Pt for hydrogenation (Lipkin, Stewart),

1956 Silk fibroin-modified Pd for hydrogenation (Akabori, Izumi),

1960 Ketene methanolysis, *O*-benzoylquinine, 76 % ee (Pracejus),

1961 Polymerisation of benzofurane with $AlCl_3$/phenylalanine catalyst (Natta),

1963 Raney Ni/tartrate for hydrogenation (Izumi).

Publication of Wilkinson's homogenous catalyst[5] $RhCl(PPh_3)_3$ in 1966 was a breakthrough destroying the belief that only heterogenous systems can activate molecular hydrogen. The sixties brought more rationalisation of known metal-catalysed processes and also creating new ones based on this rationale, not just in hydrogenation reactions:

1966 Asymmetric cyclopropanation, Cu/salen, 6 % ee (Nozaki, Noyori),

1968 Asymmetric hydrogenation, Rh/chiral phosphine, 15 % ee (Knowles, Horner),

1970 Intramol. aldol condensation, proline, 93 % ee (Hajos, Wiechert),

1970 Monsanto L-DOPA process – asym. hydrogenation (Knowles),

1971 Asymmetric hydrogenation, Rh/DIOP, 50 % ee (Kagan),

1975 Sumitomo cilastatine process – asym. cyclopropanation (Aratani),

1979 Hydrocyanation of benzaldehyde with a dipeptide catalyst, 97 % ee (Inoue),

1980 Asymmetric epoxidation of allylic alcohols, Ti/TBHP/DET, 95 % ee (Sharpless, Katsuki),

1983 Asymmetric hetero-Diels-Alder reaction, $Eu(hfc)_3$, 58 % ee (Danishefsky),

1985 Takasago (–)-menthol process – asym. hydrogenation (Noyori),

1986 Theory of non-linear effects in asymmetric catalysis (Kagan, Agami),

1987 Oxazaborolidine reductions of carbonyls, 98 % ee (Itsuno, Corey),

1988 Asym. dihydroxylation of olefins, Os/dihydroquinine, 85 % ee (Jacobsen, Sharpless),

1988 LA*-catalysed Diels-Alder reaction, 90 % ee (Yamamoto, Narasaka),

1990 Asymmetric epoxidation of olefins, Mn/salen, 98 % ee (Jacobsen, Katsuki),

1994 LB*-catalysed allylation, 98 % ee (Denmark),

1996 Asymmetric epoxidation of olefins, fructose-derived catalyst, 81 % ee (Shi),

1998 Nucleophilic additions to imines, chiral H-donors, 96 % ee (Jacobsen),

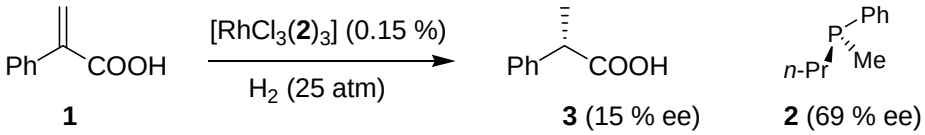
2000 Intermol. aldol condensation (enamine catalysis), proline, 96 % ee (Barbas, List),

2000 Cycloadditions (iminium catalysis), imidazolidinone, 98 % ee (MacMillan),

2001 Nobel Prize for asymmetric catalysis.[6]

1.1.3. Nobel Prize for Asymmetric Synthesis vs. Hydrogenation

The 2001 Nobel Prize awarded to three stars in asymmetric catalysis – Dr. **W. S. Knowles** (Monsanto, St. Louis, Missouri, USA), Prof. **R. Noyori** (Nagoya University, Chikusa, Nagoya, Japan) and Prof. **K. B. Sharpless** (The Scripps Research Institute, La Jolla, California, USA). The Royal Swedish Academy of Science rewarded these three scientists for *"the development of catalytic asymmetric synthesis"* where a half of the prize was received by Knowles and Noyori for *"their work on chirally catalysed hydrogenation reactions"* and the other half was awarded to Sharpless for *"his work on chirally catalysed oxidation reaction"*. All three of them have developed remarkably reliable methods for asymmetric reductions and oxidations.

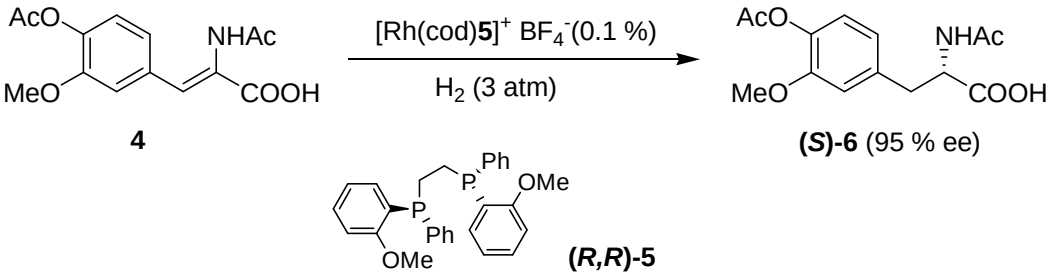


1 **3** (15 % ee) **2** (69 % ee)

Scheme 1.1. Knowles' First Asymmetric Hydrogenation

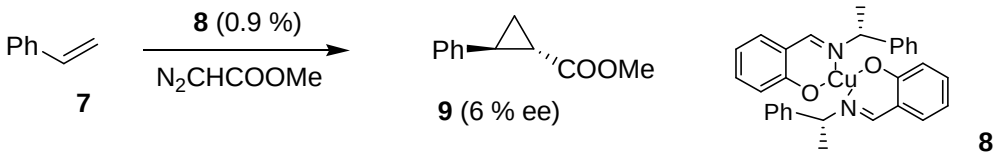
The publications about homogenous catalysis with Wilkinson's catalyst[5] in combination with new methods for preparation of optically active phosphines,[7] triggered the interest of contemporary researchers. In 1968, Knowles showed that the chirality could be transferred from a small amount of chiral ligand **2** on a metal to a large quantity of non-chiral substrate and an enantioenriched product could be obtained[8] (Scheme 1.1).

Knowles, understanding the industrial needs, kept working on the efficiency of the transformation until it reached full conversion and 95 % ee and could be applied on large scale synthesis known as The Monsanto L-DOPA Process (Scheme 1.2) – the first commercialised chiral-metal-complex-catalysed asymmetric hydrogenation.[9]



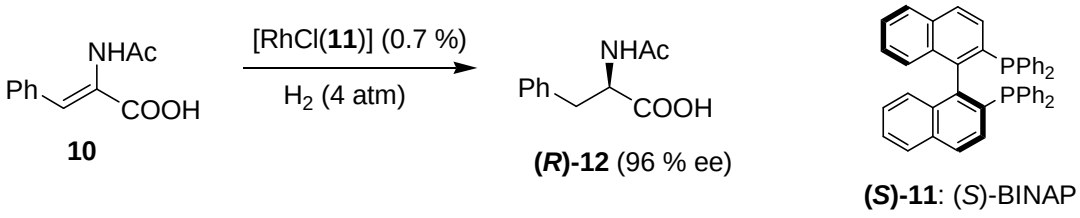
Scheme 1.2. The Monsanto L-DOPA Process

Noyori worked on different types of asymmetric reactions, his first remarkable success in asymmetric synthesis came in 1966 with his cyclopropanation reaction[10] with a salen-copper catalyst **8** affording the cyclopropane product in 6 % ee (Scheme 1.3).



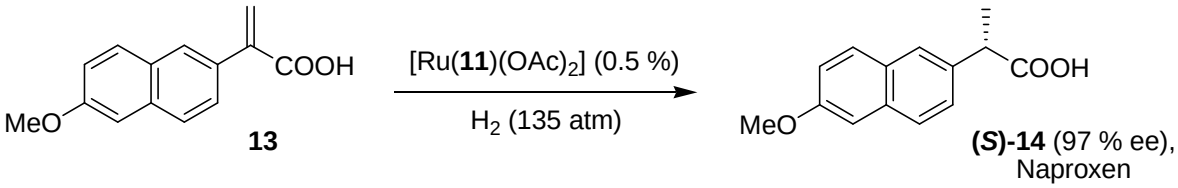
Scheme 1.3. Noyori's First Enantioselective Cyclopropanation

In 1980 Noyori and co-workers discovered that the atropoisomeric diphosphine BINAP could catalyse many types of asymmetric transformations including hydrogenations[11] (Scheme 1.4) in highly enantioselective fashion.



Scheme 1.4. Noyori's Enantioselective Rh-catalysed Hydrogenation

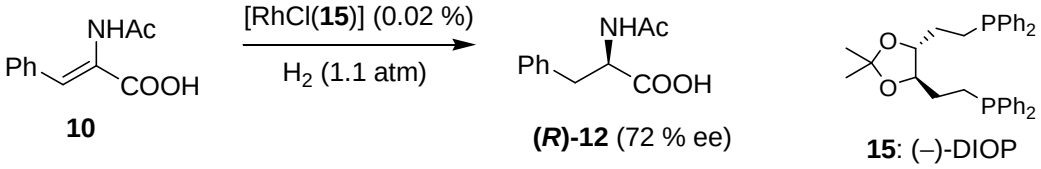
In continuation of Noyori's research within hydrogenation with BINAP ligands, in 1988, he came up with a novel idea of using Ru metal instead of Rh. This switch brought higher yields, enantioselectivity and reliability with a broad range of substrates[12] (Scheme 1.5). Noyori then developed several protocols for hydrogenation of carbonyls in the presence of double bonds[13] or transfer hydrogenation of cyclic imines[14] (*vide infra*).



Scheme 1.5. Noyori's Enantioselective Ru-catalysed Hydrogenation

Besides Knowles and Noyori, also Prof. **H. B. Kagan** (Université Paris-Sud, France) has been recognised as a pioneer of asymmetric catalysis and quoting Knowles *"he was left out of the act"*[15] which caused controversy. Only three people could be awarded at a time, however, asymmetric catalysis might be too broad a field to be rewarded by one prize. Opposite processes as asymmetric hydrogenation or asymmetric oxidation are, each consistent field on its own. Furthermore, other types of asymmetric reactions have been studied only more recently (organocatalysis) and certainly, the possibilities of asymmetric synthesis were not exhausted in year 2001!

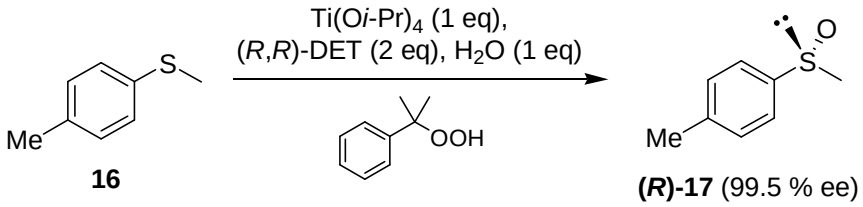
Kagan published his hydrogenation protocol in 1971 using Rh metal and DIOP ligand[16] (Scheme 1.6) which proved wrong the reasoning that the chirality must be directly on the phosphorus atom. Because of its easy preparation form tartaric acid, DIOP became widely used.[17]



Scheme 1.6. Kagan's Enantioselective Rh-catalysed Hydrogenation

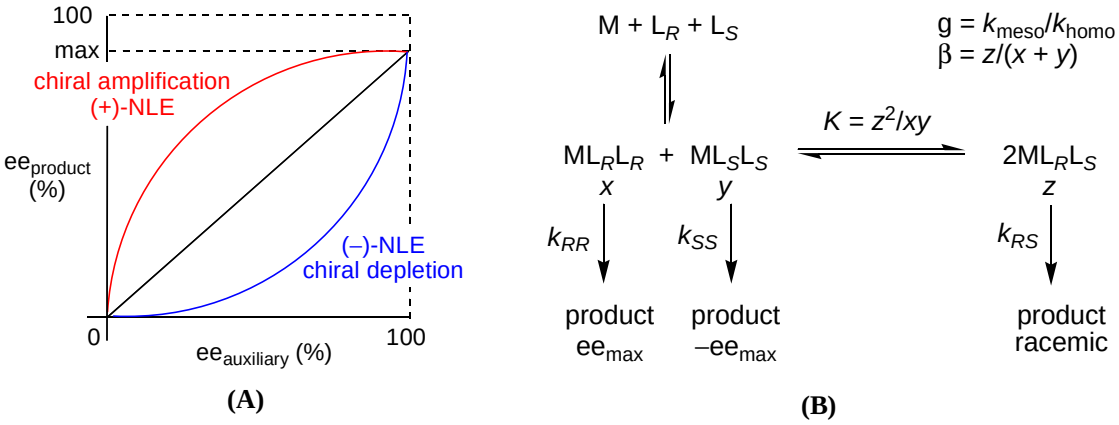
Kagan and co-workers carried out an extensive research on the family of phosphine ligands derived from DIOP and also their structure-reactivity-enantioselectivity correlations. He improved diphosphine synthesis and applied his own hydrogenation

protocol for the first hydrogentaion of imines[18] (see Chapter 2.2). He also worked on the theory of Rh-catalysed asymmetric reductions[17,19] and many other types of asymmetric reactions, as an example serves the preparation of enantioenriched sulfoxides.[20,21] Two alternative approaches were developed – the first was an enantioselective oxidation of sulfides[20] to sulfoxides where a modified Sharpless epoxidation titanium reagent was used and sulfoxides were obtained in high ee's (Scheme 1.7). The second approach exploited substitution reactions on sulfur in chiral sulfites[21] (two consecutive steps with full inversion of configuration).



Scheme 1.7. Kagan's Enantioselective Ti-mediated Oxidation of Sulfides

Kagan's group was the first to investigate the phenomenon of nonlinear effects in asymmetric catalysis,[4,22] first examples were found in asymmetric Sharpless epoxidations. Description and explanation of non-linear effects was built on the behaviour of organometallic species. The simplest and most common model is the ML_2-model where it is assumed that the reaction occurs through a mixture of three stereoisomeric complexes – two homochiral ML_RL_R, ML_SL_S, and one meso ML_RL_S which are in amounts x, y, z and have different reactivity (k_{homo}, k_{meso}) (Scheme 1.8)



Scheme 1.8. Non-linear Effects **(A)** and Model ML_2 **(B)**

Then the enantiomeric excess of the product is calculated according to equation 1:

$$ee_{product} = ee_{max}.ee_{aux}.(1+\beta)/(1+g\beta). \quad \text{(eq1)}$$

If no meso complex is formed (β = 0) or both types have the same reactivity (g = 1), the equation gives the linear correlation:

$$ee_{product} = ee_{max}.ee_{aux}. \quad \text{(eq2)}$$

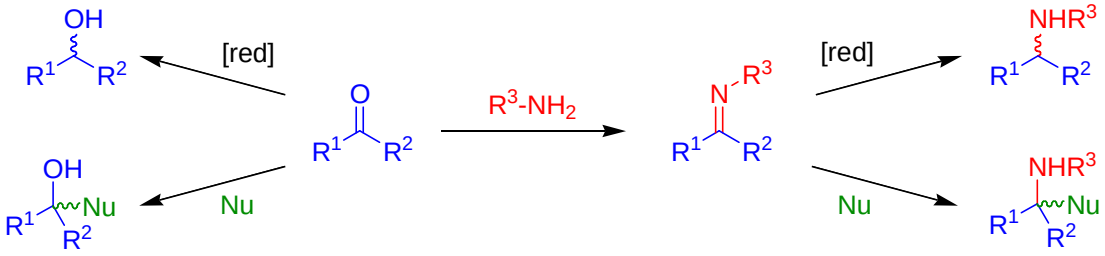
When the homochiral complex is more active than the meso one ($k_{homo} > k_{meso}$, g <1) the ee of the product is higher than expected by linear dependence and *positive non-linear effect, chiral amplification* is observed. The opposite case (g > 1) defines the *negative non-linear effect* or *chiral depletion*.

2. Reduction of Imines

2.1. Introduction

2.1.1. Carbonyl Compounds – The Core of Amine Synthesis

Carbonyl compounds, particularly aldehydes and ketones have always been favourites of synthetic chemists. They can be transformed easily to alcohols by reduction or addition of a nucleophilic species, having the advantage of choice of various reducing agents and nucleophiles. Furthermore, they can be used not just for introduction of an oxygen functionality but also for an indirect introducing of a nitrogen functionality and similarly, a wide selection of nitrogen sources is available. Therefore, the transformation ketone (aldehyde) – imine – amine is a powerful tool for obtaining amines (Scheme 2.1).



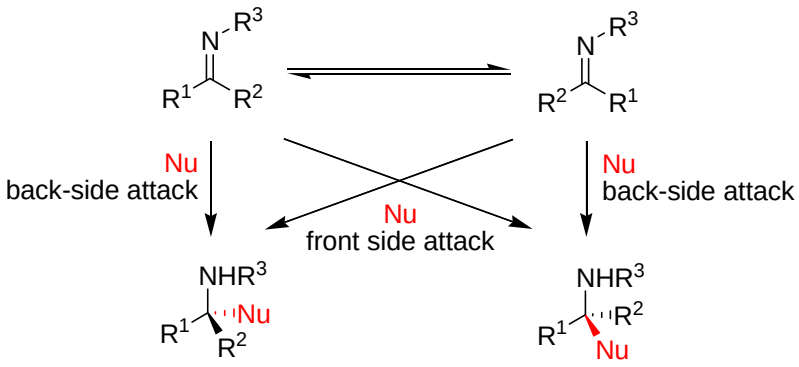
Scheme 2.1. Crucial Synthetic Utility of Carbonyl Compounds

Obviously, the products of either of the above-mentioned synthetic ways can be – and in most cases are – chiral. Besides, all the effort exerted to prepare amines simply and efficiently is caused by the vast occurrence of amines in the nature and their biological activity. It is crucial to obtain the correct isomer in enantiopure form, as the opposite enantiomer may have severe adverse effects. Asymmetric synthesis, rather than resolution of racemic mixtures, has been applied in modern preparation (since 1970s) of enantiopure amines. Often enough, it provides more cost and/or time effective method of gaining these compounds than other preparative methods or isolation from natural sources.

2.1.2. Properties and Reactivity of the Carbon-Nitrogen Double Bond[23]

The properties of carbonyl compounds and their nitrogen analogues are in many ways comparable and are often researched side by side. However, the progress in catalytic enantioselective reactions of imines is rather slower than their ketone counterparts. This is caused by the more complex behaviour of compounds containing carbon-nitrogen double bond.

The very first fact that needs to be considered is nitrogen being trivalent causing the principal geometrical isomerism of *C=N* bond. Even if the isomers exist under rapid equilibrium, each of the isomers can yield different enantiomer (Scheme 2.2). Some synthetic methods preserve or even rely on the imine geometrical set-up which makes these protocols less attractive.

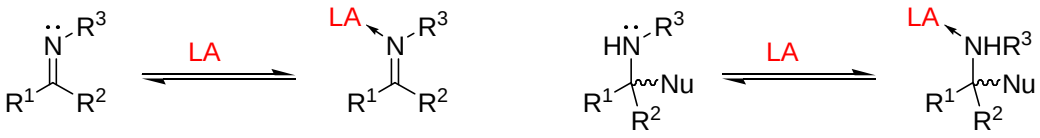


Scheme 2.2. Formation of Product Depending on Isomerism of Imine Bond and Attack Side

Another reactivity issue stems from the **lower electrophilicity of carbon atom in *C=N*** bond compared to the *C=O* bond.[26c] That is due to four properties closely related to each other:[23]

- lower polarity of the *C=N* bond than of the *C=O* bond, quantified by dipole moment ($\mu_{C=N}$ = 0.9 D and $\mu_{C=O}$ = 2.3 D),
- smaller electronegativity of nitrogen than oxygen atom, Pauling eletronegativities are χ_N = 3.0 and χ_O = 3.5,
- the *C=N* bond is slightly longer (1.28 Å) than *C=O* bond (1.20 Å),
- the energy of *C=N* bond is lower and much more variable, typically 615 ± 40 kJ.mol^{-1} (147 ± 10 kcal.mol^{-1}, mainly due to the impact of the *N*-substituent (*vide infra*) than the energy of *C=O* bond in ketones (750 kJ.mol^{-1} ~ 179 kcal.mol^{-1}).

However, the lower electrophilicity of the imine bond can be modulated by the R^3 group or by Lewis acid activation (Scheme 2.3). A desirable group on nitrogen (R^3) is a group stabilising the possible negative charge on nitrogen resulting from addition of a negatively charged nucleophile (organometallics or a hydride).



Scheme 2.3. A Lewis Acid / Imine or a Lewis acid / Amine Adduct

Another problem is the basicity of imine and/or amine nitrogen which may trap the Lewis acid before the catalytic cycle starts or is fully developed (Scheme 2.3). Typical pK_a values of the conjugate acids of arylimines $Ar(R^2)C{=}NR^3$ are in the range 5.5-7.5 (difficulties with measurements prevent obtaining more accurate data) and the basicity of the corresponding amines (i.e. *N*-substituted anilines) lies in a similar range. With increasing the electron density on the nitrogen atom, the basicity – in both cases – increases.

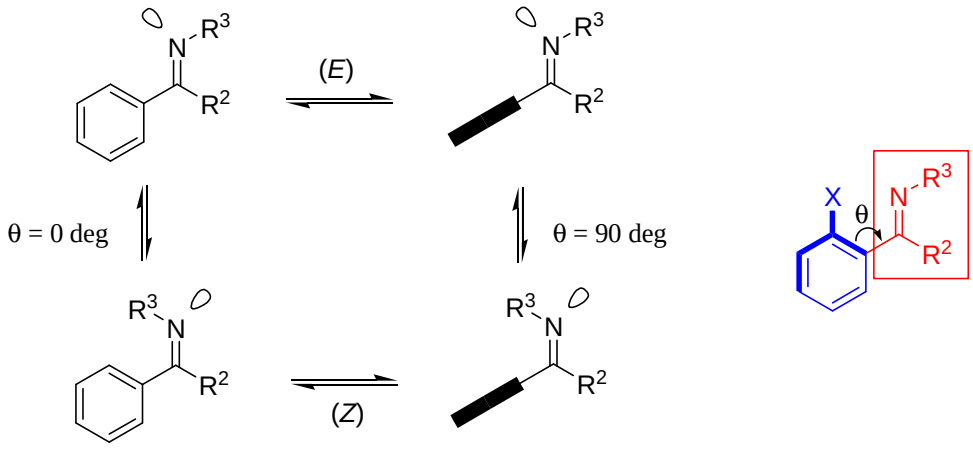
As mentioned earlier, the geometry of the imine can influence the outcome of the reaction performed on it. Regarding the **equilibrium distribution of the *E*/*Z* isomers** [of a general arylimine $Ar(R^2)C{=}NR^3$], several attributes need to be taken into account:[23,24]

1. *Steric and resonance factors*:
   - increasing the bulk of *C*-substituent R^2 (Ar = const.) destabilises the (*E*)-isomer and moves the equilibrium towards the (*Z*)-isomer,
   - [1,2]-eclipsing effects – opposed to delocalisation energy – twisting of the *C*-aryl ring from the $C{=}N\text{-}R^3$ plane decreases the steric interaction between the *ortho*-substituent (hydrogen or X) of the *C*-aryl and the $N\text{-}R^3$ (e.g. for benzylideneaniline R^2 = H, R^3 = Ph, θ ~ 10 deg; Scheme 2.4).

2. *o-Substituted C-aryl effects*:
   - preference towards the (*Z*)-isomer (~ 9.5 $kJ.mol^{-1}$, Ar = *o*-tolyl, $R^2 = R^3$ = Me),
   - the (*E*)-isomer might be destabilised by the repulsive interactions between the

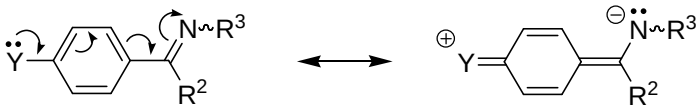
nitrogen lone pair and the aromatic π-electrons (n-π repulsions),

- increase of the dihedral angle θ tends to reduce the adverse steric interactions of the *o*-substituent with the *C*-R^2 and *N*-R^3 in the dominant (*Z*)-isomer (typically θ ~ 10-30 deg).



Scheme 2.4. Equilibrium Distribution of *E*/*Z* Ketimines

3. *p-Substituted C-aryl effects*:
   - an electron-donating group tends to stabilise the coplanar conformation by increasing the delocalisation energy, which increases the barrier of rotation around the *C*-aryl bond and moves the equilibrium towards the (*E*)-isomer (Scheme 2.5; destabilisation effect has not been observed for *p*-EWGs),
   - n-π repulsions between the nitrogen lone pair and *C*-aryl decrease with the electron-deficiency of the aryl ring (opposite effect of *p*-EDGs, can be counter-balanced by resonance energy).

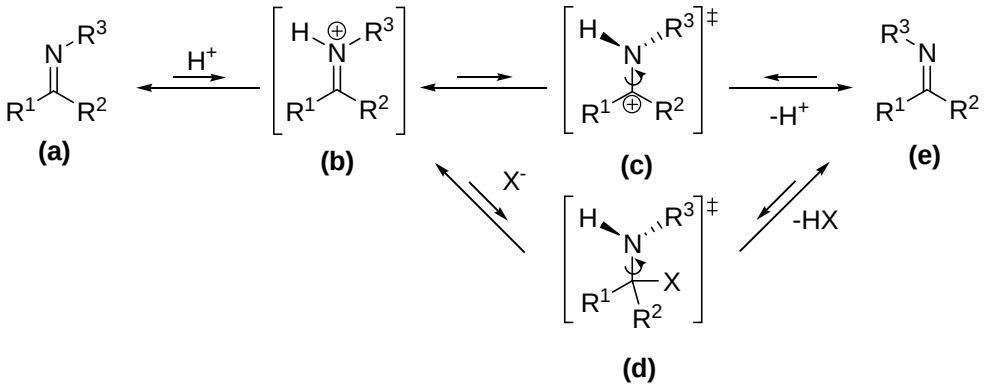


Scheme 2.5. Stabilisation of p-Substituted Ketimine

4. *Stereochemical analysis*:
   - (*Z*)-isomer shows *N*-alkyl signals at lower δ than the (*E*)- due to shielding effect of the *C*-aryl ring (ring-current effect, analogy for *N*-aryl imines),
   - IR absorption – *cis*-(Ar-*C*=*N*-R^3) at ν ~ 700 cm^{-1}, *trans* relation ν ~ 690 cm^{-1}.

The energy of the "flip" is difficult to determine precisely as it strongly depends on all substituents (R^1, R^2, R^3), their electronic and steric properties. The typical value of the isomerisaton barrier lies in the range $\Delta G^{\ddagger}$ ~ 83-108 kJ.mol^{-1} [24] which corresponds to half-life of several hours. However, traces of Brønsted acid present in the solution can catalyse this isomerisation process and decrease the half-life to tens of seconds! Two types of mechanism can be outlined for acid-catalysed isomerisation (Scheme 2.6):[25]

- protonation of the imine nitrogen generates trace amounts of the iminium ion **(b)**, the rate of isomeristaion is correlated linearly to the amount of the protonated species,
- rotation around carbon-nitrogen bond in the protonated species **(c)** (the bond order decreases with protonation and yet this might require up to ~ 190 kJ.mol^{-1} even for the stabilised carbcations generated from *C*-arylimines),



Scheme 2.6. Brønsted Acid-catalysed Isomeration of Imines

- alternatively, less energy-demanding is the nucleophilic addition of the acid counter anion X^- to **(b)** producing the corresponding tetrahedral intermediate **(d)**, which then undergoes rotation about the *C*-*N* bond,
- elimination of the acid anion and proton loss from nitrogen, yielding the opposite geometrical isomer **(e)**.

2.1.3. Asymmetric Reactions Yielding Amines

Amines, naturally occurring or their unnatural analogues, both types are pharmaceutically interesting groups of compounds. The need for their synthesis rather than

isolation is obvious. There are many approaches providing a way of obtaining enantioenriched amines from many **different starting building blocks**, mostly based on carbonyl compounds:[26]

1. *Preparation of amines from imines by additions to*:
   - *N*-alkyl/aryl imines, *N*-acyl imines,
   - *N*-silyl, *N*-boryl, *N*-alumino, *N*-phosphinyl, and *N*-thio imines.

2. *Additions to other N-derivatives of ketones*:
   - hydrazones, oxime ethers, and nitrones.

All of above-mentioned reactions are *diastereoselective* reactions performed with stoichiometric amount of the chiral inducer – chiral auxiliary which can be contained either in the substrate (carbonyl) or the attacking nucleophile. The formation of a new stereocentre is in relation to the already existing one in the chiral auxiliary and the product is a *pair of diastereoisomers* for each added centre. The separation of the diastereomers is feasible also on larger scale; however, this approach has some serious disavantages:

- the introduction and later removal of the auxiliary group might be problematic,
- the stoichiometric amount of precious enantiomerically pure chiral auxiliary is required.

One way of overcoming these problems is to use sub-stoichiometric or catalytic amounts of the chiral source which is not chemically bound to either of the reactants, only interacting with them by weak interactions. When only a catalytic amount is used, the reaction must proceed in *a catalytic cycle* and fundamentally, that makes *the catalyst* recoverable which further improves the cost efficiency.

2.1.4. Catalytic Enantioselective Additions Yielding Amines

Catalytic enantioselective reactions[27] is a term used for a class of reactions where the chirality in a large quantity of prochiral compound (**substrate**) is induced by a small amount of chiral source (**chiral catalyst**). This by itself is very efficient route for the

synthesis of chiral compounds and it can be used for a vast selection of substrates, particular interest lies on carbonyl compounds and their analogues (*vide infra*).

Usually, catalytic enantioselective reactions performed with this type of compounds (aldehydes, ketones, ald-, ketimines) are divided according to **the way of setting up the new stereogenic centre** into two main groups which can be sorted further:

1. *Transformations without carbon-carbon bond formation*:
   - reductive amination of ketones,
   - reduction of imines, including (transfer) hydrogenation of imines.

2. *Nucleophilic attack resulting in the formation of a new carbon-carbon bond.*[28] This group can be sorted according to **the type of attacking nucleophile**:
   - alkylmetals and cyanides,
   - Diels-Alder dienes for aza-Diels-Alder, and
   - enol ethers in Mannich-type reactions.

However, other way of classification of catalytic enantioselective reactions may be applied, based on the choice of **the chiral source** in the used catalyst; the primary carrier of chirality – fundamentally, the catalyst can have either Lewis-acidic or basic character:

1. *Reactions catalysed by metal complexes:*
   - "classical" transition metals – rhodium, ruthenium,
   - more recently utilised – iridium, titanium, cobalt, rhenium, copper.

2. *Reactions catalysed by metal-free catalysts – organocatalytic reactions:*
   - aminoacids as chiral source,
   - carbohydrates as chiral source, and other types.

In the specific case of preparation of amines from ketones (reductive amination) or ketimines (reduction), there is also an option to classify these reactions according to the chosen **reducing agent**:

1. *Hydrogenation with H_2 gas* – high pressure (> 10 atm) or low pressure of H_2 gas.

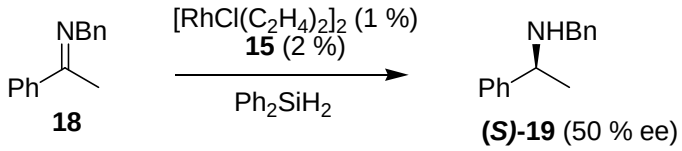
2. *Transfer of a hydride which is formed from:*
   - formic acid,
   - silanes and boranes,
   - metal hydrides and others.

Apparently, there are many combinations and in this thesis I will pay attention to reduction of imines / reductive aminations of ketones and particularly their *organocatalytic* enantioselective versions.

2.2. Highlights of Metal-catalysed Asymmetric Reductions[4a,28,29]

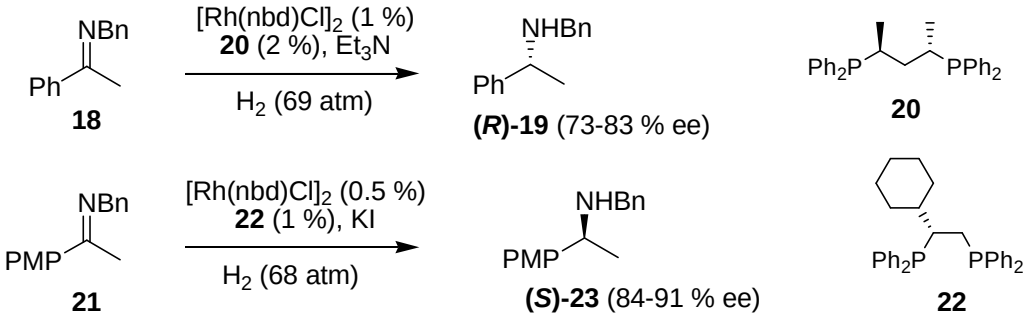
2.2.1. Rhodium Catalysis

The first report on enatioselective reduction of imines was from Kagan et al. in 1973.[18] The reducing reagent was diphenylsilane and the source of chirality was chiral ligand **15** (DIOP) coordinated to a rhodium metal (Table 2.1, entry 1; Scheme 2.7). The catalyst loading was incredibly low (only 1 mol %) considering this was a pioneering reaction. Although the moderate enantioselectivity (50 % ee) was satisfying for the novelty, it was not enough for practical applications and it encouraged further research in this field.



Scheme 2.7. First Enantioselective Reduction of Imines

However, it took ten years to improve the enantioselectivities of reductions by using transitions metals and new diphosphine ligands in high-pressure hydrogenations. Examples of the ligand structure optimisation were reported by Bakos et al.,[30] who developed a procedure for the reduction of benzylimine **18** with ligand **20** coordinated to rhodium with up to 83 % ee (Table 2.1, entries 2 and 3; Scheme 2.8).



Scheme 2.8. Enantioselective Reduction with Rh catalysts

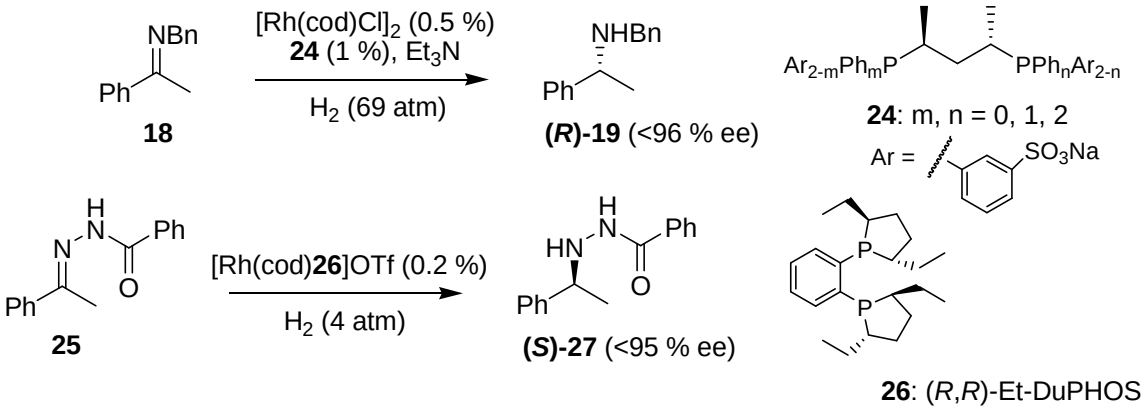
Another useful diphosphine ligand for the Rh-catalysed hydrogenation was the cyclohexyl derivative **22**,[31] which brought high enantioslectivity (up to 91 %, depending on the substrate) at very low loading (only 0.5 mol %). Potassium iodide was used as an additive to improve the enantioselectivity (Table 2.1, entries 4 and 5; Scheme 2.8).

Table 2.1. Hydrogenations Catalysed by Rh Complexes

Entry	Imine	Red. Reagent / Additive	Ligand (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**18**	Ph_2SiH_2 / -	**15** / 1.0	ambient	99 / 50 (*S*)
2	**18**	H_2 / Et_3N	**20** / 1.0	ambient	96 / 73 (*R*)
3	**18**	H_2 / Et_3N	**20** / 1.0	0	99 / 83 (*R*)
4	**21**	H_2 / KI	**22** / 0.5	ambient	99 / 84 (*S*)
5	**21**	H_2 / KI	**22** / 0.5	–25	99 / 91 (*S*)
6	**18**	H_2 / -	**24**, s = 1.65 / 0.5	ambient	94 / 96 (*R*)
7	**18**	H_2 / -	**24**, s = 3.75 / 0.5	ambient	55 / 19 (*R*)
8	**18**	H_2 / -	**26** / 0.1	ambient	99 / 95 (*S*)
9	**ketone 28**	H_2 / -	**30** / 1.0	ambient	99 / 98 (*S*)
10	**ketone 29**	H_2 / -	**30** / 1.0	ambient	99 / 90 (*S*)

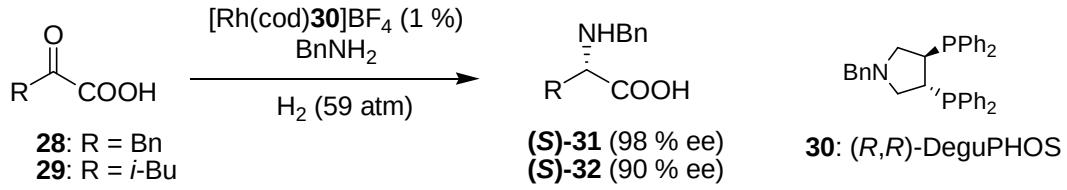
Bakos and Sinou continued their research on optimisation of the diphosphine and brought about the idea of biphasic hydrogenation systems[32] (ethyl acetate – water) and water-soluble sulfonated ligand (sodium salt) **24**, also at very low loading. The trick was in different degree of sulfonation which influenced the enantioselectivity, optimum was found at s = (m + n) = 1.4 to 1.7 (Table 2.1, entries 6 and 7; Scheme 2.9).

Burk's group[33] exploited the beneficial effect of an additional binding nitrogen atom in hydrazones, which were successfully reduced with rhodium and (*R*,*R*)-Et-DuPHOS ligand **26**, while the *N*-*N* bond in the product was cleaved with SmI_2. Aromatic hydrazone substrates afforded the highest ee's (up to 97 %; Table 2.1, entry 8; Scheme 2.9).



Scheme 2.9. More Examples of Rh-catalysed Reductions

Kadyrov and Börner[34] showed that Rh catalysis can be applied also to reductive aminations. They chose α-keto acids and benzylamine as substrates relevant to industrial production of *N*-benzyl-protected α-amino acids. However, the yields and enantioselectivities were varying, the best *N*-benzyl-phenylalanine **31** was obtained in high 98 % ee (Table 2.1, entries 9 and 10; Scheme 2.10).



Scheme 2.10. Enantioselective Reductive Amination with Rh catalyst

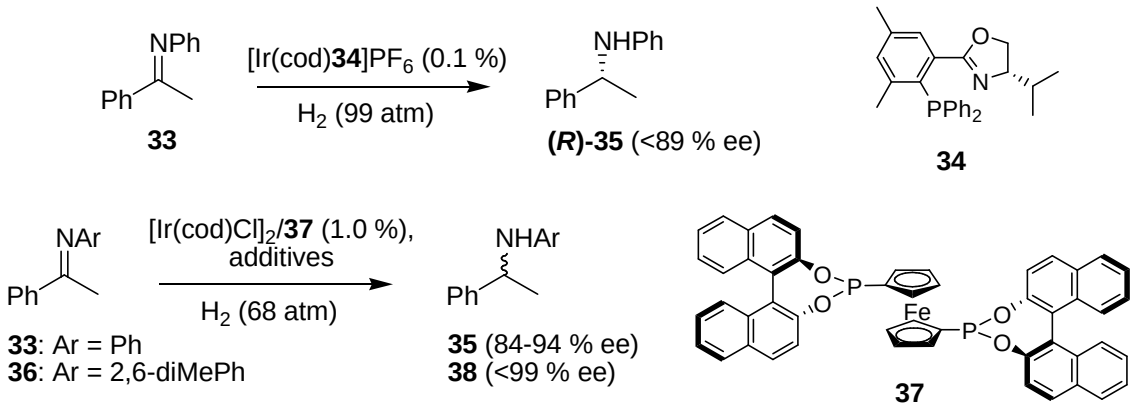
Rhodium catalysis exhibits several general trends:

- many reactions with Rh-diphosphine catalysts afford amines only in moderate ee's,
- often, high hydrogen pressure needed and/or low catalyst TOF/TON,
- halide ions may have positive effects on enantioselectivity,
- best results obtained in biphasic systems with sulfonated ligands.

2.2.2. Iridium Catalysis

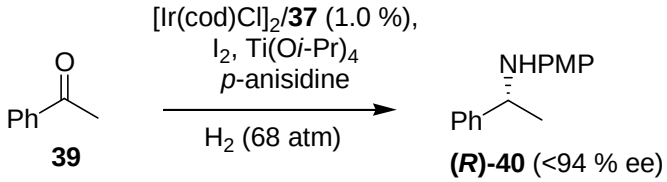
Chiral iridium complexes were also used in enantioselective hydrogenations, mainly in the late 1990s. High enantioselectivities were achieved by Pfaltz[35] (Table 2.2, entry 1; Scheme 2.11) and later Zhang[36] (Table 2.2, entries 2-4; Scheme 2.11). Pfaltz,

using his phosphine-oxazoline ligand **34**, provided the aromatic amine **35** in 89 % ee, Zhang with his ferrocene-binaphane **37** obtained even better result, 99 % ee.



Scheme 2.11. Hydrogenation Using Ir Catalysts

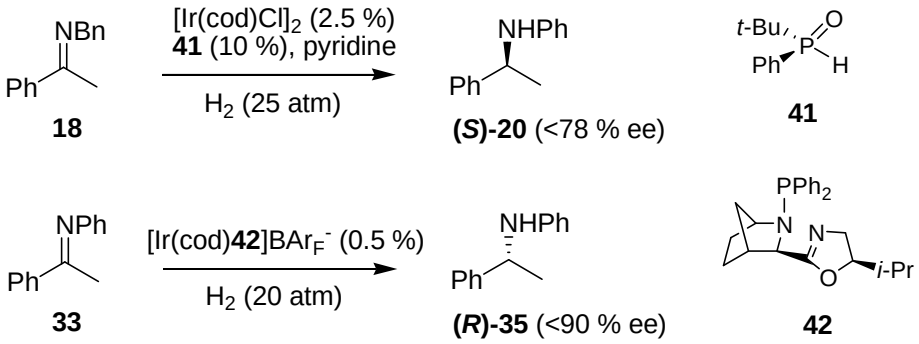
Besides hydrogenations of imines, Zhang also developed Ir-catalysed reductive aminations of aromatic ketones[36] with up to 94 % ee (Table 2.2, entry 5; Scheme 2.12).



Scheme 2.12. Ir-catalysed Reductive Amination

A very simple monodenate phosphinoxide ligand **41** was used by de Vries[37] (Table 2.2, entry 6; Scheme 2.13). Its advantage was the simplicity of its preparation in two steps and one pot, and that it did not racemise easily. The best achieved enantioselectivity with this ligand for aromatic imines was 83 % ee.

Another highly active iridium complex with ligand **42** for hydrogenation of aromatic imines by Andersson's group[38] was derived from 2-azanorbornane-oxazoline structure and promoted reduction of imines to amines with up to 90 % ee (Table 2.2, entry 7; Scheme 2.13).



Scheme 2.13. Hydrogenation Using Ir Catalysts

Iridium catalysis has been developed more recently complementing the previous methods of Rh and Ru catalysis:

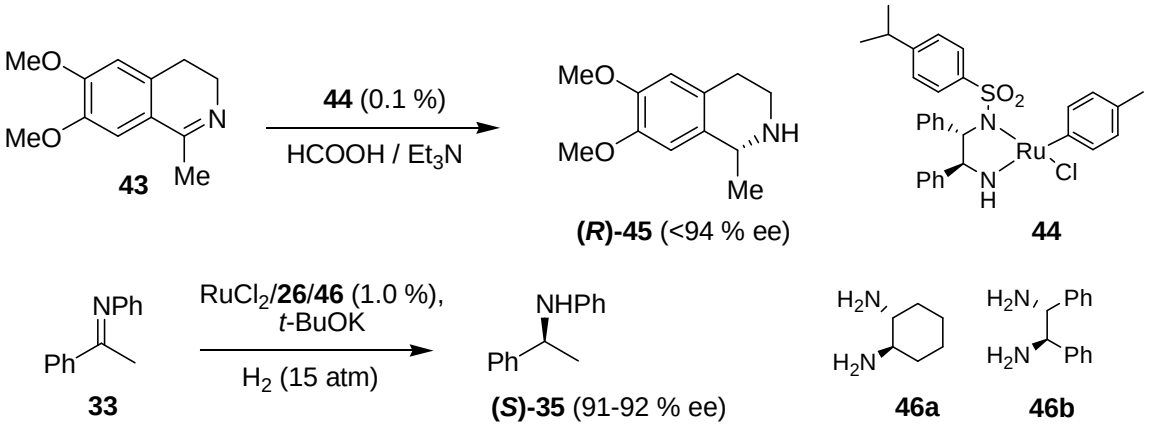
- more effective Ir analogues of Rh catalysts,
- more easily deactivated by external factors, but having high TOF/TON,
- halide ions may have positive effects on enantioselectivity, acid often needed, too.

Table 2.2. Hydrogenations Catalysed by Ir Complexes

Entry	Imine	Red. Reagent / Additives	Ligand (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**33**	H_2 / -	**34** / 0.1	ambient	99 / 89 (*R*)
2	**33**	H_2 / -	**37** / 1.0	ambient	99 / 84
3	**33**	H_2 / I_2	**37** / 1.0	–5	99 / 94
4	**36**	H_2 / -	**37** / 1.0	ambient	77 / 99
5	**ketone 39**	H_2 / I_2, Ti(O*i*-Pr)$_4$	**37** / 1.0	ambient	99 / 94 (*R*)
6	**18**	H_2 / pyridine	**41** / 10	ambient	99 / 78 (*S*)
7	**33**	H_2 / -	**42** / 0.5	ambient	98 / 90 (*R*)

2.2.3. Ruthenium Catalysis

The ruthenium complex **44** was employed in transfer hydrogenation protocol,[14] developed to avoid the use high-pressure hydrogen gas. Formic acid served as the hydride donor as other H-transfer sources (e.g. propan-2-ol) would require more active catalyst or harsher conditions. However, this method was relying on the rigidity of the structure containing the imine double bond, and in the case of cyclic imines, e.g. **43**, very high enantioselectivity was achieved (up to 97 %; Table 2.3, entry 1; Scheme 2.14).



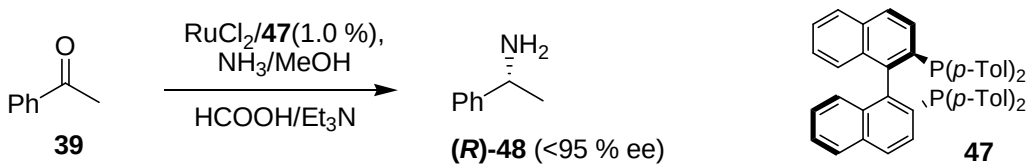
Scheme 2.14. Hydrogenations Using Ru Catalysts

Cobley and Henschke[39] chose a ligand system for Ru consisting of diphosphine and diamine, and the best combination proved to be (*R*,*R*)-Et-DuPHOS **26** and either of diamines **46a**,**b** facilitating the reduction of the aromatic imine **33** with enantioselectivity of 91 % and 92 %, respectively (Table 2.3, entries 2 and 3; Scheme 2.14). Several cyclic imines of Noyori's type, e.g. **43**, were reduced with up to 79 % ee (at 0.1 mol % catalyst loading).

Table 2.3. Hydrogenations Catalysed by Ru complexes

Entry	Imine	Reducing Reagent / Additives	Ligand (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**43**	HCOOH / Et_3N	**44** / 0.1	ambient	97 / 94 (*R*)
2	**33**	H_2 / -	**26**, **46a** / 0.1	65	99 / 91 (*S*)
3	**33**	H_2 / -	**26**, **46b** / 0.1	65	92 / 92 (*S*)
4	**Ketone 39**	HCOOH / Et_3N / NH_3	**47** / 1.0	60	92 / 95 (*R*)

An interesting procedure for reductive amination of aromatic ketones, based on transfer hydrogenation with formic acid and (*R*)-BINAP-derived ligand **47**, was developed by Kadyrov and Riermeier,[40] who prepared primary amines of up to 95 % ee (Table 2.3, entry 4; Scheme 2.15).



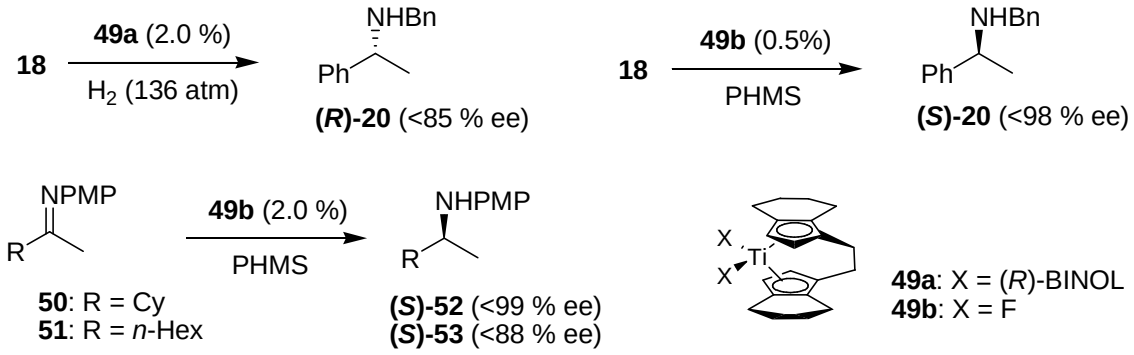
Scheme 2.15. Ru-catalysed Reductive Amination

The appearance of Kadyrov-Riermeier's and Zhang's reductive amination protocols is even more remarkable considering the generality of the methods in spite of all the intermediates possibly present in the reaction mixture – heminaminals, *N*,*O*-acetals, aminals, imines and enamines and each of them requires specific hydrogenation conditions.[41]

Ruthenium catalysis has provided several excellent methods for hydrogenations of ketones and transfer hydrogenation of imines (which is *C=N* chemoselective).

2.2.4. Titanium, Cobalt, Rhenium and Copper Catalysis

Several other metals were used for asymmetric hydrogenations. Titanium was introduced by Buchwald et al.[42] in the early 1990s (Table 2.4, entries 1-4; Scheme 2.16). Testing reactions with titanocene catalysts **49a**,**b** showed the best results with aromatic imines affording corresponding amines in 85-98 % ee.



Scheme 2.16. Hydrogenation with Ti Catalysts

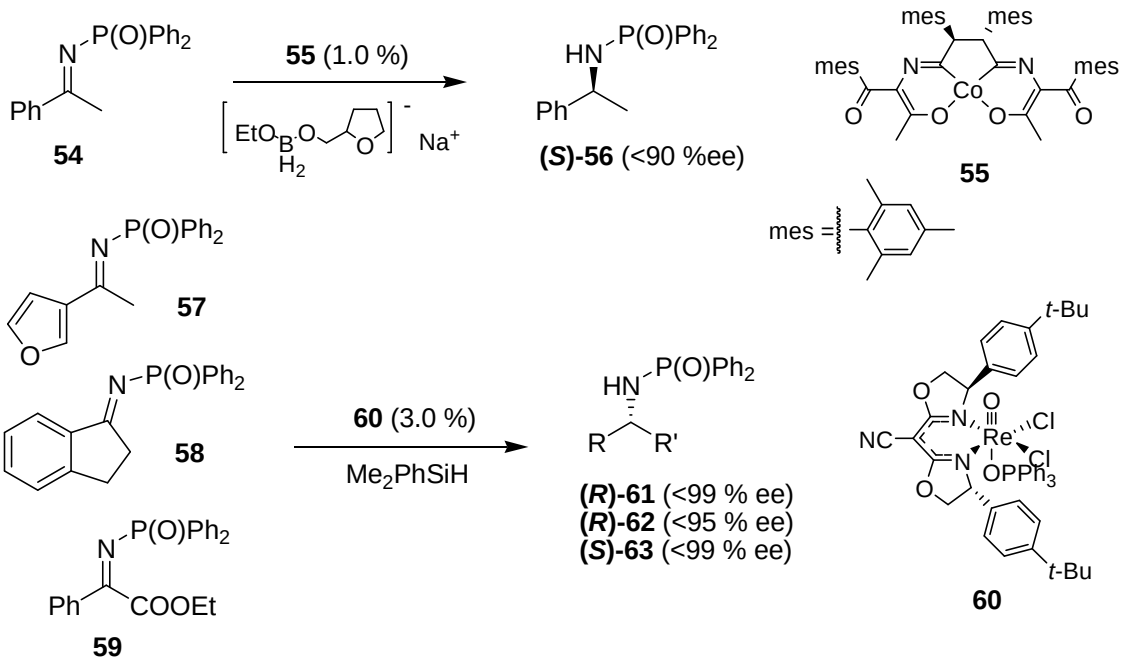
High pressure of hydrogen can be avoided by using Buchwald's protocol of $PhSiH_3$ (treated with pyrrolidine and methanol) or polymethylhydrosiloxane (PHMS) as reducing reagents.[43] Exceptionally, several alkylimines as **50** or **51** were reduced with very high enantioselectivity (up to 99 % ee).

Mukaiyama et al.[44] introduced the cobalt complex **55** which induced highly enantioselective reduction of *N*-diphenylphosphinyl imines, e.g. **54**, with a modified borohydride reducing reagent (Table 2.4, entry 5; Scheme 2.17).

Table 2.4. Hydrogenations Catalysed by Other Metals

Entry	Imine	Red. Reagent / Additives	Ligand (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**18**	H_2 / -	**49a** / 2.0	ambient	93 / 85 (*R*)
2	**18**	PHMS / *i*-BuNH_2	**49b** / 0.5	ambient	95 / 98 (*S*)
3	**50**	PHMS / *i*-BuNH_2	**49b** / 2.0	60	63 / 99 (*S*)
4	**51**	PHMS / *i*-BuNH_2	**49b** / 2.0	60	70 / 88 (*S*)
5	**54**	Borohydride / -	**55** / 1.0	ambient	97 / 90 (*S*)
6	**57**	DMPS-H / -	**60** / 3.0	ambient	76 / 99 (*R*)
7	**58**	DMPS-H / -	**60** / 3.0	ambient	89 / 95 (*R*)
8	**59**	DMPS-H / -	**60** / 3.0	ambient	83 / 99 (*S*)
9	**64**	DMPS-H / -	**65** / 6.0	ambient	89 / 96 (*R*)
10	**67**	TMDS / *t*-BuOH	**65** / 6.0	ambient	93 / 98 (*R*)
11	**54**	propan-2-ol	**70** / 120	60	85 / 96 (*R*)
12	**69**	propan-2-ol	**70** / 120	60	85 / 93 (*R*)

Recently, an oxorhenium complex **60** appeared as a catalyst for reduction of *N*-diphenylphosphinyl imines **57**-**59** with dimethylphenylsilane or diphenylmethylsilane. This reaction proceeded under mild conditions and without the need of exclusion of air or moisture[45] – aromatic imines, α-iminoesters and conjugated imines were reduced smoothly and in almost exclusive enantioselectivity (Table 2.4, entries 6-8; Scheme 2.17).

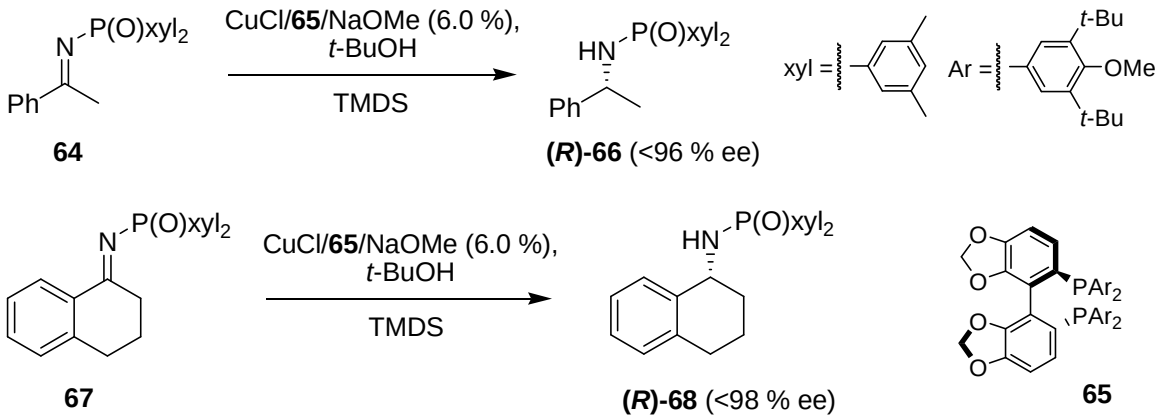


Scheme 2.17. Hydrogenation of Diphenylphosphinyl Imines Catalysed by Co and Re complexes.

One of the non-precious metals used recently in imine reductions was copper by Lipshutz and Shimizu[46] (Table 2.4, entries 9 and 10;

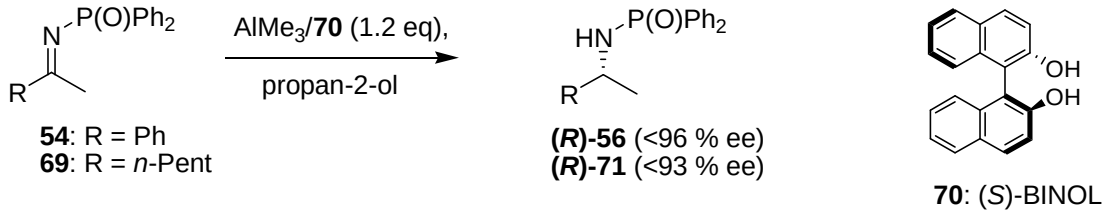
Scheme 2.18). They presumed the copper hydride as the actual reducing agent (preformed from CuCl), a chiral diphosphine ligand **65** and tetramethyldisiloxane (TMDS).

The standard amount of this catalyst is 6 mol %, by using only 1 mol % the ee's decreased by 1 %.



Scheme 2.18. Cu-catalysed Hydrogenation

An interesting protocol of Meerwein-Ponndorf-Verley-type aluminium-mediated transfer hydrogenation has been developed by Nguyen.[47] It reduces aromatic and aliphatic imines; however, it is stoichiometric in aluminium and (*S*)-BINOL (Table 2.4, entries 11 and 12; Scheme 2.19).



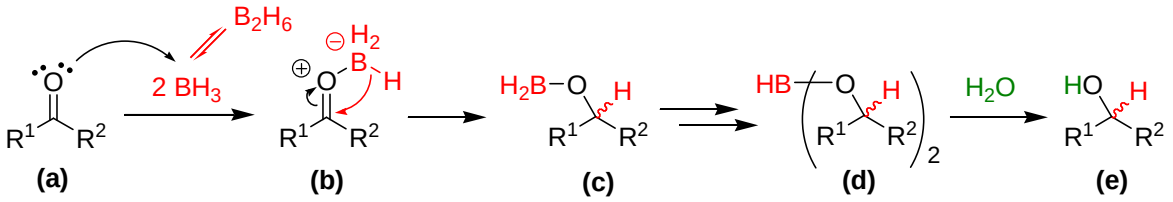
Scheme 2.19. Al-mediated Transfer Hydrogenation

Less traditional **catalysis with Ti, Co, Re or Cu** has brought several remarkable protocols for reduction of different derivatives, often *N*-diphenylphosphinyl imines. These methods vary in reaction conditions or reducing agent according to the metal used.

2.3. Hydroboration of *C=N* Bonds

2.3.1. History of Hydroboration and Early Mechanistic Views

The word *hydroboration* is linked tightly to its discoverer and major developer **H. C. Brown** (Herbert Brovarnik), the 1979 Nobel Prize winner *"for the development of the use of boron-containing compounds"*.[48] His interest in boron chemistry and mechanism of reductions with diborane goes back to his early career. The initial studies[49] (1930s) on reactivity of diborane were carried out on carbonyl compounds. It was known that diborane reduced certain carbonyl compounds, but it was not clear why and how. With the development of the techniques for the preparation of diborane itself, its availability increased and the practical applications could have been improved, too[50] (Scheme 2.20). Even if the term hydroboration is generic for *addition of boranes to multiple bonds*, nowadays, it is commonly used for the first step of preparation of alcohols from alkenes, this reaction is out of the scope of this thesis.



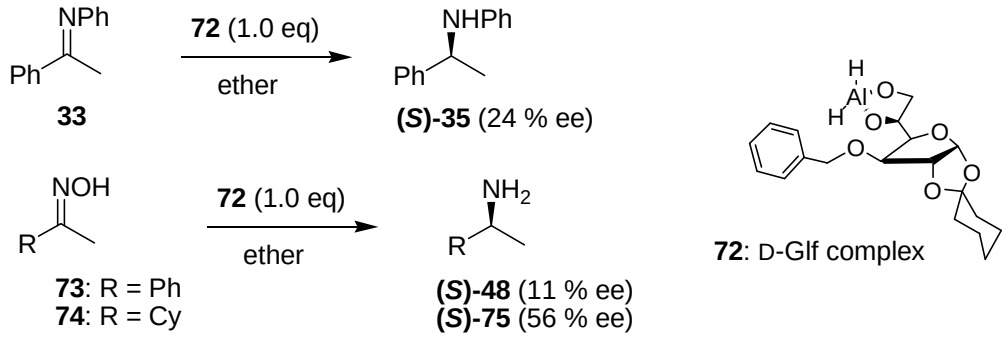
Scheme 2.20. Reduction of Carbonyl Compounds with Diborane

For the reduction of carbonyl compounds to occur (Scheme 2.20), it was suggested that borane interacts with the carbonyl group on Lewis acid-base basis. Simple carbonyl compounds (aldehydes, ketones) have sufficient electron density on the carbonyl oxygen atom **(a)** and coordinate borane rapidly. The coordination process is followed by a hydride transfer **(b)** and formation monoalkoxyborane **(c)** which is able to act as LA, as well. In a similar fashion as before, it can coordinate to another carbonyl molecule which is the new hydride acceptor. The resulting dialkoxyborane **(d)** is hydrolysed upon work-up to alcohol **(e)** and a borate salt. Clearly, the initial coordination step (and the overall reactivity) is dependent on the Lewis basicity of the carbonyl oxygen, i.e. substituents on the carbonyl or α-carbon. In the case of esters, a significant slowing down the reaction rate was observed because the carbonyl and the ether oxygen atoms compete for coordination of borane. However, the carbonyl-*O* is more probable to coordinate the boron thanks to

resonance stabilisation provided by the adjacent non-coordianted ether oxygen, even though the ester carbonyl-*O* has decreased electron density because of the same resonance stabilisation (in comparison to ketones). On the other hand, acids are readily reduced as they react through acylborane intermediates, which are stabilised through oxygen-boron resonance and the reactivity of the carbonyl then resembles that of ketones.

2.3.2. Enantioselective Hydride Reductions and Hydroborations of C=N Bonds

The research on enantioselective reduction of imines with boranes and hydrides begun to develop in mid-1970s and intensively continued in the 1980s. Naturally, the pioneering examples were carried out with ketones, readily available and stable compounds and preliminary success with them motivated researchers to explore also analogical reductions for *C=N* compounds. Among these, oximes were utilised as model compounds for they are more stable that imines, despite the fact they suffer more from the impact of the *C=N* bond geometry on stereochemistry of the product.



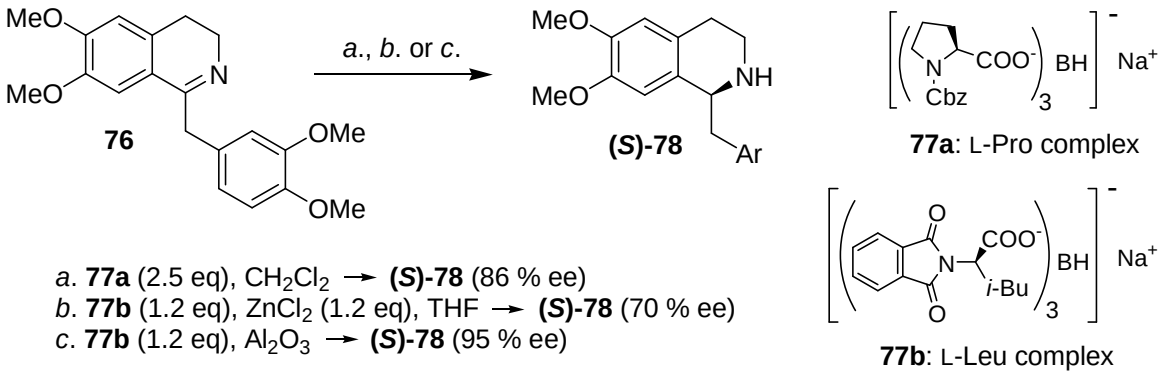
Scheme 2.21. Reduction with $LiAlH_4$-Glucofuranose Complex

First enantioselective reduction was published by Landor in 1974.[51] The publication has provided several studies on reduction of ketones and their nitrogen analogues with lithium aluminium hydride-glucofuranose complex **72**. They expected a kinetically controlled hydride transfer in the sterically least hindered transition state. However, this was quite a vague statement and their experiments only suggested that the transfer was intermolecular and two molecules of the reducing reagent were needed.

Table 2.5. Reductions with Modified Hydrides

Entry	Imine / Oxime	Reducing Reagent (equiv.) / Additives (ambient temp.)	Yield (%) / ee (%)
1	**33**	$LiAlH_4$.D-Glf (**72**) / 1.0	82 / 24 (*S*)
2	**73**	$LiAlH_4$.D-Glf (**72**) / 1.0	>70 / 11 (*S*)
3	**74**	$LiAlH_4$.D-Glf (**72**) / 1.0	>70 / 56 (*S*)
4	**76**	$NaBH_4$.L-Pro (**77a**) / 2.5	90 / 86 (*S*)
5	**76**	$NaBH_4$.L-Leu (**77b**) / 1.2	76 / 70 (*S*)
6	**76**	$NaBH_4$.L-Leu (**77b**) / 1.2 / $ZnCl_2$	72 / 78 (*S*)
7	**76**	$NaBH_4$.L-Leu (**77b**) / 1.2 / Al_2O_3	81 / 95 (*S*)

The best obtained level of enantioselectivity was around 25 % ee for imines and up to 56 % ee for oximes (Table 2.5, entries 1-3; Scheme 2.21). Somewhat better results (40-50 % ee for several aliphatic oximes) were achieved using cyclohexyl-protected glucofuranose instead of the benzyl-protected one (as in complex **72**).[52]



Scheme 2.22. Reductions with $NaBH_4$-Amino Acids Complexes

In early 1980s, Iwakuma brought the idea of modifying sodium borohydride by an amino acid (L-proline) and he investigated reduction of imines with the novel chiral triacyloxyborohydride **77a**.[53] The substrates of choice were 3,4-dihydropapaverine derivatives as **76**. Under the optimised conditions natural product (*S*)-(–)-norcryptostyline **78** was obtained in 86 % ee (Table 2.5, entry 4; Scheme 2.22). The same target molecule was synthesised also by Hajipour and Hantehzadeh using L-leucine-derived acylborohydride **77b** and the effect of $ZnCl_2$ additive was investigated (Table 2.5, entries 5-7; Scheme 2.22).[54] More interestingly, alumina-supported solvent-free synthesis provided the alkaloid **78** in excellent 95 % ee.

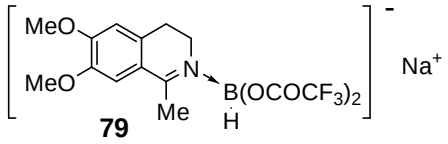
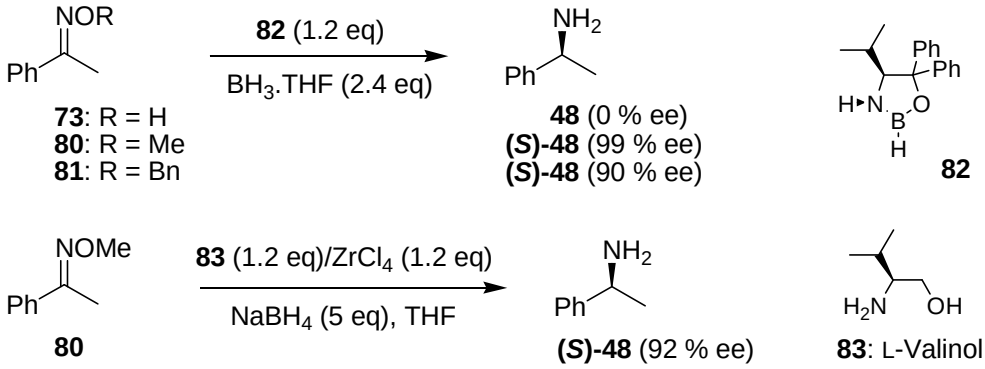


Figure 2.1. Isolated Complex from Imine **43** and $NaBH(OCOCF_3)_3$

The authors[53,54] speculated about the mechanism and proposed the formation of an imine-diacyloxyborane intermediate followed by an intramolecular hydride transfer. The idea was supported by isolation of **79** – a bis(trifluoroacetoxy)borohydride-**43** complex (Figure 2.1).



Scheme 2.23. Itsuno's Reductions with Borane and Borohydride Complex

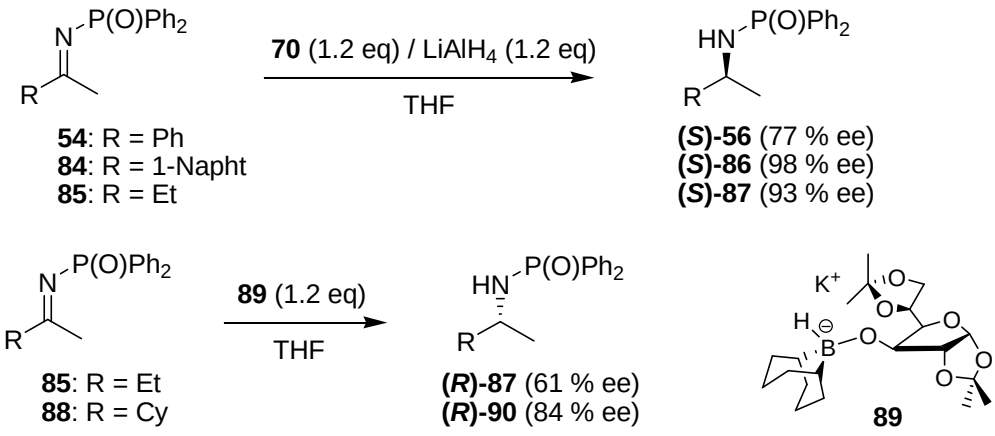
Based on previous scattered attempts of modifying the hydride reducing agents and fairly successful reduction of oxime ethers containing chiral auxiliary with BH_3.THF or $LiAlH_4$ (up to 44 % ee),[55] Itsuno's group developed a reduction protocol with BH_3.THF complex in the presence of a chiral borane.[56] The reduction of oxime ethers using this complex was efficient only in stoichiometric loading of the chiral source – an amino alcohol. Although the chiral borane, e.g. **82** did show some catalytic behaviour, attempts to decrease the loading to truly catalytic amounts failed and semicatalytic version (25 mol %) afforded the free amine **48** in 90 % ee (Table 2.6, entries 1-5; Scheme 2.23). The scope of oxime benzylethers effectively reduced with Itsuno's reagent was broadened by Fontaine.[57] Products of all tested substrates were obtained in >97 % ee and >60 % yield.

Table 2.6. Reductions of Oximes with Borane and Sodium Borohydride

Entry	Oxime	Reducing Reagent	Ligand (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**73**	BH_3.THF	**82** / 120	30	99 / 0
2	**80**	BH_3.THF	**82** / 120	30	99 / 99 (*S*)
3	**81**	BH_3.THF	**82** / 120	30	99 / 95 (*S*)
4	**81**	BH_3.THF	**82** / 25	30	99 / 90 (*S*)
5	**81**	BH_3.THF	**82** / 10	30	99 / 52 (*S*)
6	**80**	$NaBH_4$.$ZrCl_4$	**83** / 150	ambient	96 / 92 (*S*)
7	**80**	$NaBH_4$.$ZrCl_4$	**83** / 120	ambient	96 / 81 (*S*)
8	**80**	$NaBH_4$.$ZrCl_4$	**83** / 100	ambient	95 / 58 (*S*)

Mechanistic studies have shown that the reduction of oxime ethers with **82** and BH_3.THF exhibited the following characteristics:

- reduction with the BH_3.THF complex was accelerated in the presence of complex **82** (severe competition of the background reaction with catalyst loading below 25 mol %),
- the complex **82** itself could not reduce oxime ethers,
- asymmetric induction was *caused* by the complex **82**,
- only marginal change in level of asymmetric induction was observed with the polymer-supported **82**.[58]



Scheme 2.24. Reductions of Diphenylphosphinyl Imines

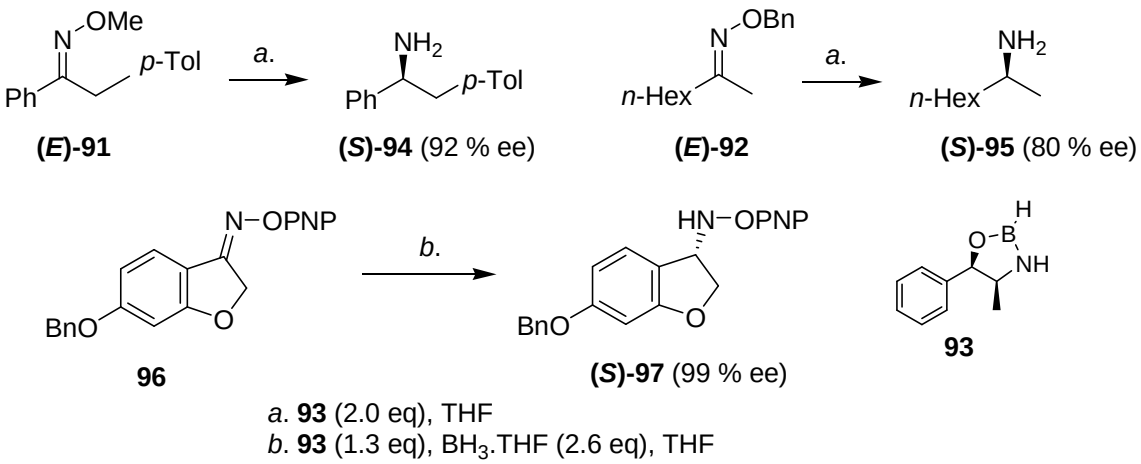
In effort to improve this technique, more convenient $NaBH_4$ was revisited.[59] Sodium borohydride could be activated by a Lewis acid so that it reacted with an amino alcohol only in presence of a LA to form the desired chiral borohydride reductant (Table 2.6, entries 6-8; Scheme 2.23); however, the structure of the active complex was not investigated. Optimised conditions afforded the free amine **48** in up to 92 % ee, the

enantioselectivity was dependent particularly on the ratio of the reagents. Unfortunately, neither this protocol could be made catalytic as any sub-stoichiometric amount of the chiral source (the amino alcohol) severely eroded the enantioselectivity and even when a transition metal Lewis acid was used.

Table 2.7. Reductions of Imines with Modified 9-BBN and $LiAlH_4$

Entry	Imine	Reducing Reagent (equiv.)	Temp. (°C)	Yield (%) / ee (%)
1	**54**	$LiAlH_4$.**70** / 1.2	25	35 / 77 (*S*)
2	**54**	$LiAlH_4$.**70** / 1.2	–78	84 / 13 (*S*)
3	**84**	$LiAlH_4$.**70** / 1.2	25	16 / 98 (*S*)
4	**84**	$LiAlH_4$.**70** / 1.2	–78	66 / 7 (*S*)
5	**85**	$LiAlH_4$.**70** / 1.2	25	38 / 93 (*S*)
6	**85**	$LiAlH_4$.**70** / 1.2	–40	63 / 40 (*S*)
7	**85**	**89** / 1.2	–78	58 / 61 (*R*)
8	**88**	**89** / 1.2	–78	95 / 84 (*R*)

Hutchins also screened several known combinations of chirally modified hydride reductant and found two of them quite successful: BINOL-$LiAlH_4$ (BINAL, Noyori's reagent) and glucofuranosyl-9-BBNH (**89**, Glucoride K, Brown's reagent).[60] Reduction of aromatic imines was more successful with BINAL system, achieving enantioselectivity up to 98 % ee (Table 2.7, entries 1-6; Scheme 2.24).



Scheme 2.25. Reductions with (–)-Norephedrine-Borane Complex

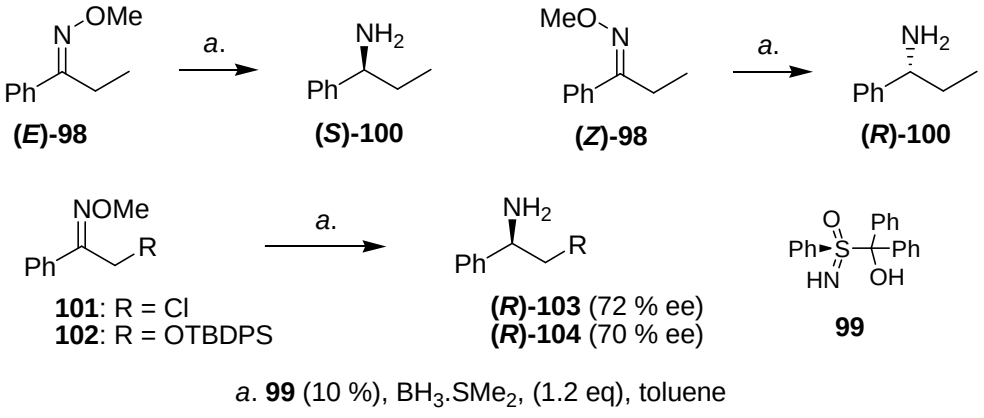
Interestingly, at lower temperatures and shorter reaction times, the yields were high and enantioselectivity low; whereas at ambient temperature the product was obtained in low yield and high ee. Reductions with complex **89** were carried out at low temperatures and afforded *N*-diphenylphosphinyl amines in moderate to good yields and ee's (Table 2.7,

entries 7 and 8; Scheme 2.24). Although some of the stated results gave almost enantiopure products, their unreliability made these experiments of little practical value.

Table 2.8. Reductions of Oximes with Borane Complexes

Entry	Oxime	Reducing Reagent	Ligand (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**(*E*)-91**	BH_3.THF	**93** / 200	20	64 / 92 (*S*)
2	**(*Z*)-91**	BH_3.THF	**93** / 200	20	58 / 92 (*R*)
3	**(*E*)-92**	BH_3.THF	**93** / 200	20	65 / 80 (*S*)
4	**(*Z*)-92**	BH_3.THF	**93** / 200	20	45 / 79 (*R*)
5	**96**	BH_3.THF	**93** / 130	ambient	52 / 99 (*S*)
6	**(*E*)-98**	$BH_3.SMe_2$	**99** / 10	ambient	68 / 50 (*S*)
7	**(*Z*)-98**	$BH_3.SMe_2$	**99** / 10	ambient	n.a. / 55 (*R*)
8	**101**	$BH_3.SMe_2$	**99** / 10	ambient	45 / 72 (*R*)
9	**102**	$BH_3.SMe_2$	**99** / 10	ambient	65 / 70 (*R*)
10	**102**	$BH_3.SMe_2$	**99** / 5	ambient	n.a. / 65 (*R*)
11	**102**	$BH_3.SMe_2$	**99** / 100	ambient	65 / 72 (*R*)

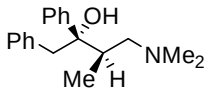
The influence of oxime geometrical isomerism on the reduction with (1*R*,2*S*)-(–)-norephedrine-borane complex **93** was tested by Sakito and Suzukamo.[61] Their results clearly showed that the absolute configuration on the amine was dependent not only on the configuration of the catalyst but also on the *C=N* geometry: **(*E*)-91** gave (*S*)-, and **(*Z*)-91** gave (*R*)-configuration of the resulting amine, maintaining the enantioselectivity (Table 2.8, entries 1-4; Scheme 2.25). Complex **93** was also utilised for a commercial synthesis of the key intermediate **97** of a potent and selective 5-lipoxygenase inhibitor and it was obtained virtually enantiopure, in low yield though[62] (Table 2.8, entry 5; Scheme 2.25).



Scheme 2.26. Sense of Asymmetric Induction vs. Geometry of Oxime

Later on, Bolm has shown a similar trend with his sulfoximine catalyst **99**[63] (Table 2.8, entries 6 and 7; Scheme 2.26). The enantioselectivity up to 72 % ee was obtained with

α-substituted oximes, e.g. **101** or **102**. Despite the moderate levels of enantioselectivity, the reaction proceeded in truly catalytic manner and increasing the catalyst loading up to 1 equivalent improved the ee's only marginally (Table 2.8, entries 8-11; Scheme 2.26).



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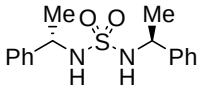

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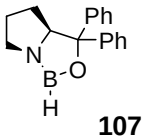

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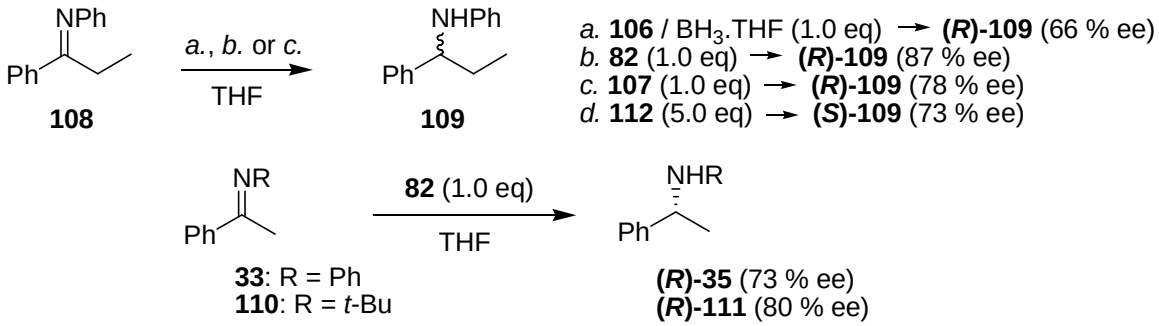
Figure 2.2. Chiral Modifiers for Asymmetric Reductions with Boranes

At the begining of the 1990s, Cho and Chun tested the known methods for reduction of open-chain imines.[64] Among the less successful were glucofuranosyl-9-BBNH **89** or Chirald **105**-BH_3 complex (Mosher's reagent; Figure 2.2) previously tested by Hutchins.[60] On the other hand, oxazaborolidines **82** (Itsuno's reagent) and **107** (Corey's reagent) or sulfoxamide **106** (Sharpless' reagent)-BH_3 complex exhibited good reactivity and enantioselectivity for a model compound propiophenone phenyl imine **108** (Table 2.9, entries 1-5; Scheme 2.27).

Table 2.9. Reductions of Imines with Oxazaborolidines and Dialkoxyborane

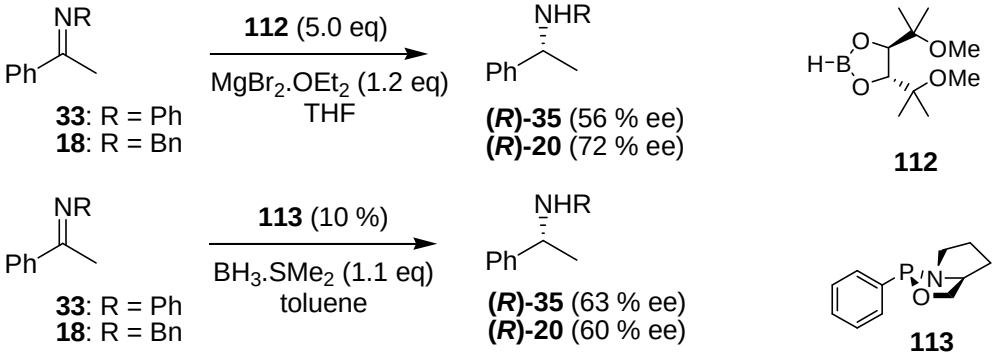
Entry	Imine	Reducing Reagent	Ligand (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**108**	BH_3.THF	**106** / 100	30	60 / 66 (*R*)
2	**108**	BH_3.THF	**82** / 100	30	98 / 87 (*R*)
3	**108**	BH_3.THF	**82** / 10	30	95 / 66 (*R*)
4	**108**	BH_3.THF	**107** / 100	25	96 / 78 (*R*)
5	**108**	BH_3.THF	**107** / 10	25	92 / 70 (*R*)
6	**33**	BH_3.THF	**82** / 100	30	98 / 73 (*R*)
7	**110**	BH_3.THF	**82** / 100	30	90 / 80 (*R*)
8	**31**		**112** / 500	0	89 / 56 (*R*)
9	**18**		**112** / 500	0	70 / 72 (*R*)
10	**31**	BH_3.SMe_2	**113** / 10	110	59 / 63 (*R*)
11	**18**	BH_3.SMe_2	**113** / 10	110	65 / 60 (*R*)

Further experiments have shown that catalyst loading of 10 mol % decreased the ee's, the least dramatically for oxazaborolidine **107** (from 78 to 70 % ee). Several aromatic imines were reduced in high yields and good enantioselectivity (Table 2.9, entries 6 and 7, Scheme 2.27). By contrast, aliphatic imines afforded the corresponding amines in low ee's.



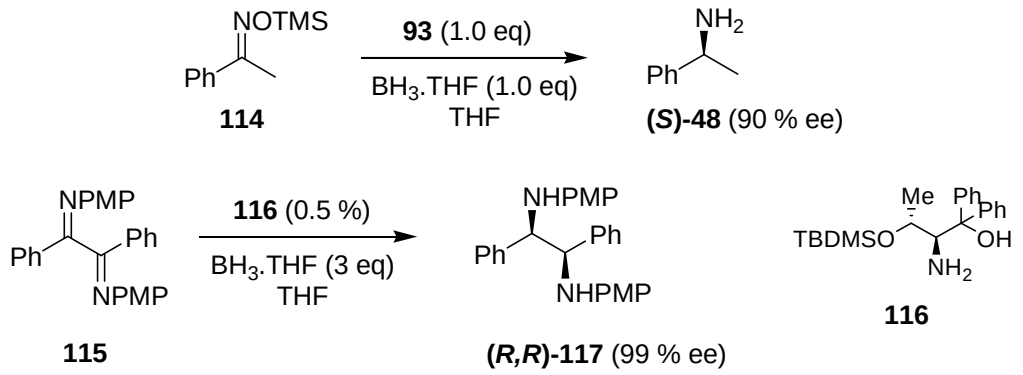
Scheme 2.27. Model Reduction of Imines with Various Reductants

Nakagawa and Hino have reported on reduction of imines with chiral dialkoxyboranes,[65] such as **112**, and showed that diols could serve as useful chiral sources alongside amino alcohols. Arylimines **33** and **18** were reduced with good yields and moderate enantioselectivities up to 73 % for model imine (Table 2.9, entries 8 and 9; Scheme 2.28).



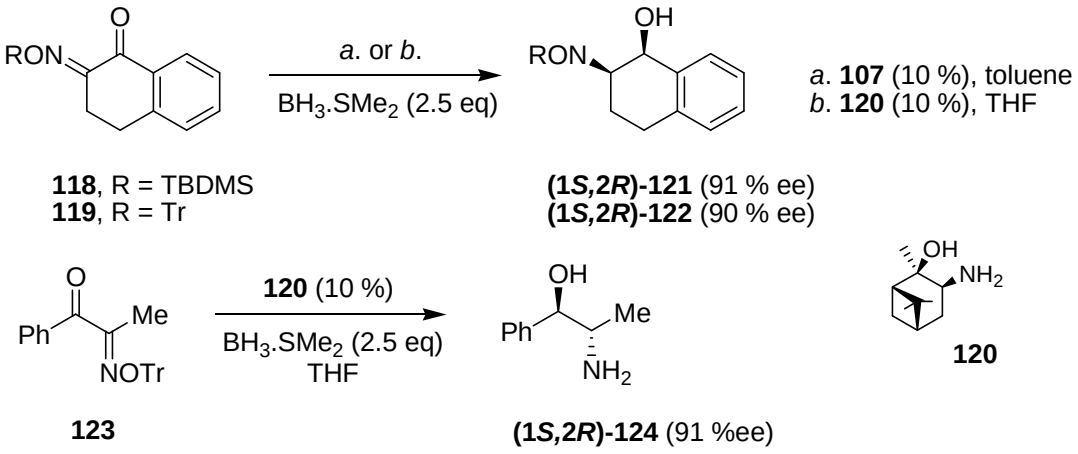
Scheme 2.28. Reduction of Imines with Other Types of Ligands

Brunel and Buono have investigated the possibility of reduction of imines with a novel oxazaphospholidine **113** in analogy to oxazaborolidines.[66] The reaction proceeded smoothly at the optimum loading 10 mol % and higher temperature (110 °C), only moderate enantioselectivities were achieved (60-63 % ee; Table 2.9, entries 10 and 11; Scheme 2.28).



Scheme 2.29. Reduction of Various Substrates with L-Thr-Borane Complex

Cho et al. also reported reduction of TMS-protected ketoximes;[67] however, high enantioselectiviy was observed only on the case of oxime **114** derived from acetophenone using (–)-norephedrine-derived oxazaborolidine **93** (Table 2.10, entry 8; Scheme 2.29). One of the few protocols where the chiral source is used in very low catalytic amounts was developed by Fujisawa for a stereoselective synthesis of 1,2-diphenylenediamines.[68] The reaction was enantiospecific when 1 equivalent of the chiral ligand **116** was used. However, loading to 0.5 mol % (!) still provided the diamine in 99 % ee and 95:5 stereocontrol (Table 2.10, entries 2 and 3; Scheme 2.29). Examples of diastereoselective reduction of 1-oxo-2-ketoximes using ligand **116** were provided, too.[69]



Scheme 2.30. Reduction of Bifunctional Substrates with Borane Complexes

In bifunctional molecules, such as 1-oxo-2-ketoximes, the oxo-functionality is reduced preferentially and determines the configuration on the forming amino group from the 1-ol-2-ketoxime intermediate,[70] the major product being the cyclic *cis*-amino alcohol with up to 80 % de and 93 % ee[71] (Table 2.10, entry 4; Scheme 2.30) or non-cyclic *anti*-

amino alcohol with up to 70 % de and 99 % ee[72] (Table 2.10, entries 5 and 6; Scheme 2.30). The enantioselectivity in this protocol was dependent on the steric bulk of the oxime ether group.

Table 2.10. Reductions of Bifunctional Substrates with Boranes

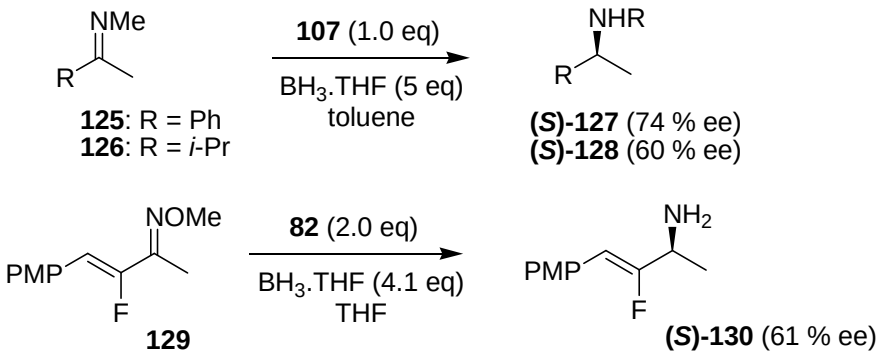
Entry	Imine	Reducing Reagent	Ligand (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**114**	BH_3.THF	**93** / 100	ambient	96 / 90 (*S*)
2	**115**	BH_3.THF	**116** / 0.5	ambient	90 / 99 (*R*,*R*)
3	**115**	BH_3.THF	**116** / 100	ambient	90 / >99 (*R*,*R*)
4	**118**	BH_3. SMe_2	**107** / 10	–20 to 25	78 / 91 (1*S*,2*R*)
5	**119**	BH_3. SMe_2	**120** / 10	ambient	91 / 90 (1*S*,2*R*)
6	**123**	BH_3. SMe_2	**120** / 10	ambient	93 / 91 (1*S*,2*R*)

In the last decade, several variations of substrates, procedures, or oxazaborolidines have been reported. Aromatic and aliphatic imines, such as **125** or **126**, were reduced with Corey's reagent **107**; however, only in moderate yields and enatioselectivities[73] (Table 2.11, entries 1 and 2; Scheme 2.31).

Table 2.11. Miscellaneous Reductions with Boranes

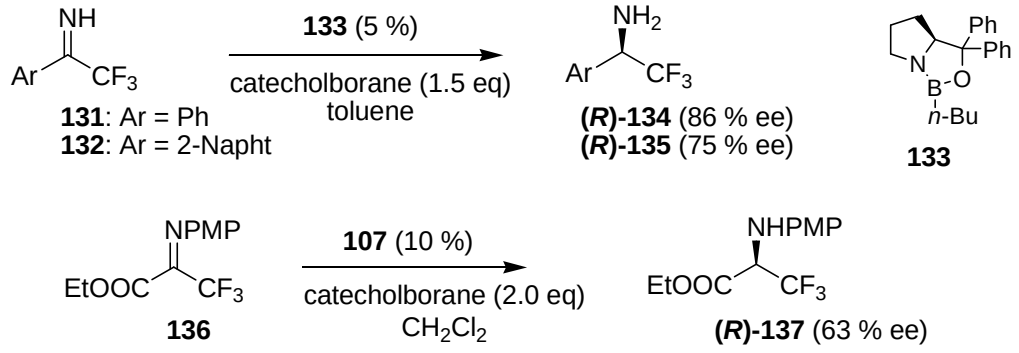
Entry	Imine	Reducing Reagent	Ligand (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**125**	BH_3.THF	**107** / 100	0	60 / 74 (*S*)
2	**126**	BH_3.THF	**107** / 100	0	79 / 60
3	**129**	BH_3.THF	**82** / 200	ambient	77 / 61 (*S*)
4	**129**	BH_3.THF	**82** / 25	ambient	60 / 37 (*S*)
5	**131**	Catecholborane	**133** / 5	–15	87 / 86 (*R*)
6	**132**	Catecholborane	**133** / 5	–15	86 / 75 (*R*)
7	**136**	Catecholborane	**107** / 10	25	94 / 63 (*R*)
8	**18**	BH_3.THF	**138a** / 100	50	39 / 4 (*S*)
9	**80**	BH_3.THF	**138a** / 100	50	61 / 84 (*S*)
10	**80**	BH_3.THF	**138b** / 223	50	56 / 72 (*R*)
11	**80**	BH_3.THF	**138c** / 223	0	70 / 99 (*R*)

Novel α-fluoro[74] **129** and α-trifluoromethyl *NH*-imines **131**, **132**[75] or imino ester **136**[76] were also successfully reduced with Itsuno's reagent **82** or Corey's oxazaborolidines **107** and **133**, to afford the corresponding α-fluoroamines, α-trifluoromethyl-arylamines, and α-amino-α-trifluoromethylcarboxylates, respectively (Table 2.11, entries 3-7, Scheme 2.32). Unlike the majority of the previous applications, these methods were catalytic. Another interesting application of the reducing system **107**-catecholborane was the reduction of α-trifluoromethyl-*C*-phosphorylated *NH*-imines[77] in analogy to the previous *NH*-imines and esters. The α-amino-α-trifluoromethylphosphonates were obtained in moderate ee, up to 70 %.



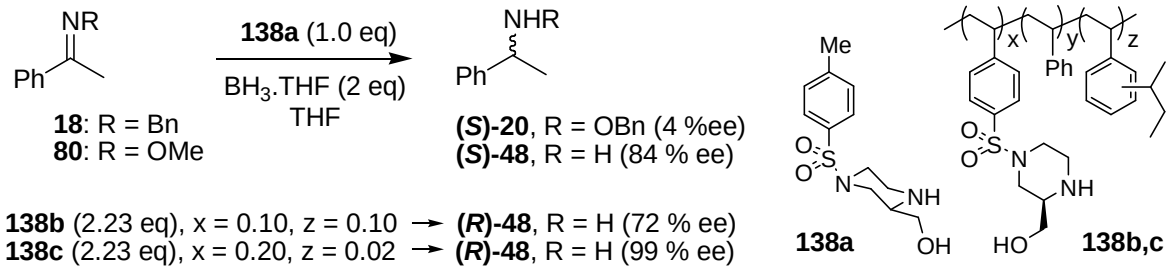
Scheme 2.31. Novel Substrates for Reduction with Oxazaborolidines

Itsuno has continued his research on enantioselective reductions of ketones, imines or oximes and he has developed a new piperazinemethanol-sulfonamide ligand **138a**.[78] Ketones were reduced catalytically (20 mol %), oximes stoichiometrically, both in moderate ee's (up to 84 % ee) and imines afforded only racemic products (Table 2.11, entries 8-11; Scheme 2.33).



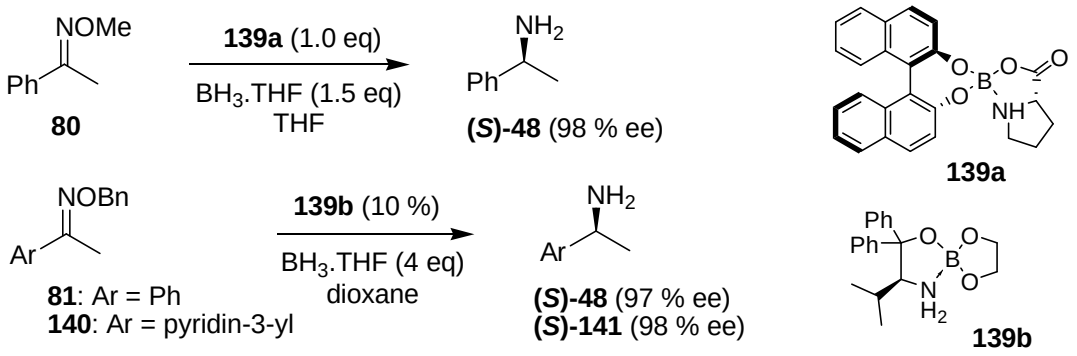
Scheme 2.32. Novel Substrates for Catalytic Reduction with Oxazaborolidines

The monomeric **138a** was anchored to a polystyrene framework and the dependency of enantioselectivity on the composition of the polymer was investigated. It was found that the optimal molar fraction of the ligand monomer was 20 mol %. The co-polymer **138c** afforded free amine **48** in 99 % ee (opposite configuration than when using **138a**) and could be reused 6 times with no loss of enantioselectivity. This was a rare case when the polymeric catalyst exhibited better enantioselectivity than the homogenous monomer.



Scheme 2.33. Polymer-supported Ligand for Reduction with Borane

A newer type of catalysts which form active reducing species with borane are spiroborate esters. The first protocol utilising the (*R*)-BINOL-proline-based spiroborate **139a** afforded free amines in high level of enantioselectivity (up to 98 % ee) only in stoichiometric amounts[79] (Table 2.12, entry 1; Scheme 2.34).



Scheme 2.34. Reduction of Oxime Ethers with Spiroborates

An improvement of this method came with the amino alcohol-ethyleneglycol catalyst **139b** which reduced the oximes in the presence of (unusual) 4 equivalents of borane to free amines in very high enantioselectivity (typically 95-98 % ee).[80] The reduction was also stereoselective, i.e. the (*E*)-oxime was reduced to (*S*)-amine, exclusively. The interesting fact was that a variety of heterocycles were tolerated in the place of the aryl group, except pyridin-2-yl substrates, which were reduced by borane in an uncatalysed (racemic) fashion.

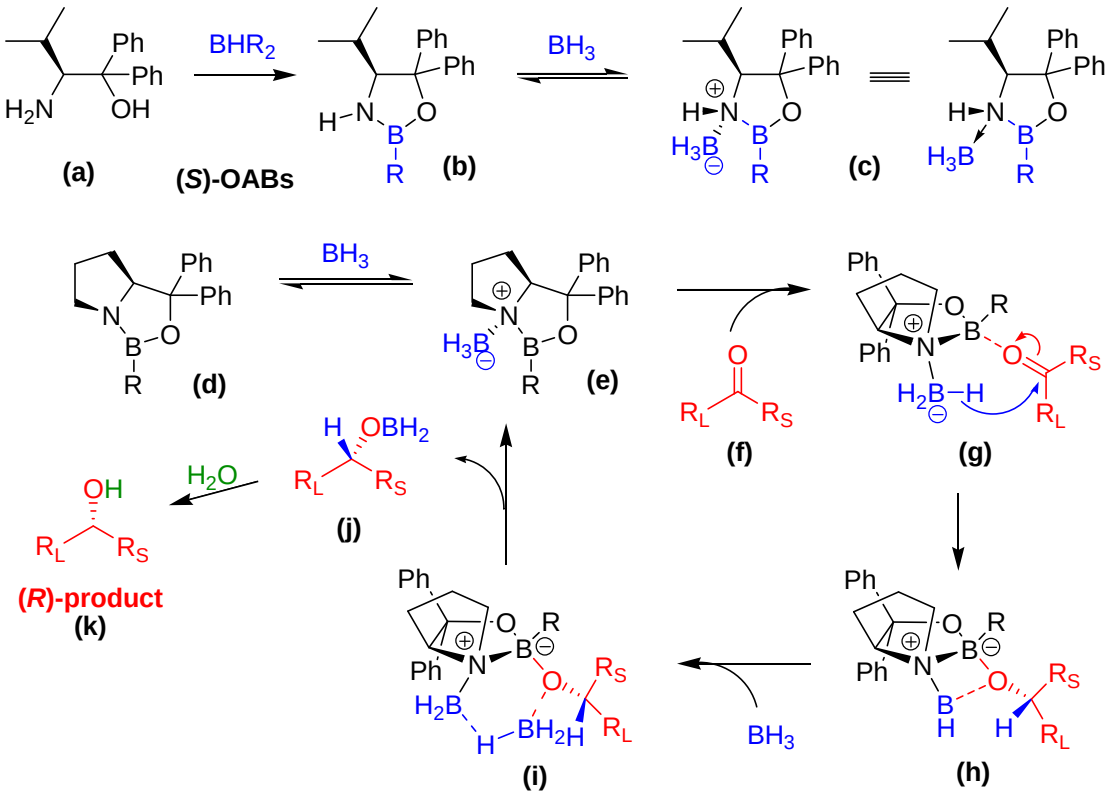
Table 2.12. Reductions with Spiroborates

Entry	Oxime	Reducing Reagent	Ligand (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**80**	BH_3.THF	**139a** / 100	0	76 / 98 (*S*)
2	**81**	BH_3.THF	**139b** / 10	25	83 / 89 (*S*)
3	**81**	BH_3.THF	**139b** / 10	0	77 / 97 (*S*)
4	**140**	BH_3.THF	**139b** / 10	0	38 / 98 (*S*)

2.3.3. Mechanistic Considerations of Reductions with Oxazaborolidines

The oxazaborolidines (OABs) play the role of Lewis acid-Lewis base bifunctional asymmetric inducers for activation of the carbonyl and the borane[81] (shown for Itsuno's **(b)** and Corey's **(d)** OAB, Scheme 2.35):

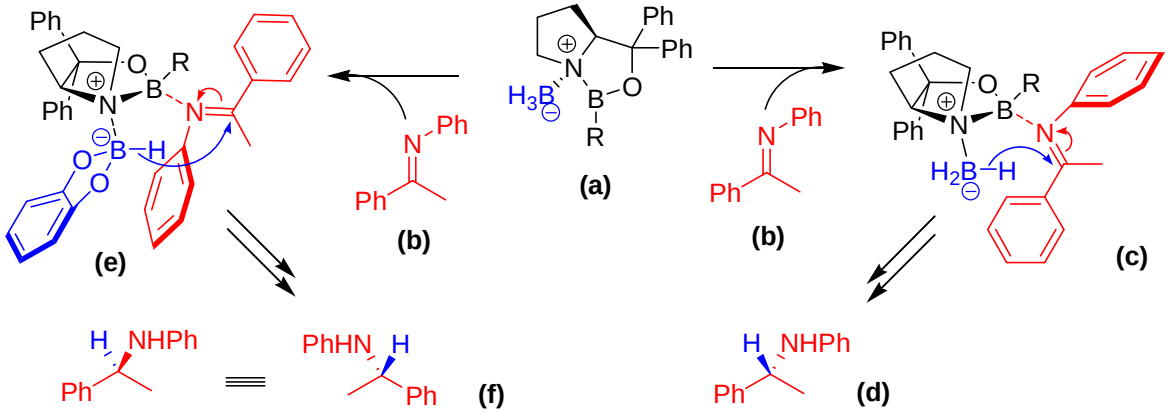
- the Lewis-basic nitrogen site of the OAB **(b, d)** coordinates a molecule of borane, forming a *cis*-fused oxazaborolidine-BH_3 complex **(c, e)**, activating the borane,
- thus, the Lewis acidity of the OAB boron atom is increased and it can bind the carbonyl compound **(f, g)** – simultaneous activation of both reacting species towards the intramolecular hydride transfer **(g, h)**,
- the substrate approaches the OAB with the larger substituent (R_L) *cis* towards the vicinal BH_3 so that the hydride is transferred to *re*-face of the substrate (providing CIP priority is also $R_L > R_S$),
- the catalytic cycle is maintained by excess of the reducing borane (BHR_2, BH_2R, BH_3) **(i, j, k)**.



Scheme 2.35. Proposed Mechanism for Reduction of Ketones with Oxazaborolidines

Tight organisation in the transition state secures that the chiral relay is unambiguous and the (*S*)-OAB is translated into (*R*)-configuration of the product. The optimal temperature was found to be 20-30 °C.[82]

From the previous overview of examples and methods for reduction of imines (and oximes) with boranes or hydrides, it is clear that severe lack of reliability persists. Only very few protocols have been made catalytic, whereas the opposite is true for reduction of ketones with oxazaborolidines.[83] Numerous examples of this have been documented in the literature, posing a question of why this system does not work for imines. It could be due to lower electrophilicity of the imine carbon and rapid equlibration between (*E*)- and (*Z*)-isomers. Often enough, Lewis acidic boron is deactivated by the basic imine/amine nitrogen of the substrate or the product as discussed in Chapter 2.1.2.



Scheme 2.36. Proposed Mechanism for Reduction of Imines with Oxazaborolidines

Another problem is the rate of the uncatalysed (background) reduction, which is – in the case of ketones – considerably slower than the catalysed reaction (using BH_3.THF) or it does not proceed at all (using catecholborane). However, for imines, the background reaction affords the racemic product in high yield for both reducing reagents[84] (Scheme 2.36). If an (*E*)-imine is taken as substrate, the organisation of the transition state can differ according to the used reductant:

- using a sterically less demanding BH_3, it is likely that the approach of the imine towards the OAB happens in similar fashion as in the case of ketones, as in **(c)** (R_L ~ Ph, R_S ~ Me), resulting in formation of an (*R*)-amine **(d)**,

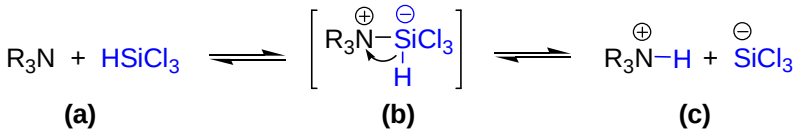
- if a sterically more demanding borane is used (e.g. catecholborane), it is likely that the less crowded conformation would be the opposite one **(e)**, affording an (*S*)-amine **(f)**.

Thus, the research of reductions of carbonyls with boranes has brought considerable achievements only for ketonic substrates. An alternative reducing reagent – virtually inactive on its own and activated by catalyst – had yet to be developed.

2.4. Hydrosilylations of Imines

2.4.1. History of Hydrosilylations and Early Mechanistic Views

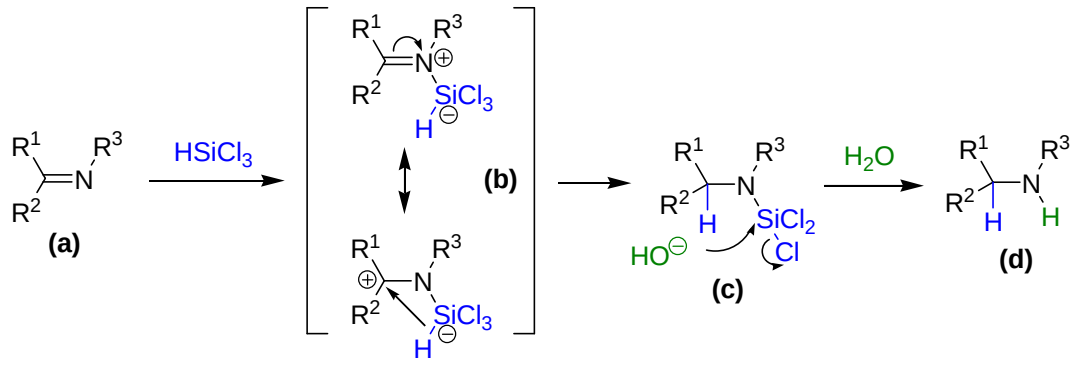
The reductive properties of trichlorosilane were extensively studied since the 1950s and resulted in reductive silylation of several classes of compounds, such as alkenes and alkynes ($HSiCl_3$ only); aldehydes, ketones and imines, acids and their derivatives ($HSiCl_3$ with a tertiary amine).[85] Though, it was not until the 1980s that the mechanistic understanding allowed development of new methods, synthetically truly useful.



Scheme 2.37. First Proposed Mechanism for Formation of Trichlorosilyl Anion

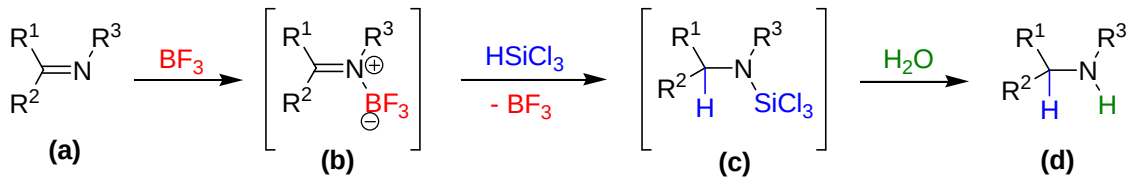
Mixtures of trichlorosilane and a Lewis base (pyridine, tertiary amine) were known to form isolable (but not very stable) adducts containing two equivalents of the base, prone to disproportionation to tetrachlorosilane and silane.[86] The early mechanistic NMR experiments were targeted to propose and prove the structure of the trichlorosilane-tertiary amine complex (Scheme 2.37) – ^{1}H NMR showed a new signal at δ 11.03 assigned as of protonated base **(c)**;[87] therefore creating trichlorosilyl anion available to act as the reactive nucleophile. Another proof of this species was the amine-catalysed deuterium exchange of ^{1}H-trichlorosilane with a tertiary amine-deuteriochloride salt where the formation of the new complex was the rate-determining step.[88] **The silicon-bonded hydrogen would gain**

a substantial hydride character (see also Chapter 3.2). Another support for the theory is gained from the properties of pyridine-trichlorosilane adducts.[89] It has been shown that the *Si-Cl* and *Si-N* bonds are predominantly ionic; however, the latter bond also featured donor-acceptor character, and the *Si-H* bond was categorised as polar-covalent. The natural charges on atoms were shifted to more extreme values upon coordination, i.e. **the ligands became more negatively charged and silicon more positively**.



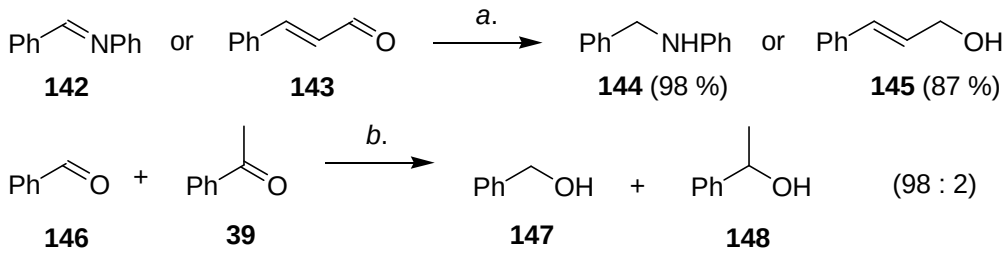
Scheme 2.38. Proposed Mechanism for Formation of Trichlorosilyl-Imine Intermediate

The first reduction of imines was successful with the standard trichlorosilane-tertiary amine mixture, but also without the addition of a tertiary amine (Scheme 2.38). Both methods afforded the corresponding amine and not expected hydrocarbon as did carbonyls. An NMR study suggested that the actual product of the reaction was trichlorosilylamine **(c)** which was hydrolysed easily on work-up to the free amine **(d)**. Supposedly inactive trichlorosilane reduced the imine double bond with no amine catalyst, suggestinng that the imine nitrogen is sufficiently Lewis basic to form an adduct with trichlorosilane, where the silicon atom is penta- or hexacoordinate (Chapter 3.2.2), similar to the species formed with a tertiary amine. The hydride transfer could then occur in an intramolecular fashion to the highly electrophilic carbon atom[85b] in **(b)** (Scheme 2.38).



Scheme 2.39. Proposed Mechanism for BF_3-catalysed Trichlorosilylation

The attraction of the simple reduction method was spoilt by the harsh conditions – reflux in acetonitrile. A modification with milder conditions was developed in 1991,[90] the use of catalytic amounts of a strong Lewis acid as BF_3 facilitated the reaction at room temperature (Scheme 2.39). Authors claimed that BF_3 and $HSiCl_3$ did not react with each other and therefore the imine **(a)** would preferentially form a complex with BF_3 **(b)** which then could be hydrosilylated **(c)** and hydrolysed to the amine product **(d)**. Another possibility was to use more potent reductant dichlorosilane, without BF_3 catalysis.

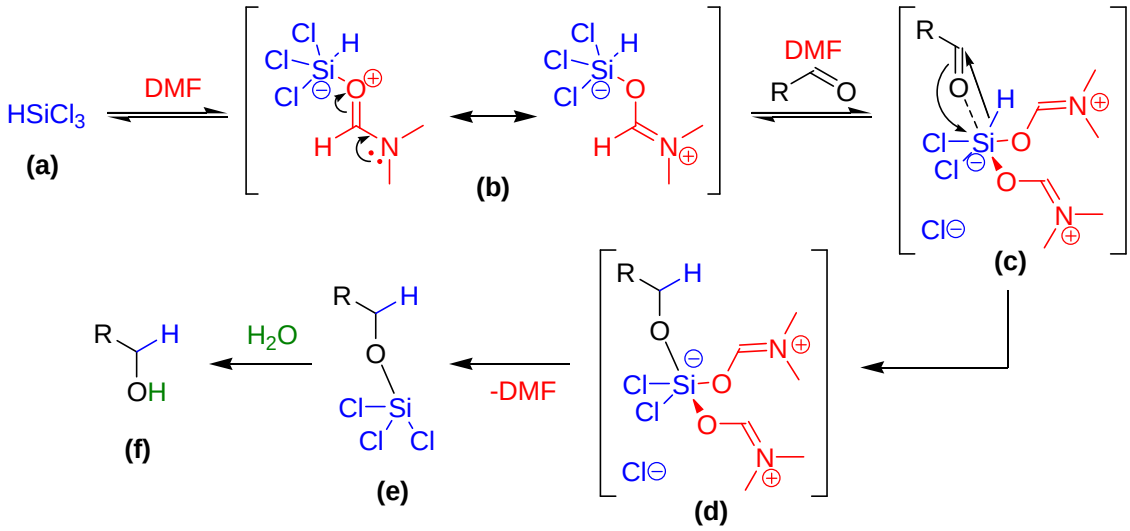


a. $HSiCl_3$, CH_2Cl_2/DMF (4:1), 0 ℃, 4h
b. $HSiCl_3$, CH_2Cl_2/DMF (4:1), –20 ℃, 4h

Scheme 2.40. Examples of DMF-catalysed Trichlorosilylation

Five years later, another method was developed by Kobayashi, where trichlorosilane was activated with DMF.[91] This method was a real breakthrough – simple, reliable, high-yielding and chemoselective! Aldehydes were reduced at –20 °C, aldimines at 0 °C in 4 hours, and ketones at room temperature and with longer reaction times (Scheme 2.40). Moreover, conjugated multiple bonds were not reduced, the reduction was entirely 1,2-selective. A ^{29}Si NMR study identified the hypervalent silicates.

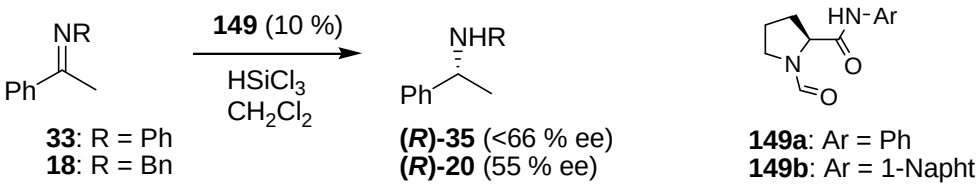
DMF is a Lewis base capable of coordinating trichlorosilane to produce penta- or hexacoordinate silicates **(b)** that are strong Lewis acids highly electrophilic towards the carbonyl. The hydrogen bonded to silicon gains hydride character and once the carbonyl compound is in proximity of the silicon **(c)**, an intramolecular hydride transfer can occur to produce trichlorosilylalcohol **(e)** which affords alcohol **(f)** upon hydrolysis (Scheme 2.41).



Scheme 2.41. Proposed Mechanism of DMF-catalysed Trichlorosilylation

2.4.2. Enantioselective Hydrosilylations of Imines

The variability of the Lewis basic component opened the door for asymmetric applications by using chiral Lewis bases. The first enantioselective reduction of imines with trichlorosilane was reported in 2001 by Matsumura.[92] His protocol was based on the Lewis base activation of trichlorosilane. In the presence of the proline-derived formamides **149a**,**b**, ee's up to 66 % and high imine chemoselectivity were achieved (Table 2.13, entries 1-3; Scheme 2.42).



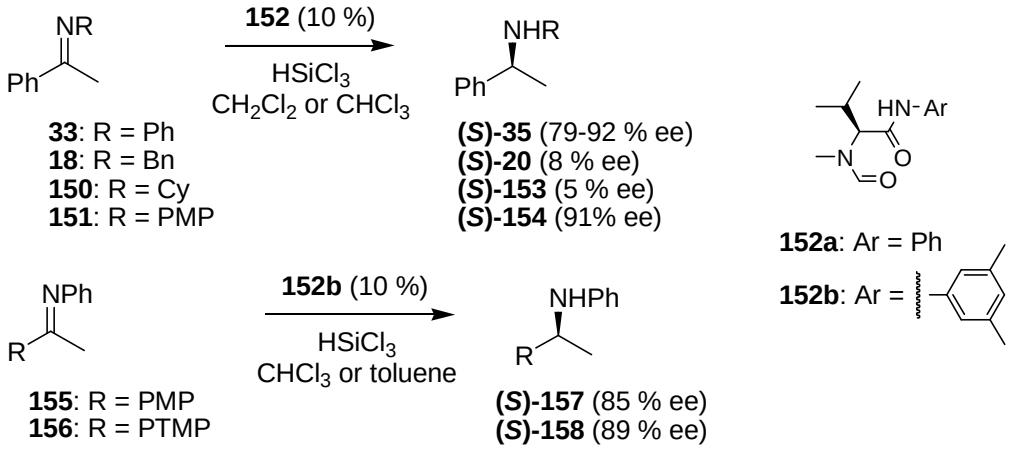
Scheme 2.42. First Enantioselective Reduction of Imines with Trichlorosilane

For the same model reaction with imine **33**, the valine derived formamide catalyst **152a** exhibited better results, aryl imines were reduced with high enantioselectivity up to 92 % ee.[93] Imines derived from aliphatic amines afforded racemic (or close) products (Table 2.13, entries 5-8; Scheme 2.43).

Table 2.13. Model Reductions of Imines with Trichlorosilane

Entry	Imine	Catalyst (mol %)	Solvent	Temp. (°C)	Yield (%) / ee (%)
1	**33**	**149a** / 10	CH_2Cl_2	ambient	91 / 55 (*R*)
2	**33**	**149b** / 10	CH_2Cl_2	ambient	52 / 66 (*R*)
3	**18**	**149a** / 10	CH_2Cl_2	ambient	97 / 55 (*R*)
4	**31**	**152a** / 10	CH_2Cl_2	ambient	68 / 79 (*S*)
5	**31**	**152a** / 10	$CHCl_3$	ambient	79 / 86 (*S*)
6	**31**	**152a** / 10	$CHCl_3$	–20	49 / 92 (*S*)
7	**18**	**152a** / 10	$CHCl_3$	ambient	46 / 8
8	**150**	**152a** / 10	$CHCl_3$	ambient	50 / 5

Interestingly, the same configuration on the amino acid scaffold afforded opposite configuration of the amine indicating different mechanism of enantiodifferentiation. Second generation analogue, catalyst **152b** performed even better and it was used for screening of its activity towards electronically modified substrates **151** to **156** (Table 2.14, entries 1-5; Scheme 2.43).[93]



Scheme 2.43. Enantioselective Reduction of Imines with Trichlorosilane and Valine Catalyst

Optimisation of the reaction conditions included variation of solvent (CH_2Cl_2, $CHCl_3$, MeCN, toluene), temperature, catalyst loading, and reaction time. Their combination has led to several practical conclusions:

- toluene as solvent increased the enantioselectivity from 79 % (CH_2Cl_2) to 92 % ee,
- lower temperature increased the enantioselectivity (mainly in case of aliphatic imines by slowing down the background reaction significantly), but decreased yields and the optimum temperature was determined to be room temperature,
- the background reaction for aromatic imines is slow and low-yielding,
- the catalyst loading could be as low as 1 mol %, the convenient optimum was

determined to be 5 mol %,

- the reaction time for full conversion was up to 24 h,
- linear relationship between the enantiopurity of the catalyst and the product; no non-linear effects were observed.

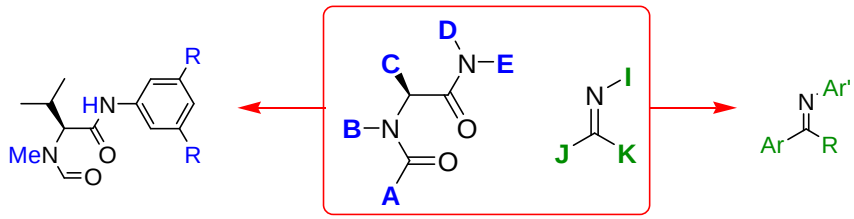


Figure 2.3. Catalyst **152** and Imine Structure Effects

From preliminary experiments it was clear that the imine must be derived from an aromatic amine (Figure 2.3, position **I**), ideally *p*-methoxyaniline which then can be oxidatively removed. The reduction proceeds with practical enantioselectivities only if it is derived from an aryl-alkyl ketone (positions **J** and **K**). The catalyst structure was also varied, virtually on every position (Figure 2.3, **A** to **E**):

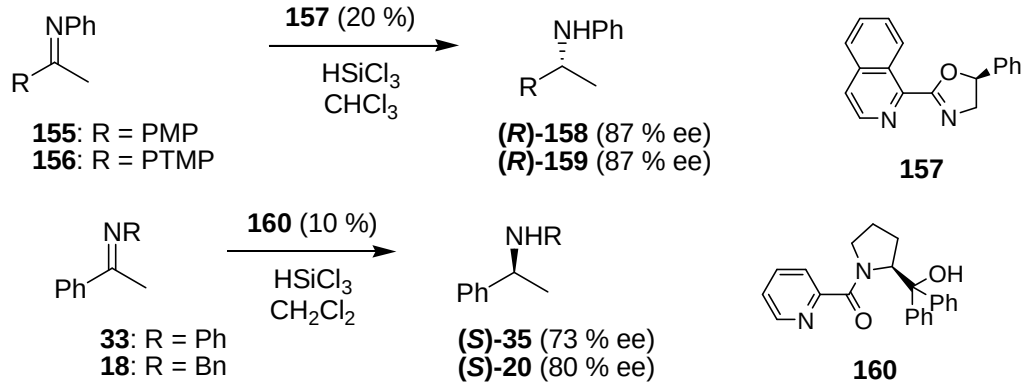
- **A** = H, the formamide moiety is crucial for the reactivity and enantioselectivity – the carbonyl group must be sufficiently Lewis basic and small,
- **B** = Me, the *N*-methyl group is important for enantioselectivity but not reactivity,
- **C** = *i*-Pr, the particular amino acid used determines not only the enantioselectivity of the reduction, but also the absolute configuration of the product, the continuum of enantioselectivity from highly enriched (*S*)-configured amine with valine-derived catalyst through phenylglycine-derived catalyst affording racemic product to moderately (*R*)-enantioenriched amine obtained with alanine-derived catalyst:

(*S*)-product ee ← *i*-Pr ~ Cy > *t*-Bu > Bn > *i*-Bu > Ph (*racemic*) < Me → (*R*)-product ee

- **D** = H, **E** = aryl, it is desirable that the catalyst is a secondary anilide derivative; a tertiary anilide or an aliphatic amide are unreactive,
- **R** group, the enantioselectivity of the reduction increases as: H < Me < *i*-Pr < *t*-Bu.

The first organocatalyst catalysing reduction of imines *and* ketones was a pyridyl-oxazoline **157** from the same group.[94] It showed appreciable results for reduction of imines

(Table 2.14, entries 6 and 7; Scheme 2.44), up to 87 % ee, though it performed better in reduction of aromatic ketones. From mechanistic views, trichlorosilane coordinates both heterocyclic nitrogens and the reaction exhibits long-ranging chiral induction.



Scheme 2.44. Enantioselective Reduction of Imines with Trichlorosilane and Non-formamides

Another non-formamide catalyst was a picolinic acid derivative **160** where the silicon atom is coordinated to the picolinyl nitrogen and carbonyl group,[95] and the transition state might be additionally stabilised by the alcohol group. The highest enantioselectivity achieved with this catalyst was 80 % ee for imine **18** (Table 2.14, entries 8 and 9; Scheme 2.44).

Table 2.14. Other Organocatalyst for Reduction of Imines with Trichlorosilane

Entry	Imine	Catalyst (mol %)	Solvent	Temp. (°C)	Yield (%) / ee (%)
1	**33**	**152b** / 10	$CHCl_3$	ambient	70 / 89 (S)
2	**33**	**152b** / 10	toluene	ambient	81 / 92 (S)
3	**151**	**152b** / 10	toluene	ambient	85 / 91 (S)
4	**155**	**152b** / 10	toluene	ambient	86 / 85 (S)
5	**156**	**152b** / 10	toluene	ambient	86 / 89 (S)
6	**155**	**157** / 20	$CHCl_3$	–20	51 / 87 (*R*)
7	**156**	**157** / 20	$CHCl_3$	–20	65 / 87 (*R*)
8	**33**	**160** / 10	CH_2Cl_2	ambient	86 / 73 (*S*)
9	**18**	**160** / 10	CH_2Cl_2	ambient	67 / 80 (*S*)

Sun's group published several organocatalysts for reduction of imines with trichlorosilane in a period of two years. The earlier work was represented by formamides based on the idea of replacing the 5-membered proline heterocycle of Matsumura's catalyst **149** with its six-membered analogue[96] (pipecolinic acid) **161** and further modification to piperazin-2-carboxylic acid[97] **162** (Figure 2.4).

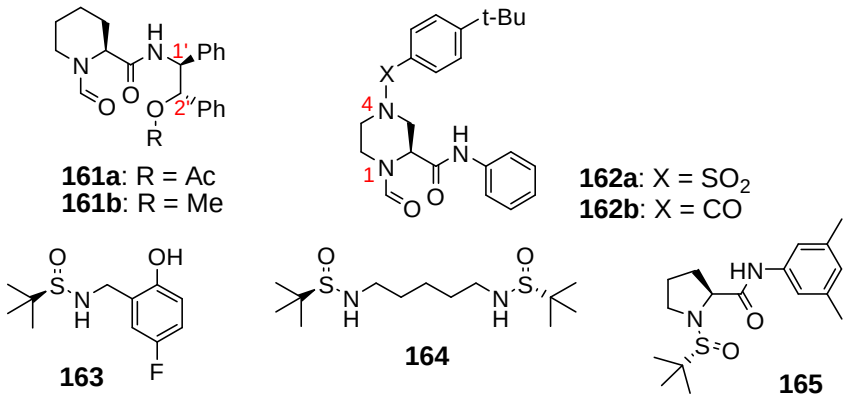
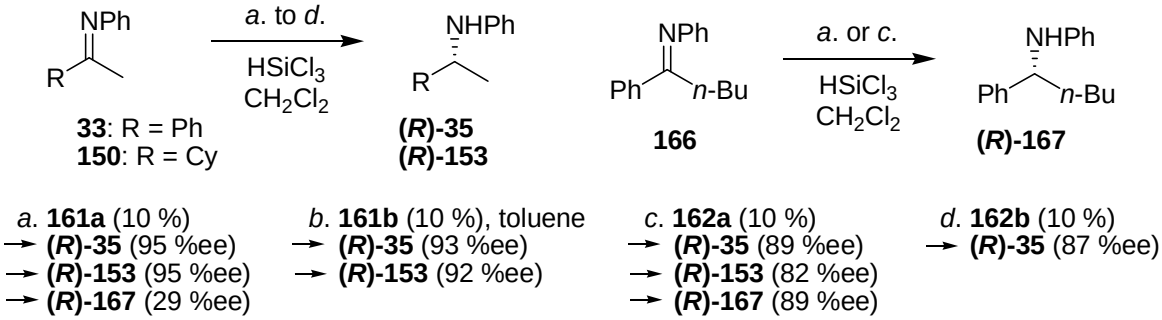


Figure 2.4. Most Successful Sun's Organocatalysts for Reduction of Imines with Trichlorosilane

Catalysts derived from pipecolinic acid, i.e. **161a** and **161b** exhibited good catalytic properties and high enantioselectivities for most of the aryl-methyl imines (up to 95 % ee; Table 2.15, entries 1 and 2; Scheme 2.45) and good enantioselectivity was reached also in the case of alkyl-methyl imines (up to 86 % ee). However, longer alkyl chain was not tolerated (Table 2.15, entry 3; Scheme 2.45). Both these catalysts showed similar reactivity in reduction of imines, the latter one **161b** however, performed much better in reduction of ketones, when enantioselectivity of **161a** dropped to ~75 % ee. Another structural feature important for reduction of ketones (but not imines) was the configuration at carbon *C*-2'. Removal of this stereogenic centre or reversing its absolute configuration [(*S*) → (*R*)] has led to a drop of enantioselectiviy (for ketones only) to ~70-80 % ee. This fact pointed to a possibility of different transition states for reduction of ketones and imines. On the other hand, (*S*)-configuration at *C*-1' was distinctively preferred. The change of *C*-2'-acetoxy for *C*-2'-methoxy group increased the catalyst reactivity (cooling to –20 °C needed) and toluene was determined as an optimal solvent (instead of typical CH_2Cl_2, Table 2.15, entries 4 and 5).



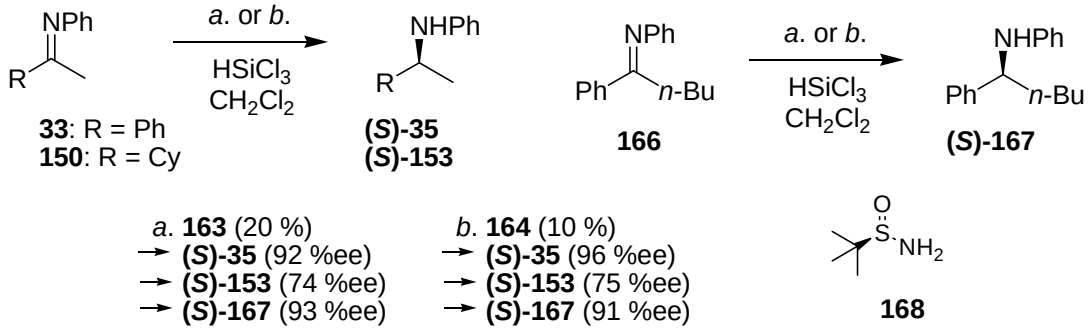
Scheme 2.45. Enantioselective Reduction of Imines with Trichlorosilane and Formamides

The second generation of formamide catalysts **162a** and **162b**, derived from piperazine-2-carboxylic acid performed better with aryl-alkyl imines (typically 92 %, up to 97 % ee; Table 2.15, entry 8; Scheme 2.45), while maintaining the selectivity for classical aryl-methyl and alkyl-methyl imines (Table 2.15, entries 6 and 7; Scheme 2.45). Imines with a substituted *N*-phenyl group were reduced only in moderate ee's, though. Interestingly, variation at position *N*-4 from sulfonamide to carboxamide influenced the enantioselectivity only marginally, but improved its reactivity (reaction carried out at 0 °C instead of at –20 °C; Table 2.15, entry 9). It seemed plausible that group X (SO_2 or CO in structure **162**) provided the right steric shielding.

Table 2.15. Other Organocatalyst for Reduction of Imines with Trichlorosilane

Entry	Imine	Catalyst (mol %)	Solvent	Temp. (°C)	Yield (%) / ee (%)
1	**33**	**161a** / 10	CH_2Cl_2	0	97 / 95 (*R*)
2	**150**	**161a** / 10	CH_2Cl_2	0	81 / 95 (*R*)
3	**166**	**161a** / 10	CH_2Cl_2	0	n.a. / 29 (*R*)
4	**33**	**161b** / 10	toluene	–20	94 / 93 (*R*)
5	**150**	**161b** / 10	toluene	–20	93 / 92 (*R*)
6	**33**	**162a** / 10	CH_2Cl_2	–20	95 / 89 (*R*)
7	**150**	**162a** / 10	CH_2Cl_2	–20	86 / 82 (*R*)
8	**166**	**162a** / 10	CH_2Cl_2	–20	84 / 89 (*R*)
9	**33**	**162b** / 10	CH_2Cl_2	0	87 / 87 (*R*)

A different class of sulfinamide catalysts was also developed by Sun. The preliminary success of commercial (*R*)-*tert*-butylsulfinamide **168** which exhibited catalytic activity with 21 % ee, has brought catalyst **163**.[98] An important feature of this catalyst was the phenolic group, whose position influenced the reactivity rather than the enantioselectivity. An additional electron-withdrawing group caused significant increase of enantioslectivity, indicating its role as a Brønsted acid and *not* a coordination site for trichlorosilane. Together with non-linear effects, it seemed probable that this phenolic hydroxyl facilitated assembly of two molecules of **163**, chelating trichlorosilane with their sulfinamide groups. New, improved catalyst **164** resulted from attempts to incorporate chemically the two sulfinamide groups in one molecule, linked together with an appropriate spacer.[99] The catalyst **164** exhibited linear dependence of product's ee on catalyst's enantiopurity and loading of 10 mol % ensured enantioenriched amines with the same levels as 20 mol % of **163** (Table 2.16, entries 2-7; Scheme 2.46), enantioselectivities up to 96 % ee for aromatic and 78 % ee for aliphatic imines. The authors also described beneficial effect of 0.3 equiv of 2,6-lutidine on enantioselectivity (Table 2.16, entry 8).

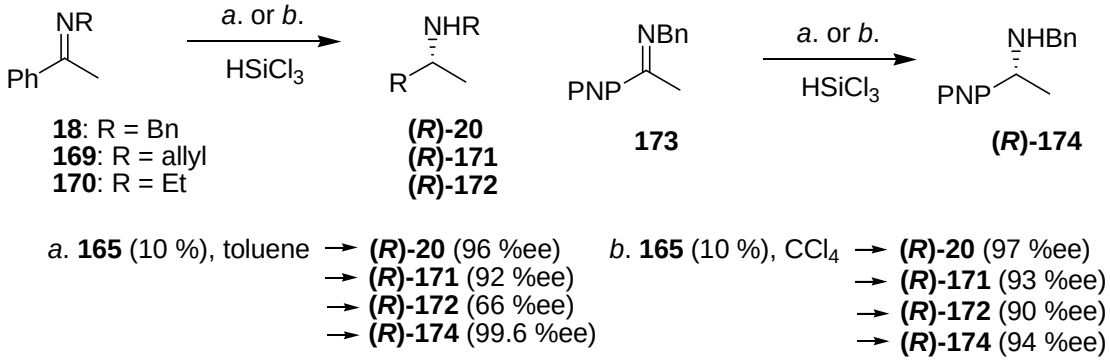


Scheme 2.46. Enantioselective Reduction of Imines with Trichlorosilane and Sulfinamides

Table 2.16. Other Organocatalyst for Reduction of Imines with Trichlorosilane

Entry	Imine	Ligand (mol %) / Additive (mol %)	Solvent	Temp. (°C)	Yield (%) / ee (%)
1	**33**	**168** / 20 / -	CH_2Cl_2	0	60 / 21 (*S*)
2	**33**	**163** / 20 / -	CH_2Cl_2	–20	92 / 92 (*S*)
3	**150**	**163** / 20 / -	CH_2Cl_2	–20	78 / 74 (*S*)
4	**166**	**163** / 20 / -	CH_2Cl_2	–20	94 / 93 (*S*)
5	**33**	**164** / 10 / 2,6-lutidine / 30	CH_2Cl_2	–20	91 / 96 (*S*)
6	**150**	**164** / 10 / 2,6-lutidine / 30	CH_2Cl_2	–20	84 / 75 (*S*)
7	**166**	**164** / 10 / 2,6-lutidine / 30	CH_2Cl_2	–20	89 / 91 (*S*)
8	**33**	**164** / 10 / -	CH_2Cl_2	–20	93 / 91 (*S*)
9	**18**	**165** / 10 / -	toluene	0	98 / 96 (*R*)
10	**169**	**165** / 10 / -	toluene	0	82 / 92 (*R*)
11	**170**	**165** / 10 / -	toluene	0	67 / 66 (*R*)
12	**173**	**165** / 10 / -	toluene	0	80 / 99.6 (*R*)

Revisiting the existing catalysts for reduction of imines with trichlorosilane offered the idea of combining structural features of formamides (an amino acid as a source of chirality) and an extra chelating sulfinamide group, such a hybrid catalyst proved very efficient.[100] Catalyst **165** exhibited deviation from the other catalysts, e.g. typical solvent CH_2Cl_2 and chloroform caused dramatic drop of enantioslelctivity (down to ~20-30 % ee), and interestingly, CCl_4 was an excellent solvent alongside with toluene. The yields were comparable in both solvents and the enantioslectivity was complementary (Scheme 2.47). First virtually enantiopure amine (99.6 % ee) was prepared by this method (Table 2.16, entry 12; Scheme 2.47) and various unusual *N*-aryl and *N*-alkyl **169**, **170** and **173** imines were reduced with very high levels of enantioselectivity (typically 96 % ee; Table 2.16, entries 9-11; Scheme 2.47).



Scheme 2.47. Enantioselective Reduction of Imines with Trichlorosilane and Sulfinamide

After a thorough analysis of structural features of the valine-derived catalyst **152**, it was recognised that introducing more bulky **R** groups (*i*-Pr or *t*-Bu) into the 3,5-positions of the anilide moiety (Figure 2.5) may cause further increase of the enantioselectivity in comparison to its unsubstituted **152a** or methyl-substituted **152b** predecessors (Figure 2.3).

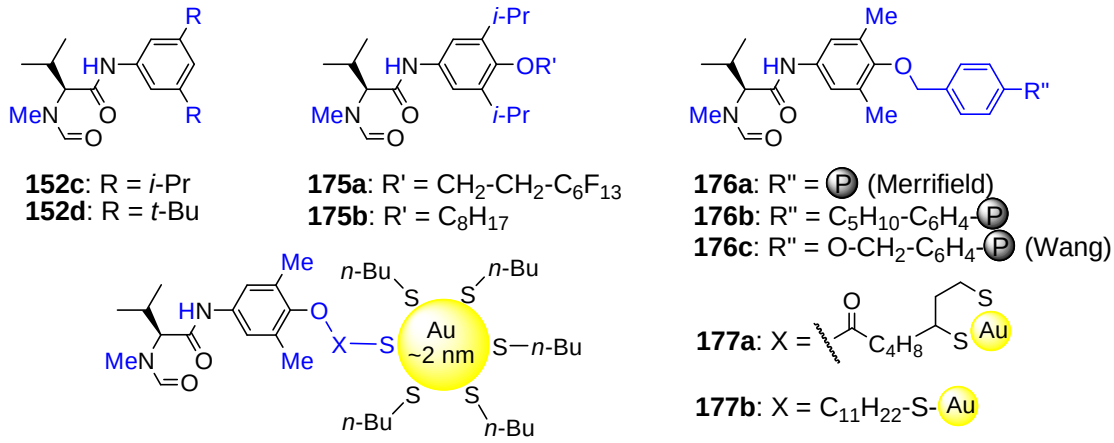
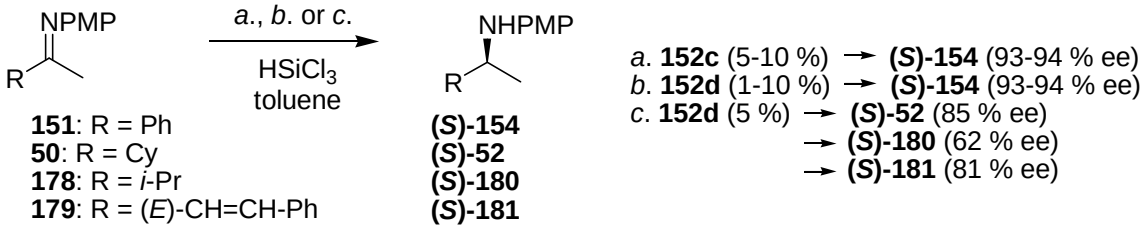


Figure 2.5. Variations on Valine-derived Catalyst **152**

This assumption was proved correct by synthesising catalysts **152c** and **152d**.[101] With the increasing bulk of the 3,5-substituents, the enantioselectivity of reduction of model imine **151** was enhanced up to 94 % ee (Table 2.17, entry 1; Scheme 2.48; compare to Table 2.14, entry 3; from 91 % ee with 10 mol% of catalyst **152b** in toluene). This beneficial role of the bulk at the anilide moiety was even more obvious for aliphatic and conjugated imines as **50**, **178** and **179** (1,2-reduction) which were reduced to the corresponding amines with 85, 62 and 81 % ee, respectively (Table 2.17, entries 5-7; Scheme 2.48). Furthermore, the catalytic activity was improved and the loading of **152d** could be decreased to 1 mol % while maintaining the same level of enantioselectivity

(Table 2.17, entries 1-4; Scheme 2.48). For convenience, though, 5 mol % of catalyst **152d** was recognised as an optimal loading, for the reaction carried out in toluene at ambient temperature for 18 hours.



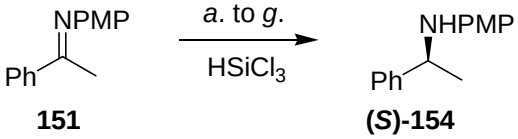
Scheme 2.48. Enantioselective Reduction of Imines with Sigamide

Investigation of the valine-derived catalyst **152** was extended also on the practical points of the methodology. The purification procedure was simplified by attaching a perfluoroalkoxy chain or polymer support to the *N*-arylamide (Figure 2.5). From previous results, it was clear that 4-methoxy anilide derivative was well tolerated and therefore there would be a possibility of derivatisation at this site.

Table 2.17. Reductions with Modified Valine-derived Catalysts

Entry	Imine	Ligand (mol %)	Solvent	Temp. (°C)	Yield (%) / ee (%)
1	**151**	**152c** / 10	toluene	ambient	99 / 94 (*S*)
2	**151**	**152c** / 5	toluene	ambient	95 / 93 (*S*)
3	**151**	**152d** / 5	toluene	ambient	95 / 94 (*S*)
4	**151**	**152d** / 1	toluene	ambient	92 / 93 (*S*)
5	**50**	**152d** / 5	toluene	ambient	86 / 85 (*S*)
6	**178**	**152d** / 5	toluene	ambient	83 / 62 (*S*)
7	**179**	**152d** / 5	toluene	ambient	94 / 81 (*S*)

Catalyst with an attached perfluoroalkoxy chain **175a** exhibited high enantioselectivity[101] (89 % ee; Table 2.18, entries 1 and 2; Scheme 2.49) as well as its *n*-octyl congener **175b** which proved no interference with the fluorous tag. The advantage was simple purification by filtration through a pad of fluorous silica gel, the amine eluted with a methanol – water mixture and the catalyst was released with pure methanol afterwards. Recycling the catalyst up to five times caused ~5 % loss of enantioselectivity, mainly because the catalyst recovery was not quantitative and the loading successively decreased.



a. **175a** (10 %), toluene → **(*S*)-154** (89 %ee)
b. **175b** (10 %), toluene → **(*S*)-154** (90 %ee)
c. **176a** (25 %), $CHCl_3$ → **(*S*)-154** (76-82 %ee)
d. **176b** (15 %), $CHCl_3$ → **(*S*)-154** (77-82 %ee)
e. **176c** (20 %), $CHCl_3$ → **(*S*)-154** (73-77 %ee)
f. **177a** (20 %), toluene → **(*S*)-154** (79-84 %ee)
g. **177b** (20 %), toluene → **(*S*)-154** (79 %ee)

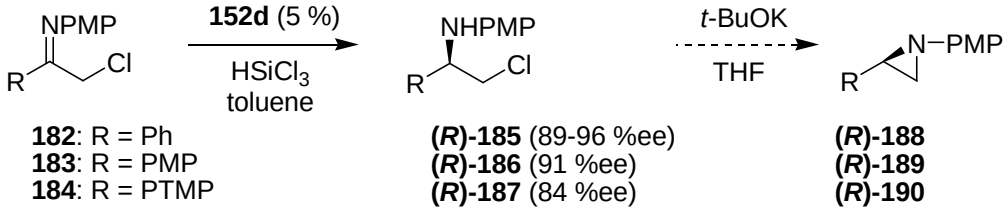
Scheme 2.49. Enantioselective Reduction of Imines with Recoverable Catalysts

The polymer supported series of catalysts **176** exhibited approximately 10 % ee lower enantioselectivity than their monomer-catalysed version.[102] This was attributed to the heterogenous character of the reaction and the background reducing activity of the polymer support. Another major difference was that toluene proved unsuitable for the polymeric catalysts as the background (polymer-catalysed) reaction was even faster. Typically, the first run afforded amines with 5 % lower ee's (73-76 % ee; Table 2.18, entries 3-5; Scheme 2.49) than the 2nd to 6th run (77-82 % ee, respectively; Scheme 2.49). It was hypothesised that formation of a small amount of gel by quenching of trichlorosilane during the first work-up would "condition" the polymer.

Table 2.18. Reductions with Recoverable Valine-derived Catalysts

Entry	Imine	Ligand (mol %)	Solvent	Temp. (°C)	Yield (%) / ee (%)
1	**151**	**175a** / 10	toluene	ambient	98 / 89 (*S*)
2	**151**	**175b** / 10	toluene	ambient	98 / 90 (*S*)
3	**151**	**176a** / 25	$CHCl_3$	25	80 / 76 (*S*)
4	**151**	**176b** / 15	$CHCl_3$	25	87 / 77 (*S*)
5	**151**	**176c** / 20	$CHCl_3$	25	83 / 73 (*S*)
6	**151**	**177a** / 20	toluene	20	90 / 84 (*S*)
7	**151**	**177b** / 20	toluene	20	86 / 79 (*S*)

The catalyst surface-immobilised on gold nanoparticles (Figure 2.5) was another option for constructing a homogenous recoverable catalyst.[103] The standard ether linker was used in **177b**; furthermore, lipoic ester linkage was tolerated well in **177a** (Table 2.18, entries 6 and 7; Scheme 2.49). The coating level in the first case was approximately 10 % of the available sulfide functions, in the latter one around 5 %. The enantioselectivity was comparable with the polymer-supported catalyst (up to 84 % ee); however, the gold-coated catalyst failed to keep it after 3rd run, probably due to washing off the catalyst from the gold support or aggregation of the nanoparticles and change to heterogenous system.



182: R = Ph
183: R = PMP
184: R = PTMP

(*R*)-185 (89-96 %ee)
(*R*)-186 (91 %ee)
(*R*)-187 (84 %ee)

(*R*)-188
(*R*)-189
(*R*)-190

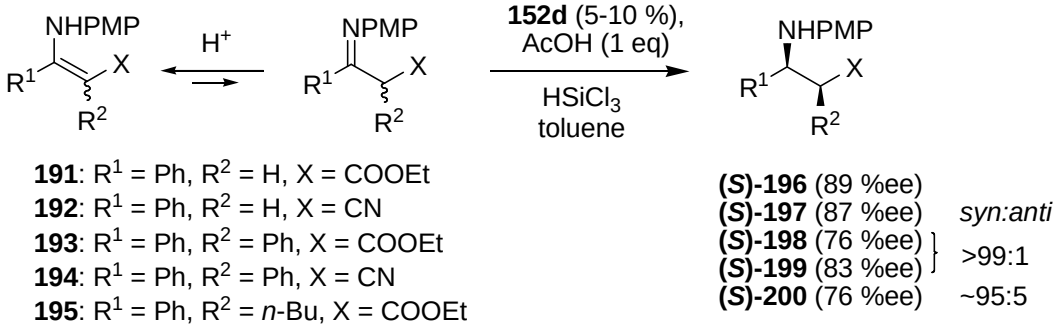
Scheme 2.50. Enantioselective Reduction of α-Chloro Imines with Sigamide

Besides the reduction of simple imines, α-chloro imines were reduced with Sigamide **152d** and trichlorosilane[104] (Method (A); Table 2.19, entry 1). This innovation offered shorter synthetic access to enantioenriched 1,2-disubstituted (terminal) aziridines than the known cyclisation of vicinal amino alcohols. Reactivity of α-chloro ketones with aliphatic amines, which would undergo substitution of the chlorine rather than to form the imine, was not an issue as the reduction protocol is effective only for less nucleophilic *N*-aromatic imines. α-Chloro imines which were not isolable were generated in situ in the presence of an excess of the ketone (Method (B); Table 2.19, entries 2-4; Scheme 2.50), affording the chloro amines with up to 96 % ee (typically 89-93 % ee). Aziridine ring closure proceeded smoothly with *t*-BuOK in THF maintaining the enantiopurity.

Table 2.19. Novel Application of Sigamide in Reductions with Trichlorosilane

Entry	**Imine**	**Ligand (mol %) / Additive (equiv.)**	**Solvent**	**Temp. (°C)**	**Yield (%) / ee (%)**
1	**182**	(A) **152d** / 5 / -	toluene	ambient	98 / 96 (*R*)
2	**182**	(B) **152d** / 5 / -	toluene	ambient	94 / 89 (*R*)
3	**183**	(B) **152d** / 5 / -	toluene	ambient	86 / 91 (*R*)
4	**184**	(B) **152d** / 5 / -	toluene	ambient	88 / 84 (*R*)
5	**191**	**152d** / 5 / AcOH / 1	toluene	ambient	98 / 89 (2*S*,3*S*)
6	**192**	**152d** / 5 / AcOH / 1	toluene	ambient	75 / 87 (2*S*,3*S*)
7	**193**	**152d** / 10 / AcOH / 1	toluene	ambient	84 / 76 (2*S*,3*S*)
8	**194**	**152d** / 10 / AcOH / 1	toluene	ambient	46 / 83 (2*S*,3*S*)
9	**195**	**152d** / 10 / AcOH / 1	toluene	ambient	84 / 76 (2*S*,3*S*)

In the case of enamine esters or enamine nitriles,[105] a clear drop of reactivity was observed. It is likely that equilibration between (*E*)- and (*Z*)-forms (promoted by the presence of an acid) proceeds through the imine form which is the actual substrate for reduction (also see Chapter 2.1.2); however, acid catalyses also the non-selective background reduction.



Scheme 2.51. Enantioselective Reduction of Enamines with Sigamide

An optimal compromise between the enantioselectivity and the reactivity was found to be with 1 equivalent of acetic acid and reaction time 48 hours. The desired β-amino esters were obtained in 87-89 % ee (Table 2.19, entries 5 and 6; Scheme 2.51). The α-substituted β-amino esters were obtained in high diastereoselectivity (>95:5) and good enantioslelctivity (typically 76 % ee; Table 2.19, entries 7 and 9; Scheme 2.51). The corresponding nitriles exhibited lower reactivity, but slightly higher ee's (entry 8).

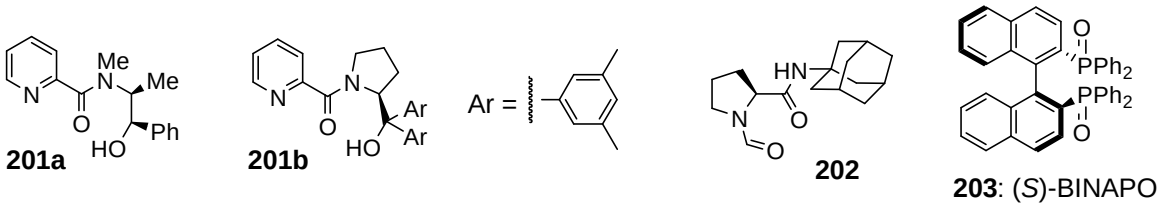


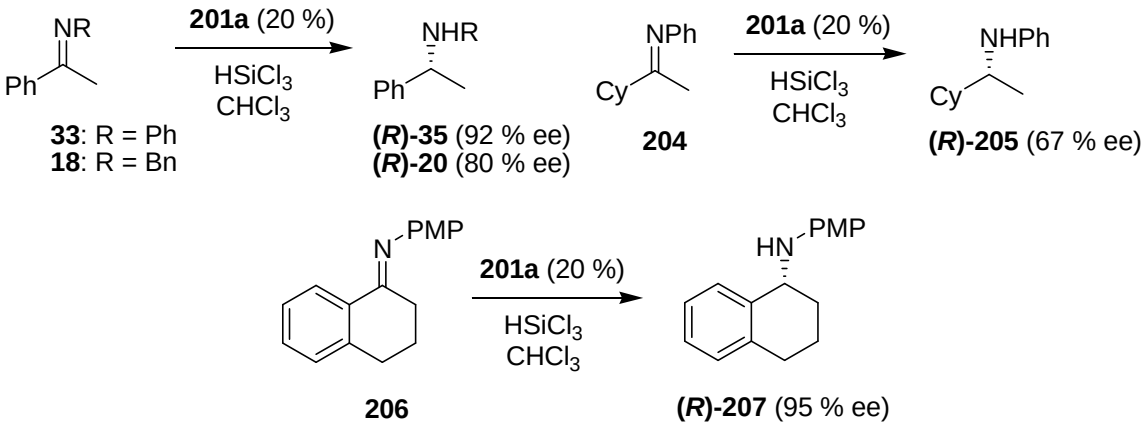
Figure 2.6. Novel Catalysts for Enantioselective Reduction of Imines with Trichlorosilane

Two main research groups (Sun and Kočovský/Malkov) have demonstrated sufficiently the utility of the reduction of imines with a system of an organocatalyst and trichlorosilane. Another Chinese group (Zheng) prepared a series of new catalysts **201**, based on those previously published by Matsumura and Sun (Figure 2.6).

Table 2.20. Novel Catalysts for Reductions with Trichlorosilane

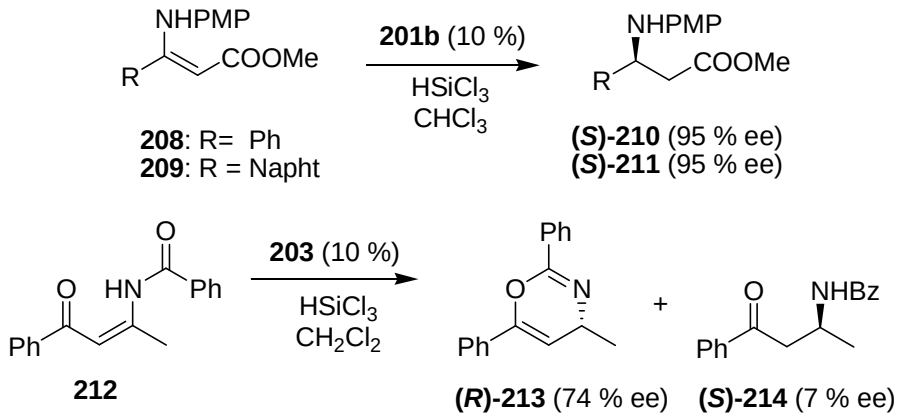
Entry	Imine	Ligand (mol %)	Solvent	Temp. (°C)	Yield (%) / ee (%)
1	**18**	**201a** / 20	$CHCl_3$	–10	85 / 80 (*R*)
2	**33**	**201a** / 20	$CHCl_3$	–10	88 / 92 (*R*)
3	**204**	**201a** / 20	$CHCl_3$	–10	70 / 67 (*R*)
4	**206**	**201a** / 20	$CHCl_3$	–10	85 / 95 (*R*)
5	**208**	**201b** / 10	$CHCl_3$	–30	82 / 95 (*S*)
6	**209**	**201b** / 10	$CHCl_3$	–30	96 / 95 (*S*)
7	**212**	**203** / 10	CH_2Cl_2	ambient	68 / 74 (*R*)

Screening of several diastereoisomers of the catalyst derived from picolinic acid and 1,2-disubstituted aminoethanol has lead to structure **201a** which exhibited the desired levels of reactivity and enantioselectivity.[106] Catalyst **201a** performed well with a variety of *N*-benzyl (80 % ee; Table 2.20, entry 1; Scheme 2.52) and *N*-aryl imines (Table 2.20, entries 2-4; Scheme 2.52). Aryl-methyl imines were reduced with up to 92 % ee, tetralone-derived imine with excellent 95 % ee and aliphatic imines with up to 67 % ee. However, the required catalyst loading was 20 mol %.



Scheme 2.52. Enantioselective Reduction of Imines with Trichlorosilane and Novel Catalysts

Catalyst **201a** gave unsatisfactory results for enantioselective reduction of enamines, whereas the opposite was true for catalyst **201b**.[107] A series of enamino esters as **208** and **209** derived from aromatic β-keto esters and aromatic amines afforded β-amino esters with 92-96 % ee (Table 2.20, entries 5 and 6; Scheme 2.53).



Scheme 2.53. Enantioselective Reduction of Enamino Substrates with Trichlorosilane

Reductive cyclisation of *N*-acylated β-amino enones[108] to 4*H*-1,3-oxazines was an elegant method utilising trichlorosilane and a phosphineoxides as catalysts. The best result was obtained with (*S*)-BINAPO **203**, the desired product **213** was formed in moderate enantioselectivity (74 % ee; Table 2.20, entry 7; Scheme 2.53) and the acyclic by-product was found to be in low enantioselectivity.

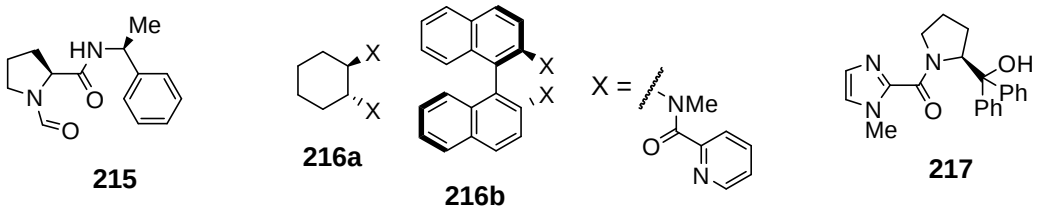
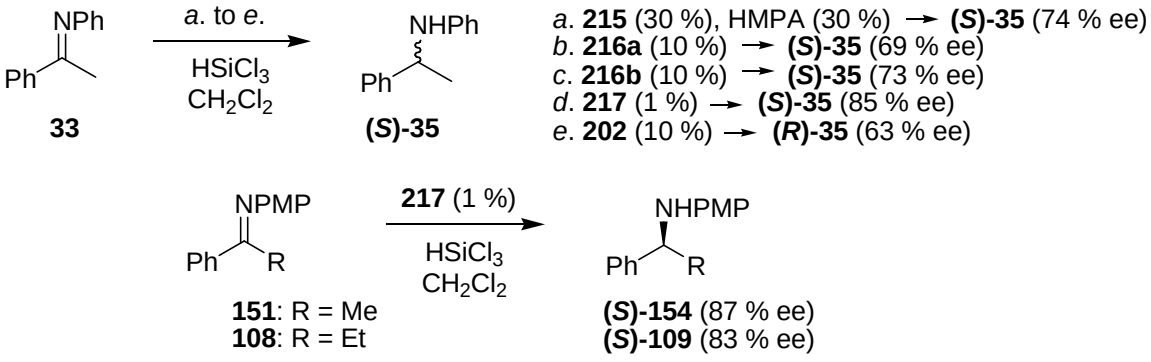


Figure 2.7. More Novel Catalysts for Enantioselective Reduction of Imines with Trichlorosilane

Several other modifications of the already existing catalysts have been published recently (Figure 2.7). Among these is formamide **215** containing an additional stereogenic centre in the amide part, designed for allylation of imines and along that, it was tested also for reduction with trichlorosilane.[109] However, the best results were achieved with addition of HMPA and even then the enantioselectivity was only up to 74 % ee (Table 2.21, entries 1 and 2; Scheme 2.54). Better results were obtained with picolinamide catalysts **216a**,**b**, carrying a chiral cyclic diamine or binaphtyl moiety; particularly when considering the simplicity of their preparation (in 1 or 2 steps).[110] They exhibited very high reactivity and good enantioselectivity up to 83 % ee (Table 2.21, entries 3 and 4; Scheme 2.54).



Scheme 2.54. Enantioselective Reduction of Imines with Trichlorosilane and Novel Catalysts

The latter of the above-shown novel catalysts, catalyst **217** used imidazole moiety instead of the previously used pyridines (imidazole version of Mastsumura's catalyst.[111] Its

extraordinary catalytic activity enabled loading only 1 mol % (!) and yet, keeping the enantioselectivity at high level for aryl-alkyl *N*-aryl imines affording corresponding amines in 83-87 % ee (Table 2.21, entries 5-7; Scheme 2.54).

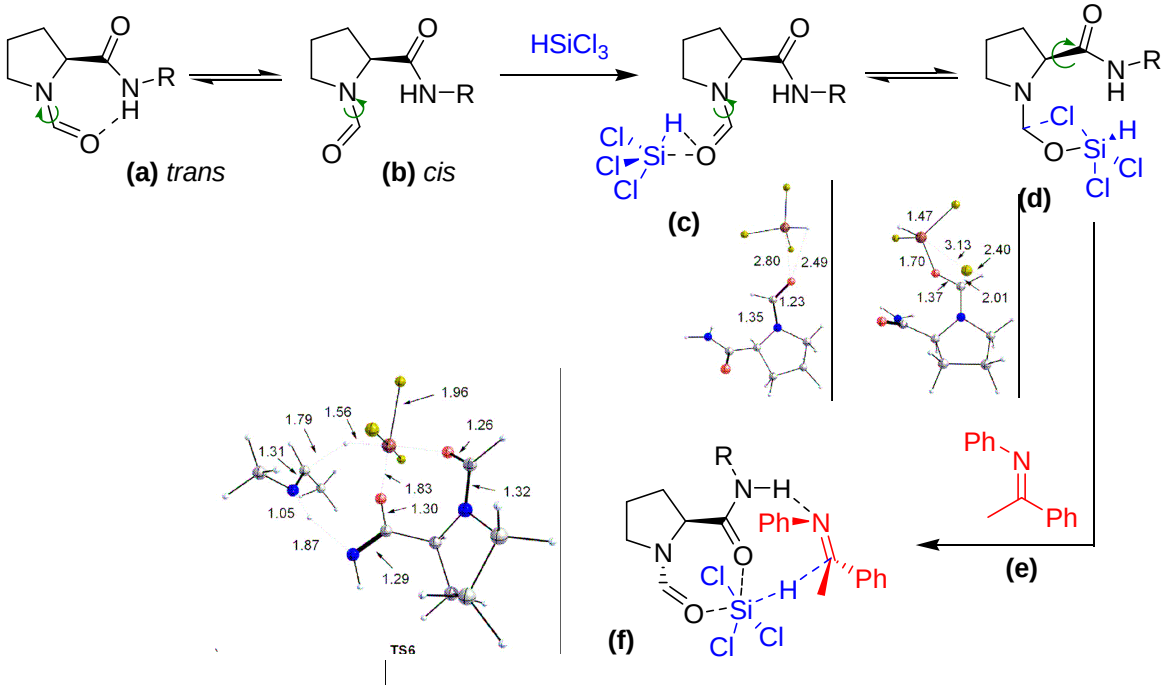
Table 2.21. Novel Catalysts for Reductions with Trichlorosilane

Entry	Imine	Ligand (mol %) / Additive (mol %)	Solvent	Temp. (°C)	Yield (%) / ee (%)
1	**33**	**215** / 30 / -	CH_2Cl_2	ambient	52 / 67 (*S*)
2	**33**	**215** / 30 / HMPA / 30	CH_2Cl_2	ambient	64 / 74 (*S*)
3	**33**	**216a** / 10 / -	CH_2Cl_2	25	99 / 69 (*S*)
4	**33**	**216b** / 10 / -	CH_2Cl_2	0	98 / 83 (*S*)
5	**33**	**217** / 1 / -	CH_2Cl_2	0	82 / 85 (*S*)
6	**151**	**217** / 1 / -	CH_2Cl_2	0	96 / 87 (*S*)
7	**108**	**217** / 1 / -	CH_2Cl_2	0	95 / 83 (*S*)
8	**33**	**202** / 10 / -	CH_2Cl_2	0	85 / 63 (*R*)

A series of secondary amides of *N*-formyl proline were synthesised for the mechanism-structural studies,[112] adamantylamide **202** used for the most of the experiments. The enantioselectivity was comparable with the Matsumura's catalyst **149**, 63 % ee (Table 2.21, entry 8; Scheme 2.54).

2.4.3. Mechanistic Considerations of the Reduction with Trichlorosilane

The mechanistic study[112] provides calculations for the mode of coordination of trichlorosilane to the catalyst's formamide moiety and the transition state upon interaction with the imine (Scheme 2.55). It is known that formamides are present in the solution as two isomers, the *trans* **(a)** being the major one, possibly thanks to hyperconjugation of the non-bonding electrons and intra-molecular hydrogen bonding. The *cis*-isomer **(b)** is, however, the more reactive species and can coordinate trichlorosilane while its conformation changes, too **(c)**. Interestingly, a strong interaction between the formamide carbon and a chloride ligand is predicted **(d)** and that is how the authors reason the importance of the formamide group. Then the imine substrate **(e)** approaches the complex and interacts with the catalyst's secondary amide hydrogen while hydride is transferred **(f)**. These calculations have a drawback – they do not include the effect of Brønsted acid present in the solution and the model catalyst is a primary amide.

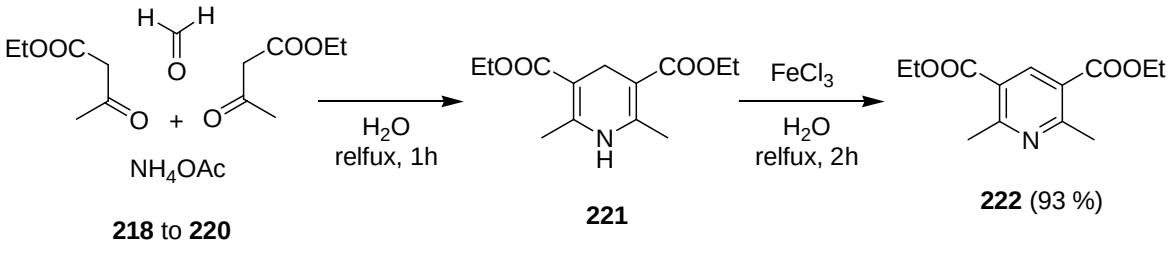


Scheme 2.55. Model Transition State with a Representative Proline Catalyst

2.5. Transfer Hydrogenation with Hantzsch Dihydropyridines

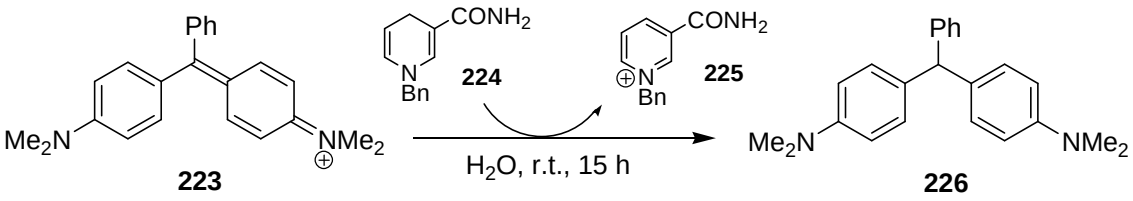
2.5.1. Hantzsch and Other Dihydropyridines (DHP)

The term *Hantzsch pyridine* and *dihydropyridine* are reserved for 3,5-bis(ethylcarboxy)-2,6-dimethyl-pyridine **222** and its 1,4(2*H*)-dihydro-analogue **221**, respectively, first synthesised by **A. Hantzsch** in late nineteenth century[113] (Scheme 2.56). He also demonstrated the ease of oxidation of dihydropyridines to their pyridine analogues.



Scheme 2.56. Hantzsch Synthesis of Pyridines

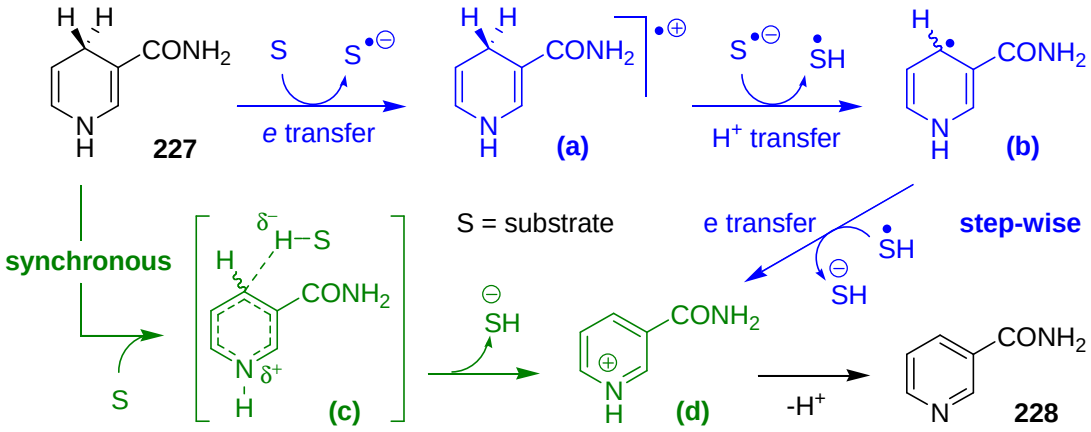
Later on, the concurrent reduction process became a spot of interest, particularly as a reduction method for organic substrates. The early experiments on reduction with dihydropyridines were inspired by the biochemical co-factor NADH and proved that its synthetic analogues showed similar activity. This character of 1,4-dihydropyridines was studied systematically by Westheimer in mid-twentieth century,[114] the first model substrate was malachite green dye **223** reduced to its leuco base **226** with *N*-benzyl-1,4-dihydronicotinamide **224** (Scheme 2.57).



Scheme 2.57. Early Experiments on Reductions with Dihydropyridines

A series of experiments with different substrates and deuterium labelling showed that only the 1,4- and not the 1,2- or 1,6-dihydropyridines carried useful reduction potential. The kinetic studies with 4-deuterio-1-hydropyridines have suggested a hydride ion transfer mechanism because of:

- the presence of common radical traps did not affect the reduction,
- the reaction proceeded faster in polar solvents,
- high kinetic isotopic effect (k_H/k_D ~ 4-5).



Scheme 2.58. Two Proposed Mechanisms for Hydride Transfer from DHP

However, the order of the kinetic isotopic effect would point to the reaction pathway through discrete intermediates.[115a] Later, it was shown that the existence of radical intermediates from productive and/or unproductive side reactions could explain this discrepancy. Furthermore, it would be difficult to distinguish kinetically an electron-transfer driven process from a synchronous hydride transfer (Scheme 2.58).

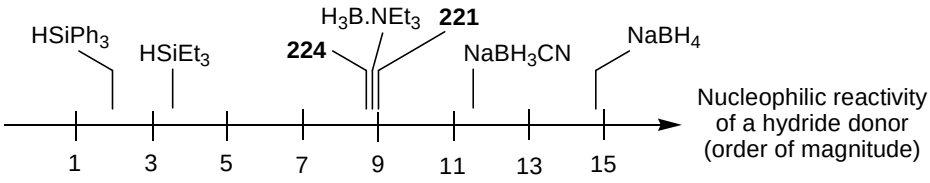
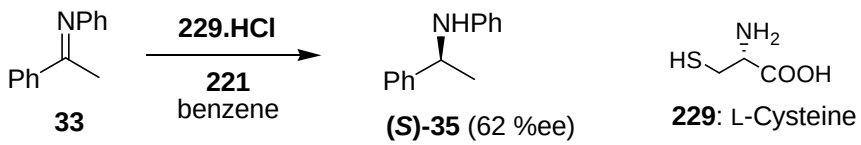


Figure 2.8. Reactivity of Common Reductants

The reactivity of different dihydropyridines and borohydride anions towards benzhydrilium ions such as **223** was studied only recently.[116] It was found that Hantzsch ester **221** was around three times more reactive than dihydronicotinamide **224** (used in reduction of malachite green). The reaction was fast in acetonitrile (in agreement with previous observations of reactivity in polar solvents) and addition of water had beneficial effect on the reaction rate. An interesting conclusion of the study was the order of reactivity of some common reductants (Figure 2.8). It was shown that dihydropyridines are much more potent hydride donors than silanes, but less potent than borohydrides.

2.5.2. Enantioselective Reductions with Hantzsch Dihydropyridines

An elegant utilisation of Hantzsch dihydropyridine **221** in asymmetric synthesis was published in 1989 by Singh and Batra.[117] It was quite a unique concept at that time studying enantioselective reduction of imines in the presence of an amino acid as the chiral inducer (Table 2.22, entry 1; Scheme 2.59).



Scheme 2.59. First Enantioselective Reduction of Imines with DHP

It was only fifteen years later, an extensive research on enantioselective reduction of imines was triggered by a publication of Rueping, who demonstrated that aromatic imines or quinolines were reduced easily an cleanly to afford the corresponding amines with DHP in the presence of various Brønsted acid catalysts[118] (10 mol % of CSA, HCl, TFA, HBF_4 or DPP).

Table 2.22. Reductions of Imines with DHP **221** and BINOL Catalysts

Entry	Imine	Ligand (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**33**	**229** / n.a.	reflux	55 / 62 (*S*)
2	**33**	**(*R*)-230a** / 20	60	71 / 72 (*R*)
3	**151**	**(*R*)-230a** / 20	60	76 / 74 (*R*)
4	**231**	**(*R*)-230a** / 20	60	82 / 84 (*R*)
5	**151**	**(*S*)-230b** / 1	35	96 / 88 (*S*)
6	**178**	**(*S*)-230b** / 1	35	95 / 85 (*S*)
7	**231**	**(*S*)-2301b** / 1	35	80 / 90 (*S*)
8	**Ketone 39**	**(*R*)-230c** / 10	45	87 / 94 (*R*)
9	**Ketone 233**	**(*R*)-230c** / 10	45	49 / 86 (*R*)
10	**Ketone 234**	**(*R*)-230c** / 10	45	60 / 83 (*R*)
11	**Ketone 235**	**(*R*)-230c** / 10	45	71 / 83 (*R*)
12	**237**	**(*R*)-230c** / 10	40	82 / 97 (*R*)

The catalysis by diphenyl phosphate (DPP) was shown to be the most successful regarding yields and the reaction rate; moreover, it could be easily modified to a chiral version which was published later.[119] Several BINOL-derived phosphates were tested and the best results were obtained with catalyst **230a** affording the aromatic amines such as **33**, **151** or **231** in good yields and enantioselectivity (typically 72-84 % ee; Table 2.22, entries 2-4; Scheme 2.60); however, relatively high catalyst loading was required (20 mol %).

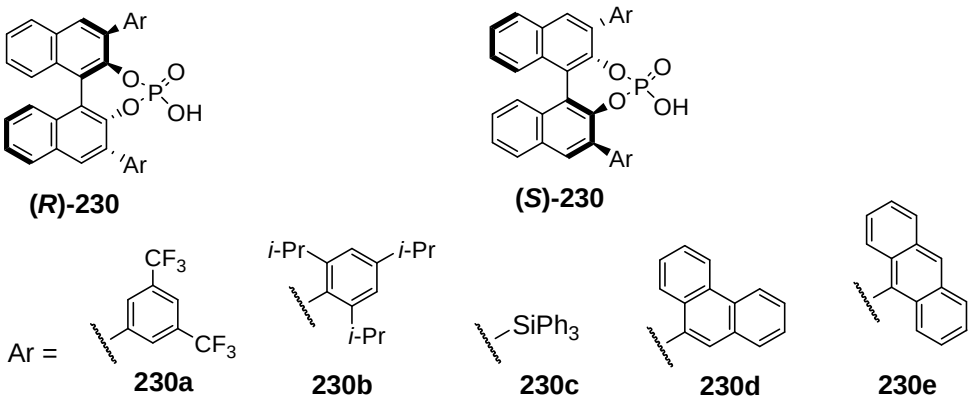
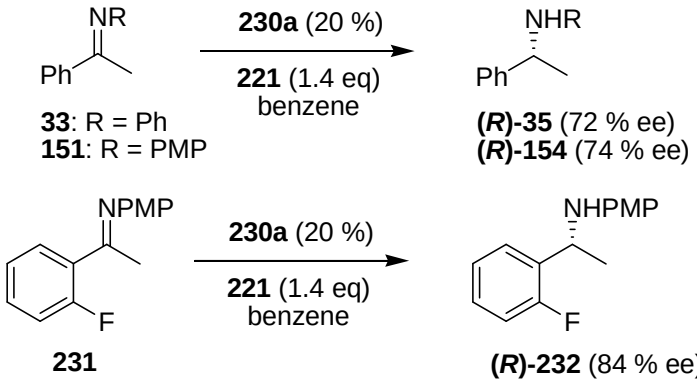


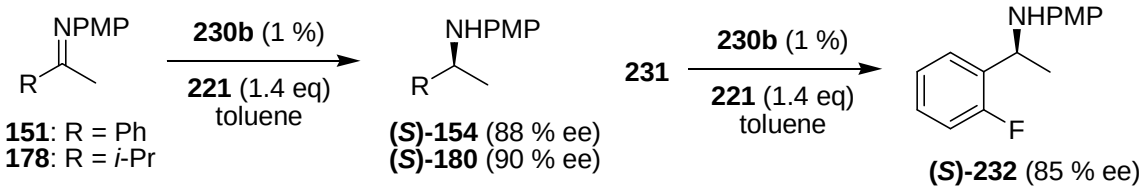
Figure 2.9. BINOL-derived Catalysts for Enantioselective Reduction with DHP

The method represented a novel example of BINOL utility, followed by improvements in the catalyst structure (Figure 2.9). In the course of two following years, the family of BINOL-derived *ortho* sterically congested phosphoric acid catalysts expanded to having five successful members – the first one substituted with 3,5-bis(trifluoromethyl)phenyl **230a**, 2,4,6-tris(*iso*-propyl)phenyl **230b**, triphenylsilyl **230c**, and two derivatives containing bulkier aromatics as 9-phenanthryl **230d** or 9-anthryl **230e** analogues.



Scheme 2.60. Enantioselective Reduction of Imines with DHP and Catalyst **230a**

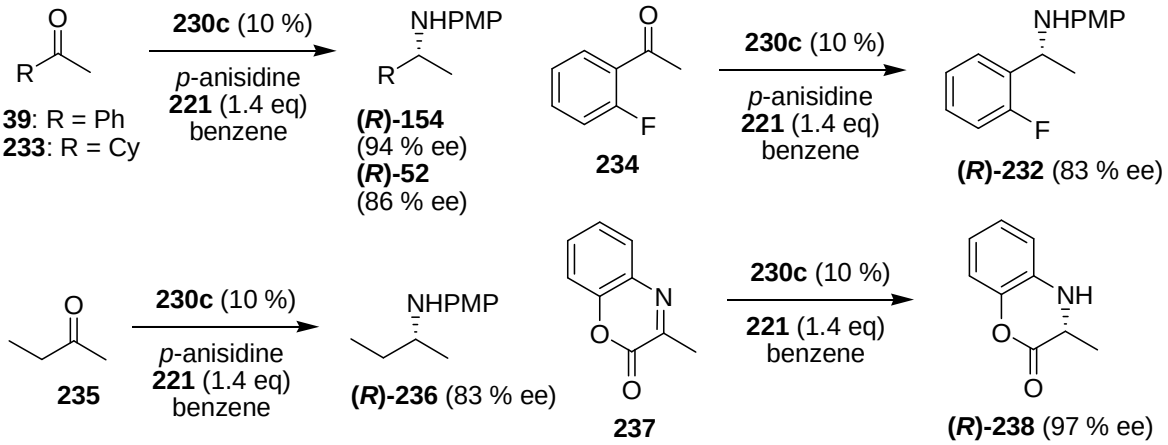
Very shortly after the Rueping's report, List published an improved procedure[120] and catalyst with bulkier aryl substituent on the BINOL-core, catalyst **230b** (Table 2.22, entries 5-7, Scheme 2.61). His method provided better yields (however, with reaction times three times longer) and also better ee's (up to 92 %) with much lower catalyst loading (1 mol %).



Scheme 2.61. Enantioselective Reduction of Imines with DHP and Catalyst **230b**

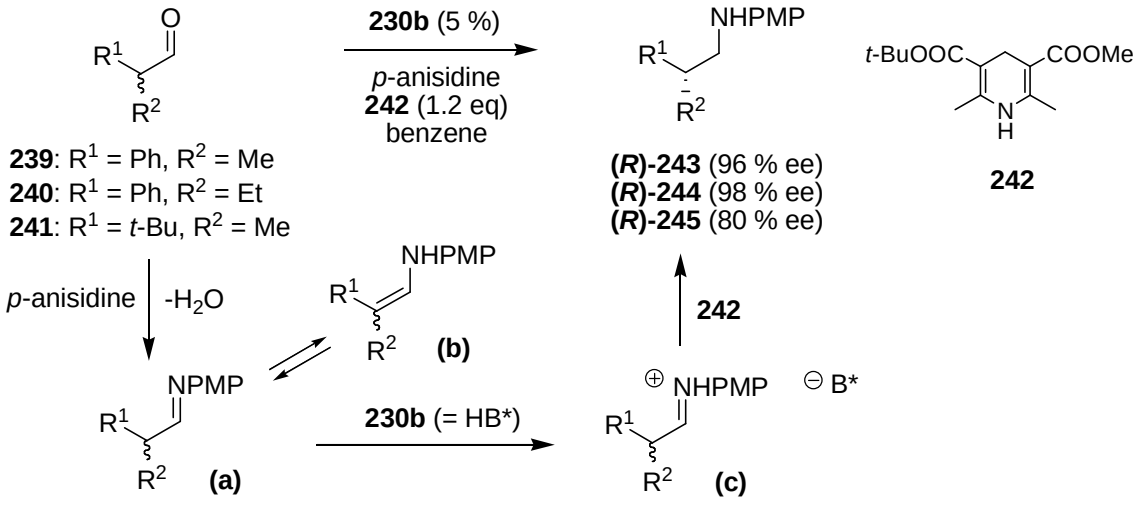
MacMillan's protocol for reductive amination[121] introduced even bulkier catalyst **230c**, affording the aromatic and aliphatic amines in good yields and enantioselectivity up to 95 % ee, typically ~85 % ee (Table 2.22, entries 8-10; Scheme 2.62). The more interesting outcome of this protocol was the high selectivity for reductive amination of

methylketones over other homologues, e.g. methyl-ethyl ketone **235** was reductively aminated to produce (*R*)-amine **236** (Table 2.22, entry 11; Scheme 2.62). The cyclic imine **237** was reduced with high enantioselectivity (Table 2.22, entry 12) affording a useful alanine precursor.



Scheme 2.62. Enantioselective Reductive Amination of Ketones with DHP and Catalyst **230c**.

Catalyst **230b** was also successful in the reductive amination of aldehydes,[122] e.g. **239**-**241**, via dynamic kinetic resolution (DKR; Table 2.23, entries 1-3; Scheme 2.63). The fact of easy racemisation of α-branched carbonyl compounds has rendered them suitable for DKR and the corresponding amines were obtained in excellent ee's up to 98 %.



Scheme 2.63. Enantioselective Reductive Amination of a-Branched Aldehydes.

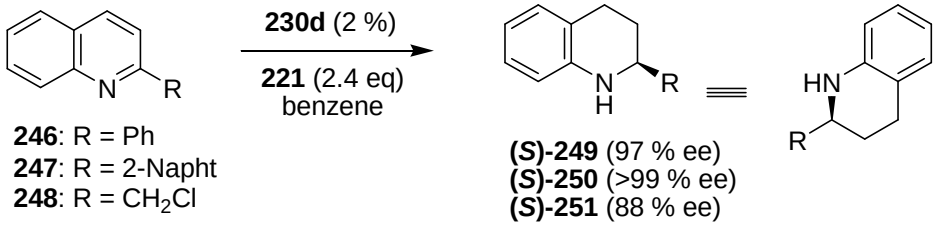
The latter reaction required efficient removal of water to attain the optimal enantioselectivity and oxygen-free conditions to prevent the cleavage of the enamine

intermediate **(b)** to ketone and *N*-formyl-*p*-anisidine. The optimisation of reaction conditions also included the use of a different DHP; the mixed methyl-*tert*-butyl ester **242** provided a good compromise between reactivity and enantioseletivity.

Table 2.23. Reductive Amination and Reduction of heterocycles with DHP

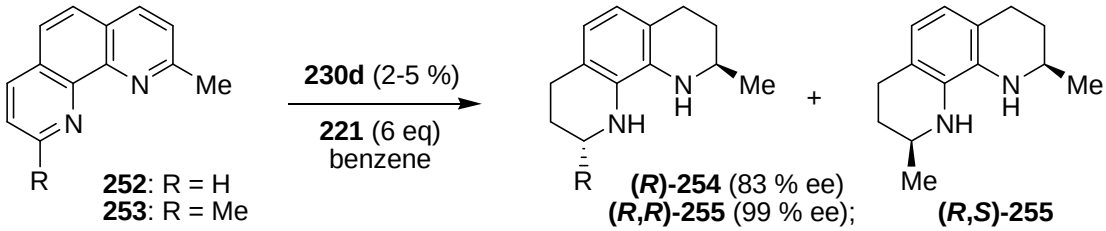
Entry	Imine	Reducing DHP	Ligand (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**239**	**242**	**(*R*)-230b** / 5	6	87 / 96 (*R*)
2	**240**	**242**	**(*R*)-230b** / 5	6	92 / 98 (*R*)
3	**241**	**242**	**(*R*)-230b** / 5	6	77 / 80 (*R*)
4	**246**	**221**	**(*R*)-230d** / 2	60	92 / 97 (*S*)
5	**247**	**221**	**(*R*)-230d** / 2	60	93 / >99 (*S*)
6	**248**	**221**	**(*R*)-230d** / 1	60	91 / 88 (*S*)
7	**252**	**221**	**(*R*)-230d** / 2	60	54 / 83 (*R*)
8	**253**	**221**	**(*R*)-230d** / 5	60	43 / 99 (*R*,*R*) and 29 / n.a. (*R*,*S*)

Rueping has adopted the strategy of employing his methodology on wide selection of substrates formally containing *C=N* bond,[123] such as quinolines, benzoxazin(on)es or activated pyridines. The best enantioselectivities were obtained with catalysts **230d**,**e** containing bulky aromatics.



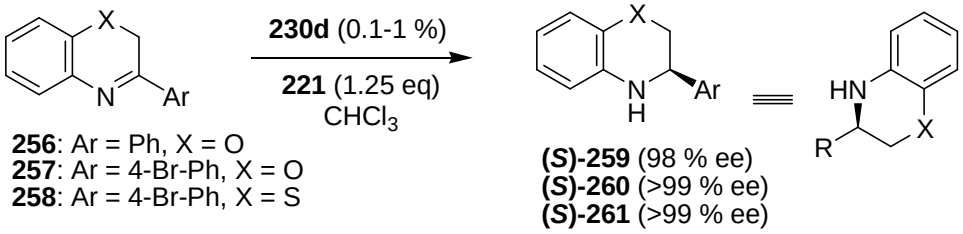
Scheme 2.64. Enantioselective Reduction of Quinolines with DHP

The quinoline substrates[123a] were easily reduced to tetrahydroquinolines by a cascade hydrogenation (Table 2.23, entries 4-6; Scheme 2.64). Even if only 1.2 equivalents of DHP were used, no 1,4- or 3,4-dihydroquinoline was formed. Thus, it was suggested that 1,4-hydride addition (as rate determining step) was followed by acid-catalysed isomerisation to 3,4-dihydroquinolinium and second hydride addition in a 1,2-fashion. Excellent yields and enantioselectivities (typically 97-99 % ee), and tolerance of functional groups (e.g. substrate **248**; Table 2.23, entry 6) was shown. The tetrahydriquinoline motive is found in numerous alkaloids and enantioselective syntheses (90-91 % ee) of three such examples (Cuspareine, Galipinine, Angustureine) were provided.



Scheme 2.65. Enantioselective Reduction of Phenanthrolines with DHP

In addition to reduction of quinolines, 2-substituted or 2,9-disubstituted phenanthrolines were reduced,[124] as well, by another group (Table 2.23, entries 7 and 8; Scheme 2.65). The enantioselectivity and yields were lower, though. Disubstituted substrates produced along the expected (*R*,*R*)-octahydrophenanthroline also (*R*,*S*)-*meso*, which was probably formed from the minor (*S*)-tetrahydrophenanthroline after partial reduction of one ring and thus helped to increase the enantiopurity of the (*R*,*R*)-isomer.



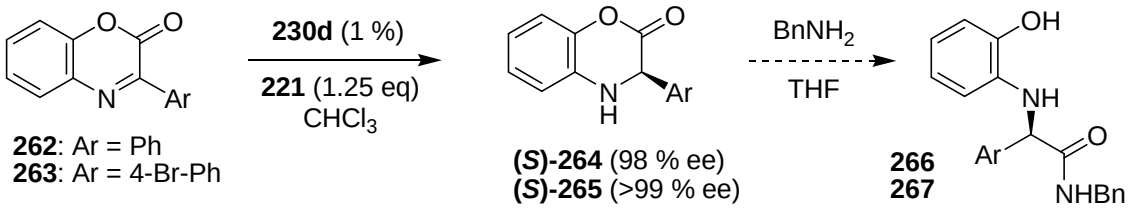
Scheme 2.66. Enantioselective Reduction of Benzoxazines and Benzthiazines with DHP

Another remarkable employment of the method was in reduction of benzoxazines and benzthiazines[123b] (Table 2.24, entries 1-3, Scheme 2.66) or benzoxazinones[123b] (*vide infra*). Unlike the previous quinoline reduction, chloroform was found to be the optimal solvent for benzoxazines, e.g **256** and **257**. Unusually low catalyst loading, only 0.1 mol % (!) was sufficient to drive the reaction to completion at room temperature overnight, maintaining the high yields and enatioselectivities (93-99 % ee). The sulfur analogues, such as **258**, were reduced at the same level of enantioselectivity but with 1 mol % catalyst loading (Table 2.24, entry 3).

Table 2.24. Reductions of Heterocycles with DHP **221** and BINOL Catalysts.

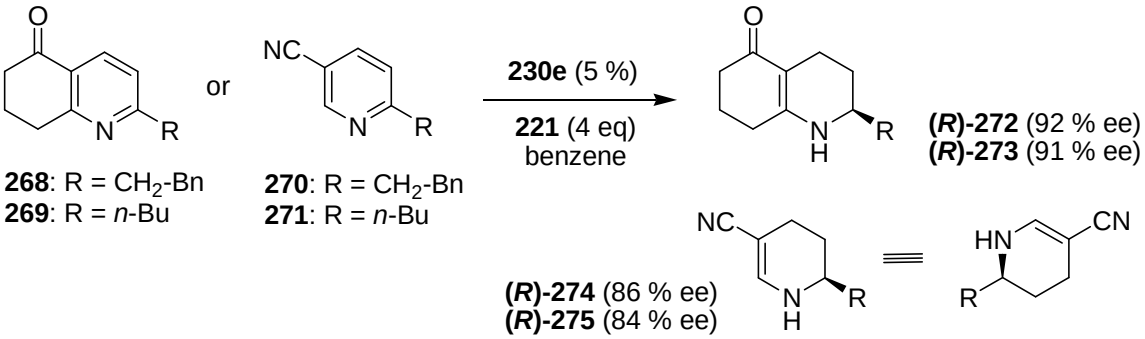
Entry	Imine	Ligand (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**256**	(*R*)-**230d** / 0.1	ambient	95 / 98 (*S*)
2	**257**	(*R*)-**230d** / 0.1	ambient	93 / >99 (*S*)
3	**258**	(*R*)-**230d** / 1	ambient	87 / >99 (*S*)
4	**262**	(*R*)-**230d** / 1	ambient	85 / 98 (*S*)
5	**263**	(*R*)-**230d** / 1	ambient	92 / >99 (*S*)
6	**268**	(*R*)-**230d** / 5	60	n.a. / 82 (*R*)
7	**268**	(*R*)-**230e** / 5	60	66 / 92 (*R*)
8	**269**	(*R*)-**230e** / 5	50	72 / 91 (*R*)
9	**270**	(*R*)-**230e** / 5	50	47 / 86 (*R*)
10	**271**	(*R*)-**230e** / 5	50	73 / 90 (*R*)

The reduction of 3-aryl benzoxazinones like **262** and **263** (Table 2.24, entries 4 and 5; Scheme 2.67) was investigated in order to open the dihydrobenzoxazinones with a primary amine (in the presence of 2-pyridone to prevent the racemisation) to afford the arylglycine amides **266** and **267** retaining its enantiopurity in around 90 % yield over two steps (Scheme 2.67).



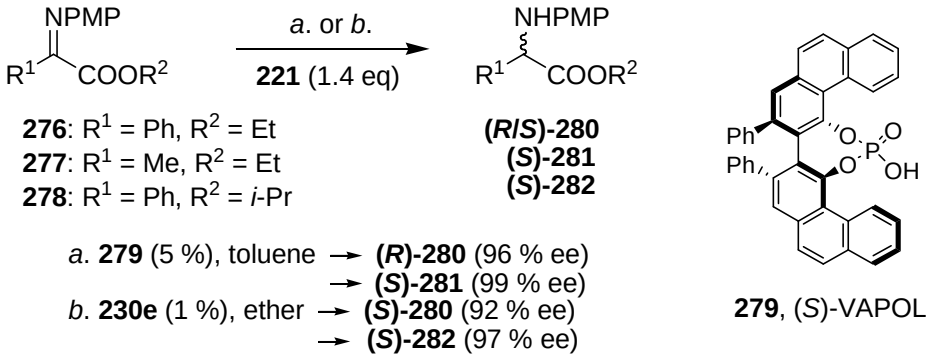
Scheme 2.67. Enantioselective Reduction of Benzoxazinones with DHP

Another important nitrogen-containing heterocycle that was reduced successfully by the Rueping method was substituted pyridine.[123c] For the reaction to work in terms of rate and enantioselectivity, position-3 of the substrate must be a carbonyl or equivalent. A series of trisubstituted pyridines **268** to **271** was investigated (Table 2.24, entries 6-10;) and their reduction was found to proceed in moderate yields and good enantioselectivities (86-92 % ee). The reaction conditions were similar to those employed for the reduction of quinolines; however, better enantiomeric excess of the reduced species was obtained with catalyst **230e** (Table 2.24, entry 6 vs. 7; Scheme 2.68). The diethyl DHP ester **221** was found to be the optimal reductant. Tetrahydropyridine or piperidine is also an abundant moiety in alkaloids.



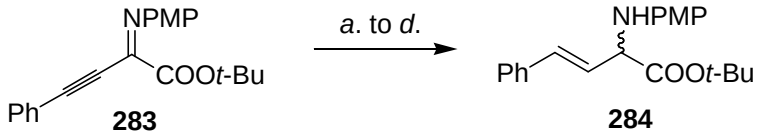
Scheme 2.68. Enantioselective Reduction of Pyridines with DHP

Acyclic α-imino esters proved suitable substrates[125] for reduction with DHP (Table 2.25, entries 1-3; Scheme 2.69). The screening of several BINOL and other biaryls showed that 4,4'-dihydroxy-3,3'-biphenanthrene (VAPOL **279**, compare to **230e**, Table 2.25, entry 1 vs. 2) was the most successful catalyst yielding the α-aryl (or alkyl) α-amino esters in high ee's (95-99 %). The arylglycinates, e.g. **280**, were of (*R*)-configuration, while alaninate **281** was obtained as (*S*)-isomer. Reductive amination version provided the amino acids in lower yields (10-20 %) but maintained the enantioselectivity.



Scheme 2.69. Enantioselective Reduction of α-Imino Esters with DHP.

Another group investigated the same substrates with catalyst **230e**[126] (Table 2.25, entries 4 and 5; Scheme 2.69) and found that substrates with bulky ester groups (*t*-Bu, *i*-Pr) were reduced with higher enantioselectivity (up to 97 % ee); in particular, methyl ester was obtained in only 33 % ee. The ester group on DHP did not affect the enantioselectivity much; however, it did influence the reaction rate and **221** was found to be the optimum. The reaction was carried out in ether, unlike the previous ones.



a. **230c** (5 %), **221** (2.2 eq), ether → **(*R*)-284** (85 % ee)
b. **230e** (5 %), **221** (2.2 eq), ether → **(*S*)-284** (90 % ee)
c. **230e** (1 %), **221** (2.2 eq), toluene → **(*S*)-284** (92 % ee)
d. **230e** (1 %), **242** (2.2 eq), toluene → **(*S*)-284** (86 % ee)

Scheme 2.70. Enantioselective Reduction of β,γ-Alkynyl-α-imino Esters with DHP.

Reduction of α-imino esters as **283** containing β,γ-triple bond gave rise to (*E*)-alkenyl-α-amino esters[127] (Table 2.25, entries 6 and 7; Scheme 2.70). The influence of the ester group of the reductant (Scheme 2.70) and the substrate was screened. The bulkier esters in substrate (*t*-Bu vs. Et) improved the conversion but influenced the enantioselectivity only marginally; similar effects were observed with the change in the reductant's ester group (Table 2.25, entry 8). The (*E*)-alkenyl-α-amino esters were not reduced further under these conditions and it was proposed that the triple bond was reduced much faster than the imino bond.

Table 2.25. Reductions of Imino Esters with DHP and BINOL Catalysts

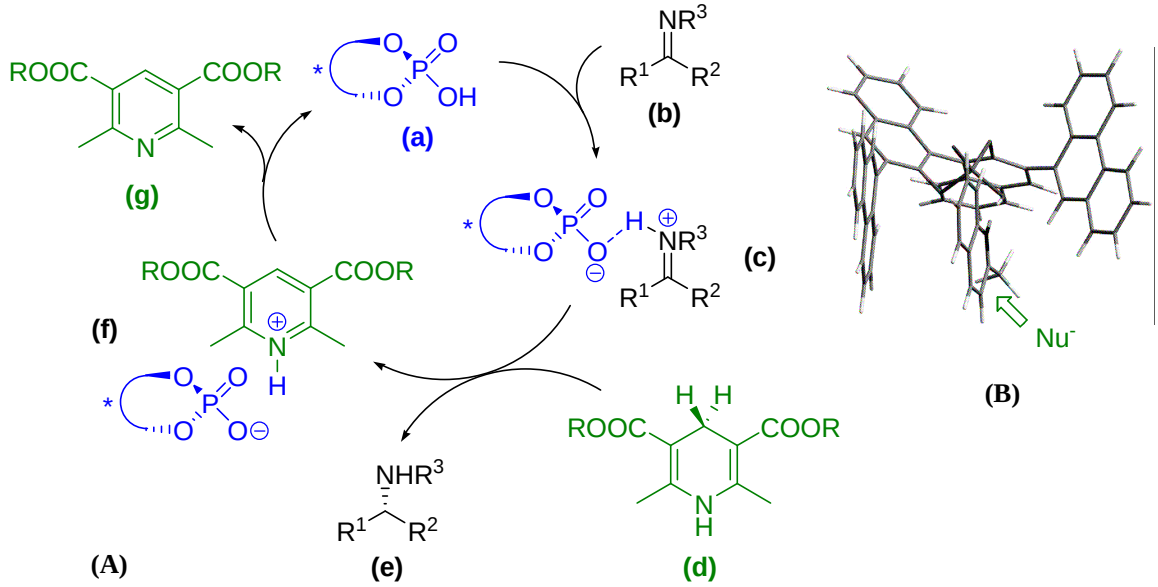
Entry	Imino Ester	Reducing DHP	Ligand (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**276**	**221**	**(*S*)-230e** / 5	50	77 / 80 (*R*)
2	**276**	**221**	**(*S*)-280** / 5	50	93 / 96 (*R*)
8	**277**	**221**	**(*S*)-280** / 5	50	88 / 99 (*S*)
4	**276**	**221**	**(*S*)-230e** / 1	ambient	88 / 92 (*S*)
5	**278**	**221**	**(*S*)-230e** / 1	ambient	87 / 97 (*S*)
6	**283**	**221**	**(*S*)-230e** / 1	ambient	34 / 92 (*S*)
7	**283**	**221**	**(*S*)-230e** / 1	ambient	58 / 94 (*S*)
8	**283**	**242**	**(*S*)-230e** / 1	ambient	n.a. / 86 (*S*)

Polymer-supported Hantzsch ester was also developed; however, it was used only for the 1,4-reduction of unsaturated aldehydes and reductive amination of aldehydes.[128]

2.5.3. Mechanistic Considerations

The proposed catalytic cycle (Scheme 2.71, **(A)**) of the reduction of imines with DHP involves the LUMO-lowering activation of the imine **(b)** by protonation with the chiral (*S*)-Brønsted acid **(a)** generating the highly organised iminium ion pair **(c)** (plausible transition structure from acid **230d** and 2-methylquinoline is shown at Scheme 2.71, **(B)**).

The nucleophilic DHP **(d)** can then approach the complex **(c)** from the less hindered face and transfer the hydride ion which in turn affords amine **(e)** and pyridinium salt **(f)**. Proton transfer recycles the acid **(a)** and releases the free pyridine **(g)**.



Scheme 2.71. Proposed Mechanism **(A)** and Transition Structure **(B)**

3. Lewis Base Organocatalysis

3.1. Organocatalysis[129]

3.1.1. What is Organocatalysis?[129]

Organocatalysis is a younger brother of metal catalysis, a group of reactions that are promoted by small organic molecule catalyst, metal-free catalysis. The well-established metal-catalysed synthesis has been built on the advantageous properties of metal complexes:

- diversity in the metallocentre and the ligands,
- possible "tailoring" the complex structure and reactivity,
- usually high TON/TOF and low catalyst loading (<1 mol %).

However, as every method, metal catalysis has certain disadvantages and drawbacks, which calls for the development of new methods because of:

- price of the metal and the ligand, complicated access to it,
- toxicity and pollution issues,
- product contamination with metal residues.

On the other hand, organocatalysis can be considered as a relative of enzyme catalysis. Organocatalytic reactions show some of the features of bioorganic reactions – the catalyst can get saturated, the kinetics often follows the Michaelis-Menten equation describing the reversible formation of a catalyst (enzyme)-substrate complex. Organocatalysts, however, are *not* exclusively substrate-specific and they are able to catalyse a vast area of organic reactions. The main focus is inherently on asymmetric reactions and application of the well known, simple chiral small molecules for catalysing a growing number of reactions. These can be sorted according to the mechanism pathways:

1. *Activation via covalent transition complexes – nucleophilic*:
   - aldol condensations, α-amination, α-aminooxylation, Mannich reaction,
   - nucleophilic epoxide opening,

- conjugate additions to α,β-unsaturated carbonyls,
- Morita-Baylis-Hillman reaction,
- cycloadditions ([4+2] Diels-Alder, [2+2] of ketenes, [3+2] of allenes),
- S_N2 alkylation, α-halogenation of carbonyls,
- hydrocyanations, acylations, and
- benzoin condensation and Stetter reaction (heteroazolium catalysts).

2. *Activation via covalent transition complexes – electrophilic*:
   - 1,4-additions, cycloadditions ([4+2], [3+2], [4+3]),
   - epoxidations, Baeyer-Villiger reaction.

3. *Activation via reactive intermediates – non-covalent activation*:
   - allylation reactions, hydride reductions,
   - epoxidations, oxidation of sulfides to sulfoxides,
   - desymmetrisation of vicinal diols by oxidation, benzylic oxidations, and
   - ylide reactions (epoxidation, cyclopropanation, aziridination).

4. *Phase-transfer catalysis*:
   - alkylations, protonations, reductions,
   - Michael additions and 1,2-additions, aldol condensations
   - Horner-Wadsworth-Emmons olefination,
   - oxidations (epoxidation, ox. of sulfides), and Darzen reaction.

5. *Chiral-cavity-accelerated transformations*:
   - hydrocyanations, reductions, transaminations of α-ketoacids (with cyclodextrins and calixarenes),
   - ester hydrolysis (template imprinting).

Several catalysts have an amazingly broad spectrum of catalytic activity, whereas others are very specific for certain types of reactions or substrates. Overall, it is possible to define several groups of catalysts that are used most commonly and assign the typical reactions catalysed by them:

1. *Cinchona alkaloids catalysts*:
   - aldol reactions,
   - acyl transfer reactions, desymmetrisation of cyclic anhydrides,
   - kinetic resolution of secondary alcohols,
   - phase-transfer catalysis.

2. *Oligopeptides* – aldol reactions, phosphorylations, and hydrocyanations.

3. *Lewis base activation* – aldol reactions, allylations, and reductions.

4. *Catalysis with enamine intermediates – proline analogues*:
   - aldol condansations, α-amination, α-aminooxylation, Mannich reaction,
   - Michael additions, Morita-Baylis-Hillman reaction,
   - cycloadditions ([4+2] Diels-Alder, [2+2] of ketenes, [3+2] of allenes),
   - S_N2 alkylation and acylations.

5. *Carbene catalysts* – benzoin condensation and Stetter reaction.

Organocatalysis has become a well accepted part of organic synthesis and the understanding of the reaction mechanisms is improving with its current rapid development. This is a good foundation for novel, more efficient methods to grow.

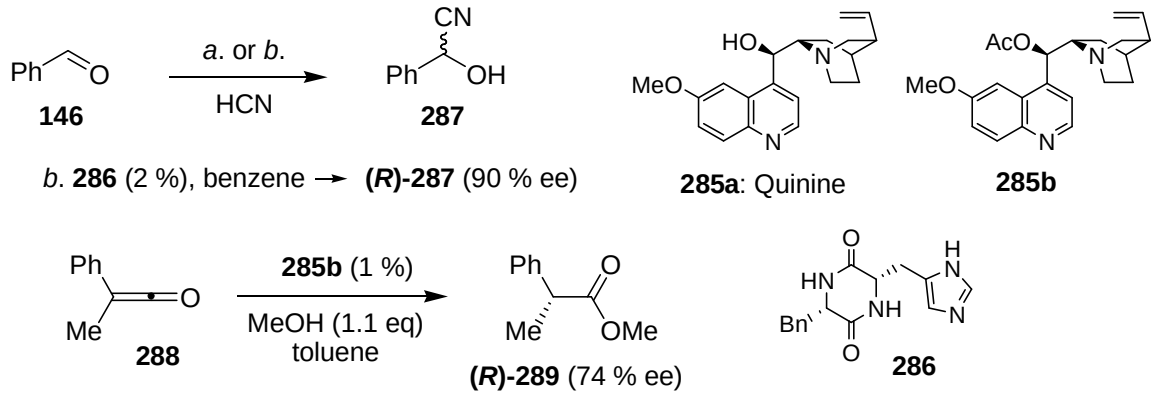
3.1.2. Highlights of Organocatalytic Reactions[129]

Organocatalysis is a relatively new term, only used since 2001 when it was coined by MacMillan. However, if looked thoroughly into the numerous methodologies in organic chemistry, it can be dated back to beginning of 20th century when Rosenthaler and Bredig studied hydrocyanations of benzaldehyde in the presence of quinine **285a** (Table 3.1, entry 1; Scheme 3.1). The milestones of asymmetric catalysis are also depicted in Chapter 1.1.2. As the first highly enantioselective organocatalytic reaction can be considered Pracejus' ketene methanolysis[130] catalysed with *O*-acetylquinine **286b** achieveing remarkable 74 % ee of the methyl ester (Table 3.1, entry 3; Scheme 3.1).

Table 3.1. Highlights of Organocatalysis

Entry	Substrates	Catalyst (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**146**	**285a** / n.a.		n.a. / < 10
2	**146**	**286** / 2	35	40 / 90 (*R*)
3	**288**	**285b** / 1	–111	90 / 74 (*R*)
3	**290**	**291** / 3	20	84 / 93 (*R*)
4	**146, 294**	**291** / 30	ambient	62 / 60 (*R*)
5	**293, 294**	**291** / 30	ambient	97 / 96 (*R*)
6	**297, 298**	**299** / 10	–78	73 / 74 (*endo*)
7	**301, 302**	**303** / 10	–40	90 / 10 (*endo*), 5 / n.a. (*exo*)
8	**143, 305**	**306** / 5	23	43 / 93 (*endo*), 56 / 93 (*exo*)
9	**308**	**309a** / 100	0	65 / 94 (*R*,*R*)
10	**308**	**309b** / 10	0	95 / 90 (*R*,*R*)

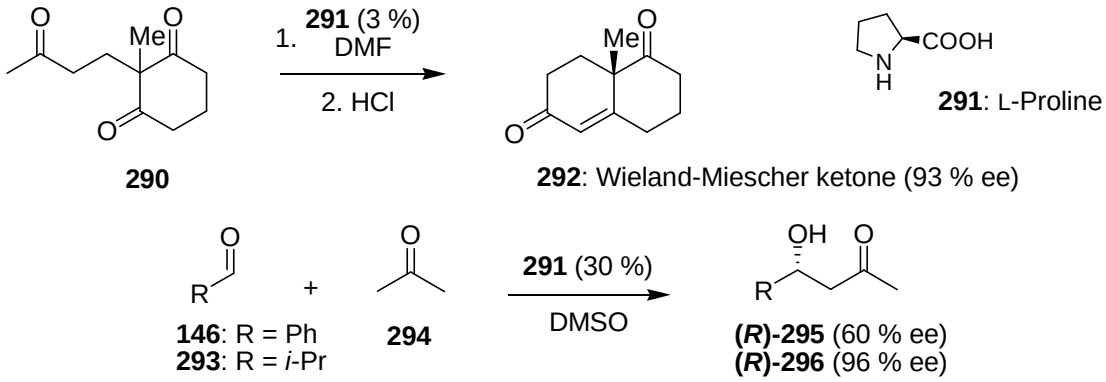
The hydrocyanation reaction was revisited in late 1970s by Inoue[131] and later by others. He developed a dipeptide catalyst **286** that afforded cyanohydrin **287** in enantioselectivity as high as 90 % ee at low conversion (Table 3.1, entry 2; Scheme 3.1). Unfortunately, racemisation occurred under the reaction conditions, lowering the ee to 69 % at 80 % conversion.



Scheme 3.1. Organocatalytic Enantioselective Hydrocyanation and Ketene Methanolysis

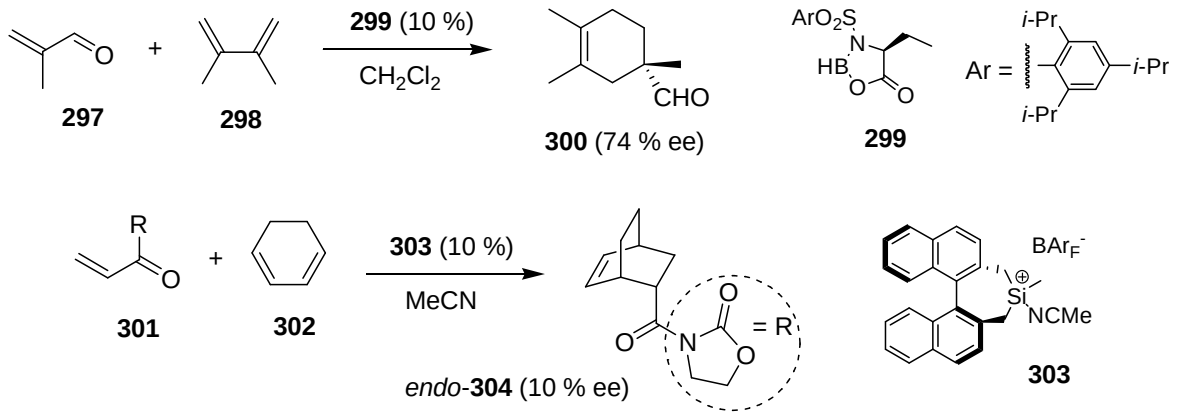
In early 1970s, Hajos and co-workers published a remarkably simple organocatalytic intramolecular aldol reaction[132] using 3 mol % of proline as the catalyst (Table 3.1, entry 2; Scheme 3.2). The enantiomeric excess of the Wieland-Miescher ketone **292** was 93 %! This method was already known in stoichiometric version leading up to 84 % ee.[133] After this sporadic report, proline was forgotten for the following 30 years, not only for aldol reaction – it proved difficult to develop a highly enantioselective intermolecular version, due to self-condenstaion by-products, as one can expect.[134] The successful protocol is inspired by aldolase I-catalysed biochemical reactions via enamine formation. The yields and enantioselectivities for aromatic aldehydes were moderate;

however, isobutyraldehyde gave the aldol product **296** in excellent 97 % yield and 96 % ee (Table 3.1, entries 4 and 5; Scheme 3.2).



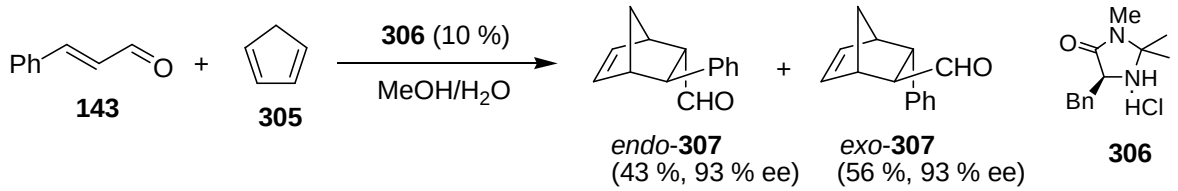
Scheme 3.2. Organocatalytic Enantioselective Aldol Condensation

In 1989, a report on the first Diels-Alder (DA) addition catalysed by a chiral boron-based Lewis acid **299** appeared.[135] In analogy to the traditional metallic Lewis acids catalysing this reaction, lowering of the LUMO-energy was assumed. The enantioselectivity was around 70 % ee for a range of dienes and dienophiles (Table 3.1, entry 6; Scheme 3.3).



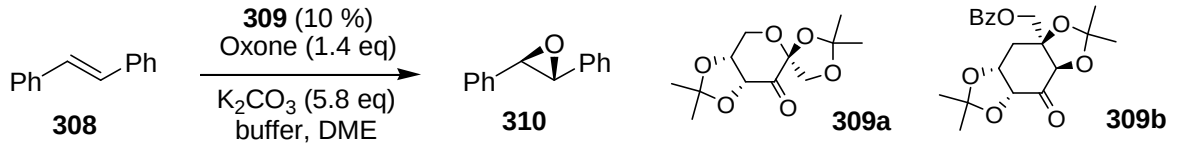
Scheme 3.3. Organocatalytic Enantioselective Diels-Alder Addition

The first DA reaction catalysed by a silicon-based Lewis acidic catalyst[136] containing covalently bonded chiral backbone to the silicon atom and upon treatment of the hydrosilane precursor with a base (e.g. trityl cation), the silylium cationic catalyst **303** was obtained (Table 3.1, entry 7; Scheme 3.3). As initial results, the reaction proceeded in low enantioselectivity (10 % ee) which only triggered an extensive research in this field.



Scheme 3.4. Organocatalytic Enantioselective Diels-Alder Addition

The reversible iminium ion formation from imidazolidin-4-one catalyst **306** can be considered as the first truly organocatalytic, showing also characteristics of Lewis acid catalysis.[137] Addition of α,β-unsaturated aldehyde to cyclopentadiene was achieved with excellent 93 % ee, even though a mixture of isomeric cyclo-adducts was obtained (Table 3.1, entry 8; Scheme 3.4).



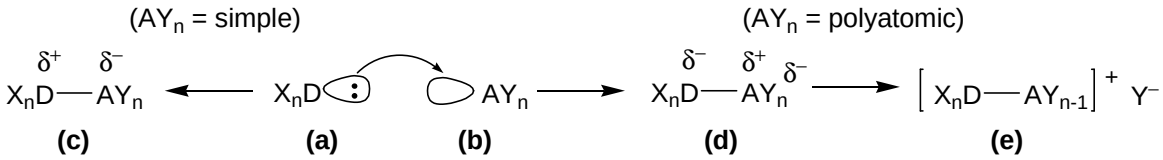
Scheme 3.5. Organocatalytic Enantioselective Epoxidation

Oxidations proved more difficult to realise in an organocatalytic fashion. The first report on enantioselective organocatalytic epoxidation exploied the idea of chiral dioxirane oxidant – the chiral ketone precursors are very versatile an easy to access, e.g. from sugars. The first catalyst was the fructose-based ketone **309a** and its dioxirane epoxidised (*E*)-alkenes in very high ee (typically 95 %); however, only in stoichiometric amounts (Table 3.1, entry 9).[138] System **309b**/Oxone mediated epoxidation of a large number of (*E*)- and trisubstituted alkenes (Table 3.1, entry 10; Scheme 3.5) and optimisation of the reaction conditions extended the substrates scope to *cis*-alkenes, dienes, enynes, 2,2-disubstituted vinylsilanes, enol silylethers and esters *and* the process became catalytic.[139]

3.2. Lewis Base Catalysis[140]

3.2.1. Lewis Bases in Organic Synthesis and Catalysis[140]

Definition of *acid* and *base* by **G. N. Lewis** (1923) has changed the view of the chemical society on acid-base interactions. It elegantly unified the earlier theories and simply explained chemical behaviour by electron sharing phenomenon – a *base* is an electron pair donor and an *acid* is an electron pair acceptor. Over the many years of studying the Lewis acid-base behaviour and reactivity, they have found a firm place in organic synthesis, Lewis acids, in particular. Lewis-base-catalysis is less common, because of a lack of Lewis acidic sites in common organic molecules (substrates) and limited possibilities of valence expansion on carbon centres. However, it can be well used to interact with a reagent of the desired Lewis acidic properties.



Scheme 3.6. Formation of an Acid (Acceptor) - Base (Donor) Adduct

An acid-base adduct as the product of neutralisation is commonly expected to have increased thermodynamic stability and decreased reactivity. The binding of a Lewis base **(a)** to an acid **(b)** does **increase the overall electron density at the Lewis acid centre** (Scheme 3.6); however, it is more important to consider **where the electrons are localised and how they are distributed in the molecule.** This can result in either quenching each-other's reactivity **(c)** or the opposite – the acidity (electrophilicity) of the Lewis acid is enhanced **(d,e)**!

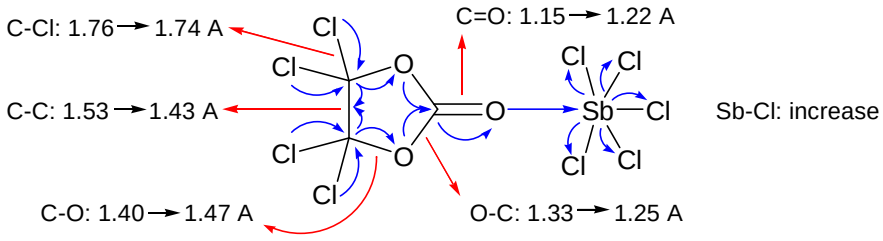


Figure 3.1. LB-LA Adduct and the Change of Bond Lengths

It is the enhancement of the electrophilicity of the Lewis acid centre that is synthetically useful. Even though the net electron transfer is from the donor towards the acceptor, in polyatomic species **the accepted electrons are redistributed over the peripheral ligands Y** which results in a net decrease of the electron density at the acceptor central atom (Scheme 3.6). The donor (D) – acceptor (A) adducts exhibit characteristics formulated by Gutmann rules (an example examined by X-ray crystallography on Figure 3.1):[141]

- the smaller the distance between the donor and the acceptor, the smaller the polarisation of D-A bond and the longer the peripheral bonds (D-X or A-Y)
- the higher the coordination number, the longer the peripheral bonds on this centre,
- the peripheral bonds compensate (by elongation or contraction) the changes of electron density at D and A.

For example, the Mulliken charges at the silicon atom in SiF_4, $(SiF_5)^-$ and $(SiF_6)^{2-}$ are +1.19, +1.14 and +2.12 or in series of $SiCl_4$, $(SiCl_5)^-$ and $(SiCl_6)^{2-}$ are +0.178, +0.279 and +0.539,[140c,142] respectively, even if an additional *anionic* ligand (Cl^-) coordinates! The synthetic consequence of this phenomenon is that the Lewis acidic (acceptor) centre becomes more acidic and electrophilic while its ligands become more nucleophilic.

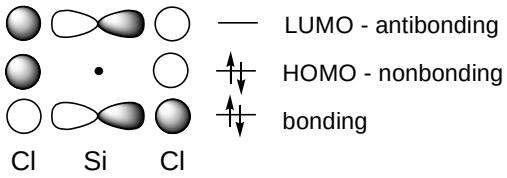


Figure 3.2. Three-centre Four-electron Bond in Hypervalent Silicates

Silicon Lewis acids are among the most common non-metallic acids that are used in organic synthesis. Silicon's ability to coordinate beyond the octet rule was originally explained by the availability of 3*d* orbitals in analogy to transition metals. Later, these orbitals were shown to be too diffuse to provide bonding and theory of three-centre four-electron bond of 3*p* orbitals formed instead. Thus, the expanded pentavalent silicon atom is formally sp^2-hybridised and of trigonal bipyramid geometry the hexavalent species is sp-hybridised octahedral (bond lengths in SiF_4 are 1.560 Å, $(SiF_5)^-$: *ax* 1.660 Å, *eq* 1.622 Å and $(SiF_6)^{2-}$: 1.685 Å).[142] The hypervalent bonds are electron-rich at the ligands and

electron-deficient at the central silicon atom. Two *n*-orbitals of the donor and one silicon *σ*-orbital create three molecular orbitals (Figure 3.2), whose HOMO has a node at the silicon atom and concentrate the electron density at the ligands. As the strength of the donor increases, the energy gap between the HOMO and LUMO can be sufficiently large to cause ionisation of the A-Y bond (Scheme 3.6). This molecular orbital theory is in agreement with the empirical Gutmann analysis.

Lewis base-catalysed reactions cover a broad range of reactions, with or without the formation of a new stereogenic centre (room for enantioselective modifications). Any of the three types of interactions might be significant for the catalytic process:

1. *Reactions occurring via n-π* interactions – nucleophilic additions*:
   - electrophilic acylations, nucleophilic reactions of acylated LB,
   - reactions of ketenes, cycloadditions,
   - Morita-Baylis-Hillman reaction (alkenoates, alkynoates),
   - amine organocatalysis.

2. *Reactions via n-σ* interactions – polarised or ionised intermediates*:
   - allylations, alkylations, epoxide ring-opening
   - aldol condensations, Mannich reaction, Michael additions,
   - trifluoromethylation, silylcyanation, Strecker reaction,
   - reductions of carbonyls.

3. *Reactions via n-n* interactions – boron*:
   - reductions of carbonyls, allylations.

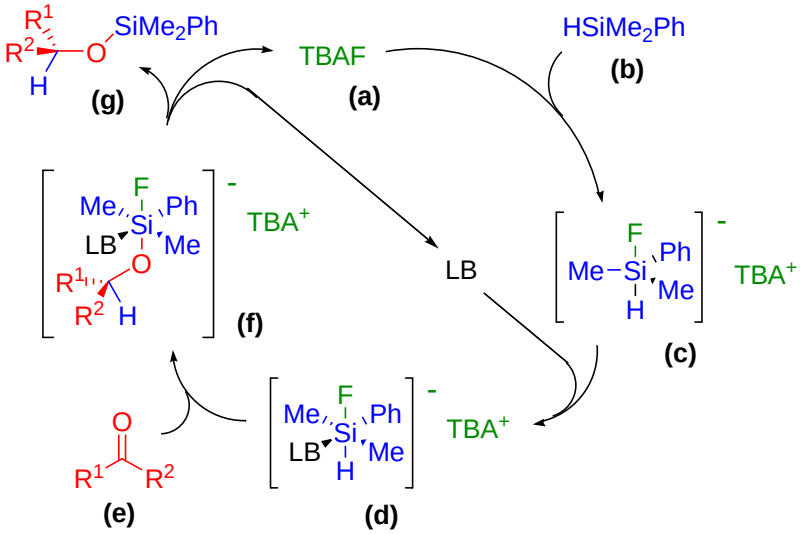
4. *Bifunctional catalysis*:
   - *n-σ** Lewis base / Lewis acid catalysis –
     alkylations with diethylzinc, silylcyanation, fluoride-catalysed reactions,
   - *n-π ** Lewis base / Brønsted acid catalysis –
     Morita-Baylis-Hillman, amino-acid-catalysed reactions,
   - dual activation – carbene catalysts.

3.2.2. Hypervalent Silicates[143]

Reduction potential of silanes has been studied along with their other properties since the 1950s. Over the following decades, it was reported that their reducing activity could be enhanced with acids, fluorides, alkoxides, or transition metal complexes. Silicon complexes activated by fluoride anion – pentavalent fluorosilicates – were the first group of hypercoordinate silicon reagents that were not only studied structurally, but also used in organic synthesis for reduction of carbonyl compounds[144] or allylation reactions.[145] They became particularly popular in late 1970s when soluble fluoride sources (e.g. TBAF)[145a] were introduced to replace the insoluble inorganic salts (such as KF or CsF),[144] which triggered a major expansion of their synthetic applicability. The bond energies[146] shed some light onto the activation of silicon with fluorides:

- very high *Si-F* bond energy (in average 143 kcal.mol^{-1} ~ 599 kJ.mol^{-1}; for comparison, the *Si-Cl* is 71 kcal.mol^{-1} ~ 297 kJ.mol^{-1}),
- relatively low energy of the newly formed *C-C* (83 kcal.mol^{-1} ~ 348 kJ.mol^{-1}) or *C-H* bond (99 kcal.mol^{-1} ~ 414 kJ.mol^{-1}).

It was noticed that not only fluorides but also neutral strong nucleophiles, such as HMPA, DMSO and DMF can activate silicon and this process is entropy-controlled.[144c]



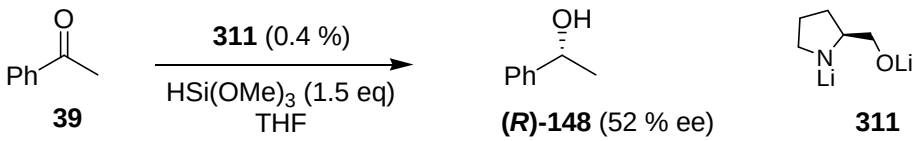
Scheme 3.7. Proposed Mechanism of Fluoride and/or a Neutral LB-catalysed Reduction of Carbonyls.

The mechanism of silicon-activation with fluorides (Scheme 3.7) was based on fast bonding of fluoride to silicon, generating a pentacoordinate fluorosilicate **(c)** which is assumed to be the active hydride donor.[147] However, in the presence of a Lewis basic solvent (e.g. HMPA), this species **(c)** can coordinate another molecule of Lewis base to form a hexacoordinate silicate **(d)**. Intermolecular hydride transfer from **(d)** to carbonyl compound **(e)** is then followed by immediate trapping of the alkoxide by the solvent-coordinated fluorosilane. The resulting hexacoordinated complex **(f)** dissociates to produce silylated alcohol **(g)** and two molecules of Lewis bases (F^- and HMPA).

Table 3.2. Selected Lewis-Base-catalysed Reactions Involving Hypervalent Silicates

Entry	Substrates	Catalyst (mol %)	Temp. (°C)	Yield (%) / ee (%)
1	**39**	**311** / 0.4	ambient	89 / 52 (*R*)
2	**146, 312**	**313a** / 100	–78	85 / 63 (*R*)
3	**146, 312**	**313a** / 10	–78	40 / 53 (*R*)
4	**146, 315**	**313b** / 10	–78	93 / 93 (*anti*), 2 / n.a. (*syn*)
5	**146, 312**	**317** / 7	–60	72 / 98 (*S*)
6	**318, 312**	**17** / 300	–78	80 / 98 (*S*)
7	**146, 320**	**321** / 5	–78	99 / 81 (*syn*) or 99 / 59 (*anti*)
8	**146, 323**	**321** / 5	–78	95 / 98 (*S*)

Similar catalytic process was observed in reduction and allylation reactions with alkyl-, aryl-, alkoxy- or mixed silanes because they exhibit the desired nucleophilic character under Lewis base activation. Polyalkoxy- and chlorosilanes are naturally (weakly) electrophilic, in contrary to polyalkyl- or arylsilanes, and can attain nucleophilic character *solely* under LB activation (*vide infra*). The understanding that alkyl- and alkoxysilanes can perform analogous reactions and that inherently more versatile alkoxides can be conveniently used for activation of the silane caused rapid development of the alkoxide activation.[148,149]

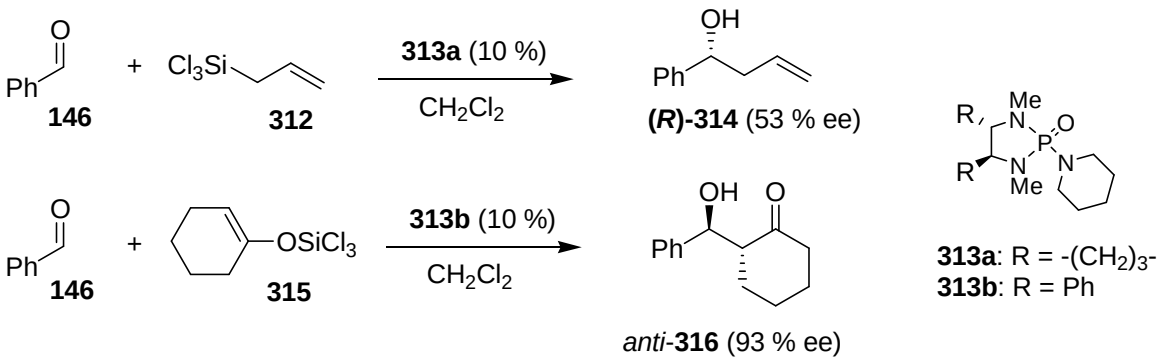


Scheme 3.8. Organocatalytic Enantioselective Reduction of Acetophenone.

The first organocatalytic (Li is not mechanistically involved) enantioselective version of reduction of ketones with activated alkoxysilanes appeared only 2 years after the discovery of its racemic parent.[148] The trimethoxysilane was activated and desymmetrised

by dilithium salt of prolinol **311**.[150] This catalyst mediated extremely efficient cycle in only 0.4 % (!) loading and the product was obtained in remarkable 52 % ee (Table 3.2, entry 1; Scheme 3.8).

The realisation that neutral Lewis bases can activate silanes as efficiently as anions,[151] set the scene for developing mild catalytic methods and new opportunities in enantioselective modifications. Even milder conditions could be achieved by using chlorosilanes instead of alkylsilanes because the nucleophilicity of the dialkylchlorosilane is approximately 1000 times lower than the trialkylsilane – i.e. electrophilicity of the hypervalent centre increases ~300 times with the first methyl-for-chloride substitution, and up to 10^5 times for all three methyl-for-chloride substitutions on silicon![152] Furthermore, halosilanes gain greater nucleophilic character at the halogen (or carbon) ligands *and* greater electrophilic character at the silicon atom. That provides a binding site for substrates as carbonyls, in other words – dual activation for both reactants – the substrate and the reagent. The choice of an appropriate activator (fluoride, alkoxide, neutral LB) and the silane (from polyalkyl- to polyhalosilanes) and their right combination shows how the reactivity can be tailored according to the needs.



Scheme 3.9. Organocatalytic Enantioselective Allylation and Aldol Reaction.

Lewis acidic silicon reagents activated by a Lewis base were used as very potent hydride and allyl donors from the 1990s when enantioselective allylation[153] attracted much attention. The first addition of allyltrichlorosilane **312** to benzaldehyde **146** was carried out with 10 mol % of phosphoramide catalyst **313a** and afforded the homoallylic alcohol in moderate yield and 53 % enantioselectivity[154] (Table 3.2, entries 2 and 3; Scheme 3.9). Analogous catalyst **313b** was more successful in catalysing the addition of enol silylethers[155] (Table 3.2, entry 4; Scheme 3.9), which was known to proceed uncatalysed.

However, it was significantly accelerated by the addition of a Lewis base. The product was almost exclusively of *anti*-configuration (>95:5) and high enantiopurity (95 % ee). This was a breakthrough in the reactions of Lewis-base-activated Lewis acids as it demonstrated its applicability in enantioselective (organo)catalysis. Other Lewis bases used in analogous reactions were chiral formamides, *N*-oxides and sulfoxides (*vide infra*).

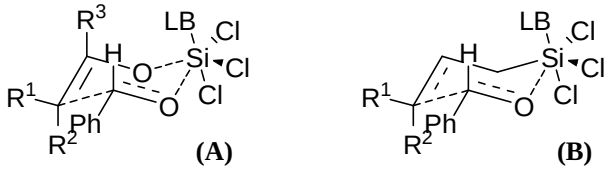
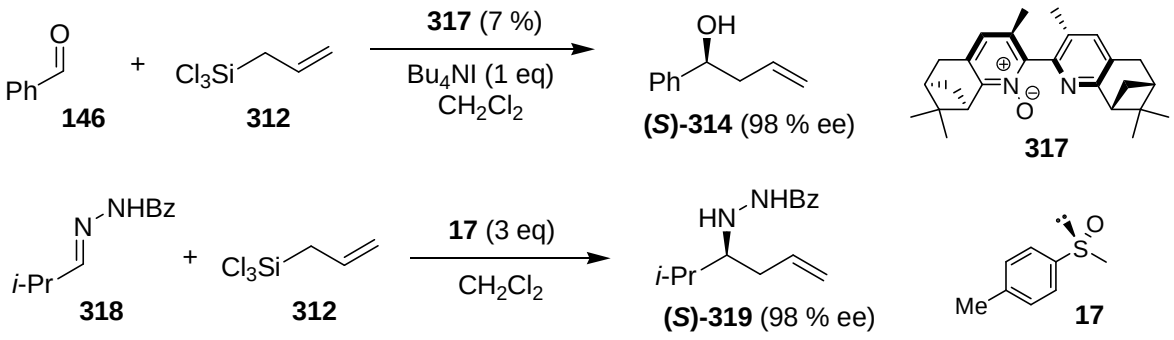


Figure 3.3. Proposed Transition Structure for Addition of Enol Silylethers **(A)** and Allylation **(B)**

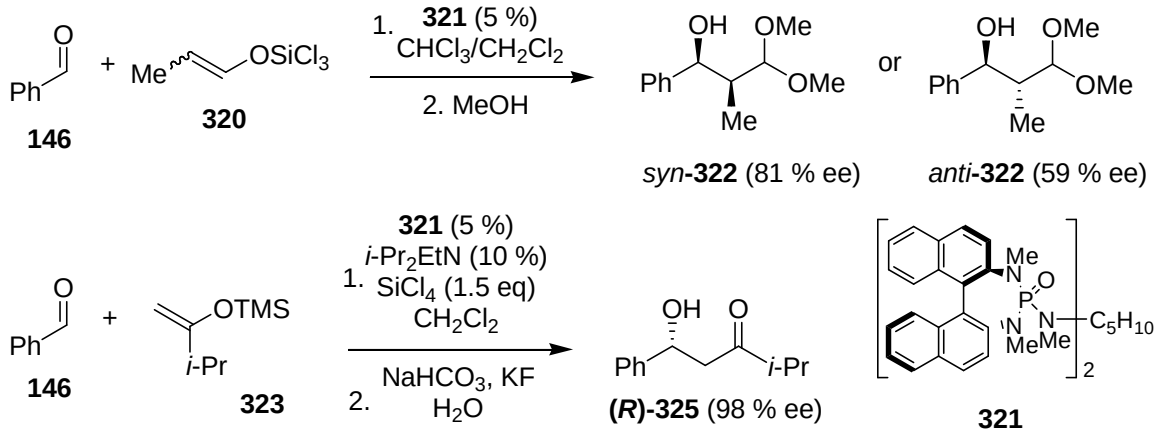
The diastereoconvergency of the enol silylether addition [(*E*)-enol → *anti*, (*Z*)-enol → *syn*] and allylation [crotylation: (*E*)-alkene → *anti*, (*Z*)-alkene → *syn*] indicates that the reaction proceeds through a cyclic, chair-like transition state organised around the hypervalent (hexavalent) silicon (Figure 3.3). Among the best performing catalysts were the mono-*N*-oxide **317** for allylation of aldehydes affording the homoallylic alcohol in very high yields and enantioselectivity[156] (both 98 %; Table 3.2, entry 5; Scheme 3.10). Interestingly, the allylation reaction of nitrogen analogues of carbonyls has not been very successful. One exception, yet only in stoichiometric amounts (3 equivalents!) of sulfoxide activator **17** performed well in allylation of hydrazones[157] with ee up to 98 % (Table 3.2, entry 6; Scheme 3.10).



Scheme 3.10. Organocatalytic Enantioselective Allylation.

Aldol reactions are commonly catalysed by Lewis acids, thus they can be suitable model reactions for catalysis by a chiral Lewis acid or a Lewis acid activated by a chiral Lewis base (Scheme 3.9, Scheme 3.11). Various bis(phosphoramides) were tested as

potential catalysts for aldol reactions and the best results were achieved with binaphtyl-derived catalyst **321** – particularly for the addition of enol silylethers. The mechanism of addition of enol silylethers[158] as **320** to aldehydes (Table 3.2, entry 7; Scheme 3.11) was expected to be similar to the allylation mechanism (six-membered chair-like TS; Figure 3.3), producing the alcohol in high diastereoselectivity. The enantioselectivity was higher in the case of (*E*)-enols (up to 90 %). *Exo*-enols also reacted with aldehydes in the presence of the catalyst **321** affording β-hydroxy ketones in excellent enantioselectivity[159] (Table 3.2, entry 8; Scheme 3.11).



Scheme 3.11. Organocatalytic Enantioselective Aldol Reactions

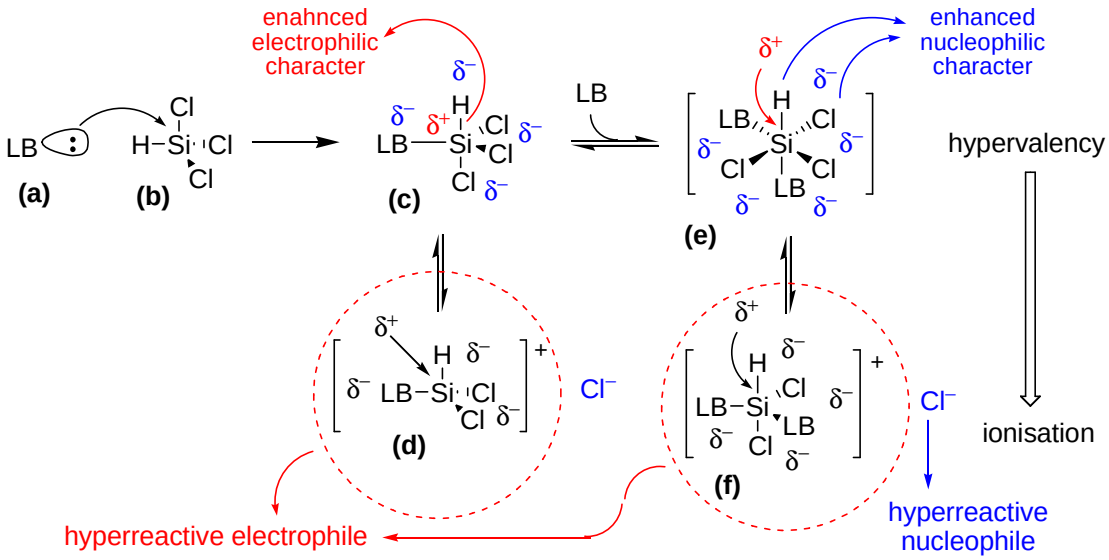
Formamide and sulfinamide catalysts became very popular for the reductions of imines with silanes, as described in detail in Chapter 2.4.

A generalised mechanistic picture can be drawn for the described reaction as they all have common features of LB-activated LA-catalysis:

- a Lewis acidic silicon reagent is used as a carrier of a carbon fragment or a hydride,
- the silicon atom in the reagent is activated by a (chiral) Lewis base,
- the LB-activated hypervalent silicon species is the true intermediate.

The example of trichlorosilane and a neutral Lewis basic activator (Scheme 3.12) is the most common combination used up-to-date. The coordination of a Lewis base **(a)** to silicon forms the pentavalent silicate **(c)** in which the silicon is more electrophilic and the chlorides are more nucleophilic than in the original weakly Lewis acidic tetravalent trichlorosilane **(b)**. The highly Lewis acidic silicon in **(c)** can now bind another Lewis

basic molecule – either another catalyst or a substrate (typically carbonyl) to form a hexavalent species **(e)**. Depending on the character of the LB-catalyst, a ligand (chloride) may dissociate from either of these hypervalent silicates **(c)** or **(e)** to form a pair of hyperreactive electrophiles **(d)** or **(f)** and nucleophile (Cl^-).



Scheme 3.12. Activation of Trichlorosilane (Lewis Acid) with a Lewis Base

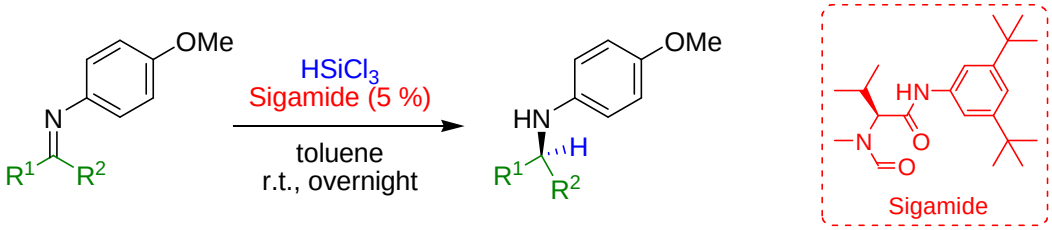
While many metal centres are often good Lewis acids, many known organic catalysts tend to react as heteroatom N(O)-, P(O)- and S(O)-centred Lewis bases. Side by side with enamine catalysis which also does exhibit features of Lewis acid catalysis, these methods of catalysis are complementary.

Part B:

Results and Discussion

Aims

The field of enantioselective organocatalysis became very competitive in the new millennium. The enantioselective organocatalytic reduction of imines with trichlorosilane became quickly one of the research targets in Kočovský / Malkov group, where it has been in development since 2004.[II]



Scheme A3. Scope of Enantioselective Reduction of Imines with $HSiCl_3$ and Sigamide

My contributions to the advancements in understandings of the methodology are based on investigating the scope and synthetic utility of the new methodology using the improved catalyst Sigamide (Scheme A3). The synthesis of Sigamide has already been established (see Chapter 2.4.2). The choice of substrates of interest is based on their possible practical use as synthetic intermediates or in synthesis of natural products. A diverse substrate scope has to be explored to gain pieces of information for the mechanistic proposal. Thus, imines derived from acetylheteroaromatics containing nitrogen, sulfur or oxygen are of importance for they prove the (in)tolerance towards different heteroatoms. On the other hand, aromatic or aliphatic imines with varied groups in the proximity of the *C=N* bond may demonstrate the impact of setric and electronic variations in the substrate structure and tolerance to functional groups.

The experimental results gathered from a library of prepared enantioenriched amines will be assessed and a mechanistical picture will be drawn concluding the scope and limitations of the methodology. The practical use of the method in a short total synthesis will be demonstared, as well.

II. (a) Malkov, A. V.; Mariani, A.; MacDougall, K. N.; Kočovský, P. *Org. Lett.* **2004**, *6*, 2253; (b) Malkov, A. V.; Stončius, S.; MacDougall, K. N.; Mariani, A.; McGeoch, G. D.; Kočovský, P. *Tetrahedron* **2006**, *62*, 264; (c) Malkov, A. V.; Stončius, S.; Kočovský, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 3722; (d) Malkov, A. V.; Figlus, M; Stončius, S. Kočovský, P. *J. Org. Chem.* **2007**, *72*, 1315.

4. Preparation of Imines

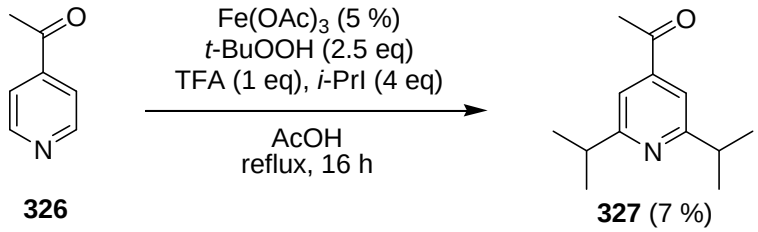
4.1. Synthesis of Ketones

A majority of the ketones used in this study were either commercially available or synthesised according to the literature procedures, without optimisation. For future reference, I will keep sorting according to the type of group in the side chain:

- *N*- (pyridines); *N*,*S*- (thiazoles) or *S*-heterocyclic (thiophene),
- *O*-heterocyclic (furan) and *O*- or *N*-bicyclic (benzo[*b*]furan, indole),
- aryl-alkyl chain with functional groups or increasing bulk, and
- miscellaneous.

4.1.1. Ketones containing N-; N, S-; S- and O-heterocycles

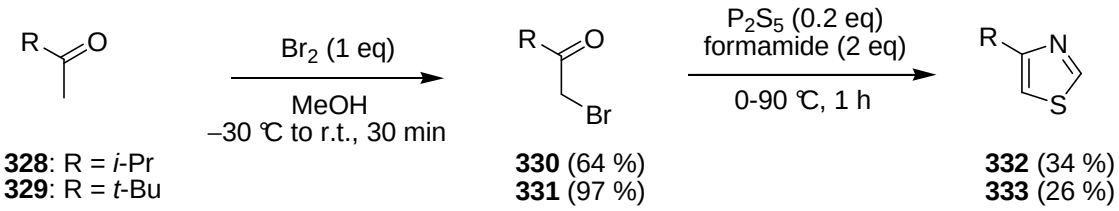
The only prepared ketone from the pyridine series was the bulky 2,6-di-*iso*-propyl-analogue of 4-acetylpyridine (Scheme 4.1). Elevated temperature and acidic conditions were required for the formation and propagation of the radical chain.[160] On the other hand, the presence of radicals and the harsh condition might have been also the reason why the yield was so poor (7 %).



326 **327** (7 %)

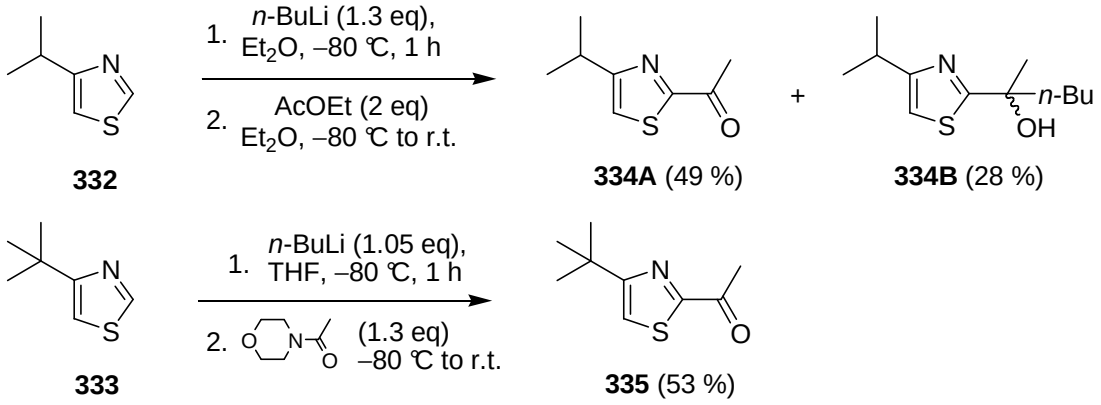
Scheme 4.1. Derivatisation of 4-Acetylpyridine

Precursors for 2-acetyl-4-alkylthiazoles, the 4-alkylthiazoles, were constructed from the corresponding α-bromo ketones and thioformamide (Scheme 4.2). Bromination of simple ketones[161] afforded essentially pure α-bromo ketones which were cyclised with formamide in the presence of phosphorus pentasulfide as the source of sulfur.[162] Distillation of the crude mixtures yielded the 4-alkylthiazoles.



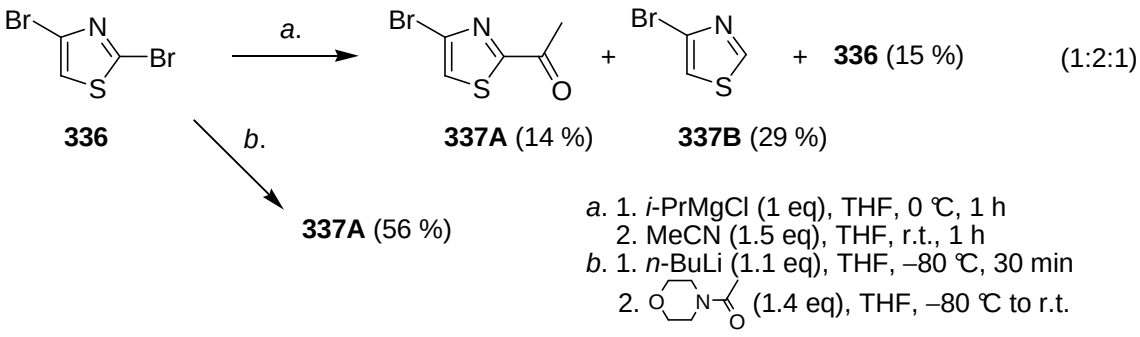
Scheme 4.2. Synthesis of 4-Alkylthiazoles

Acetylation of 4-alkylthiazoles was carried out in two different ways (Scheme 4.3). Ethyl acetate acted as a potent acetylating reagent and the 2-lithiated intermediate was acetylated in at least 75 %.[163] However, approximately a third of the product **334A** thus formed over-reacted with *n*-butyllithium to produce the corresponding alcohol **334B**. Using less base only caused decreased conversion and yields. Hence, *N*-acetylmorpholine, an acetyl-transfer reagent, was used to diminish the risk of over-reacting while the amount of the base was decreased to 1.05 equivalents.[164]



Scheme 4.3. Acetylation of 4-Alkylthiazoles

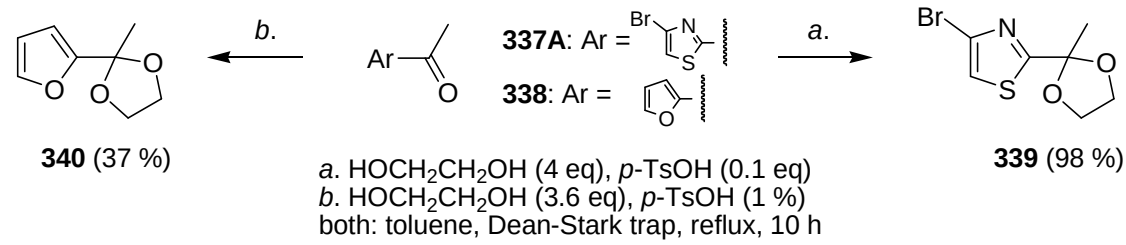
Another acetylthiazole derivative was prepared by derivatisation of 2,4-dibromothiazole **336**, starting by acetylation at the most reactive position-2. This step proved rather tricky as extensive decomposition of the material occurred easily.[165] Metal-halogen exchange with *iso*-propylmagensium chloride or ethylmagnesium bromide at temperatures varying from –20 ºC to room temperature and subsequent quenching with acetonitrile or ethyl acetate,[166] afforded only a mixture of unreacted dibromo-compound, the desired 2-acetylated compound **337A** and 2-debrominated species **337B** in 1:1:2 ratio and combined maximum 60 % yield (Scheme 4.4). This only showed that the electrophile was not sufficiently reactive.



Scheme 4.4. Acetylation of 2,4-Dibromothiazole

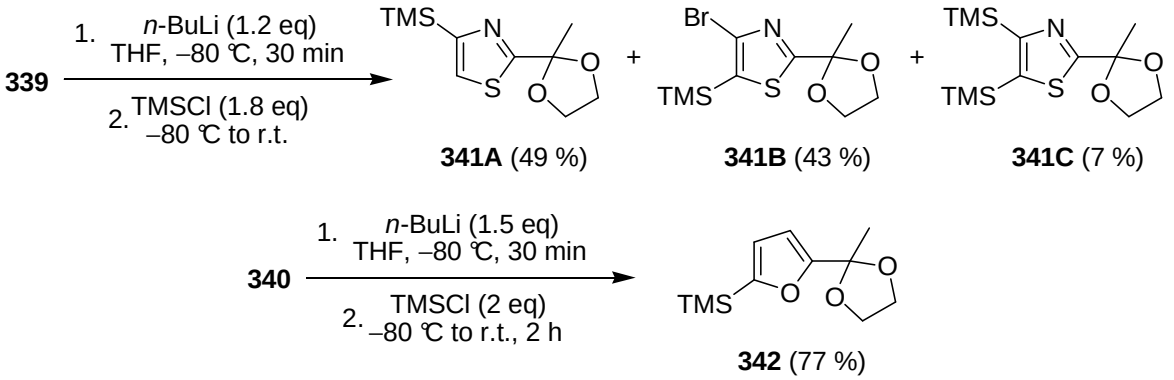
Alternatively, metal-halogen exchange with *n*-butyllithium at low temperature (–80 ºC) and 4-acetylmorpholine as acetylating agent were utilised instead[164] and this method resulted in clean conversion to 2-acetylated thiazole in 56 % yield (Scheme 4.4).

Before further derivatisation at the position-4 was carried out, the carbonyl group was protected as a ketal[167] (Scheme 4.5) in excellent 98 % yield of **339**. For comparison, analogous furan derivative **340** was obtained in low 37 % yield, possibly due to the higher volatility of the product and co-evaporation with toluene during the work-up. These protected acetyl-heterocycles were metallated and reacted with an electrophile, such as trimethylsilyl chloride or carbon dioxide.



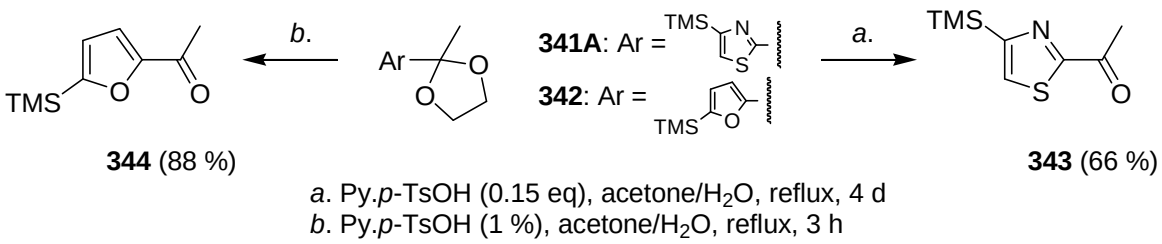
Scheme 4.5. Protection of the Carbonyl Group

Even if the reaction of **339** with *n*-butyllithium was quantitative, the yield of the desired 5-trimethylsilylated thiazole **341A** was low (49 %). The relatively similar acidity of the positions 4 and 5 in thiazole ring could explain why the expected metal-halogen exchange at position-5 was accompanied by concurrent undesired deprotonation at position-4, despite the cooling (Scheme 4.6). This resulted in the formation of a mixture of two major products 5-TMS **341A**, 5-bromo-4-TMS **341B**; moreover, double lithiation yielded the 4,5-di-TMS **341C**. This is in contrast to clean silylation[167] of furan derivative **340** in 77 % yield (Scheme 4.6), where the positional reactivity is clearly differentiated.



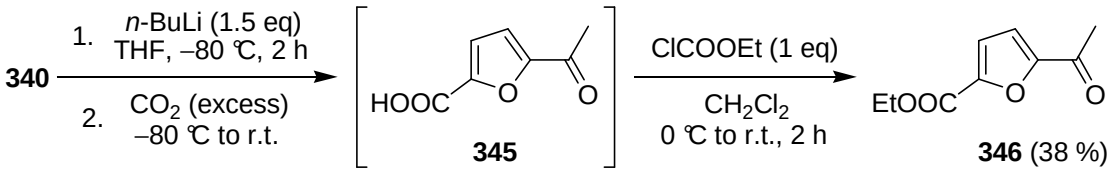
Scheme 4.6. Silylation of Protected 2-Acetylthiazole and 2-Acetylfuran

Reactivity of both heterocycles was very different also in the ketal-deprotection step. The furan-derived dioxolane **342** was deprotected in 3 hours while the thiazole analogue **341A** was quite resistant to the acid catalysed transketalisation with acetone and the reaction mixture had to be refluxed for 4 days (Scheme 4.7). However, the deprotection step was not optimised because enough of material was obtained.



Scheme 4.7. Deprotection of the Carbonyl

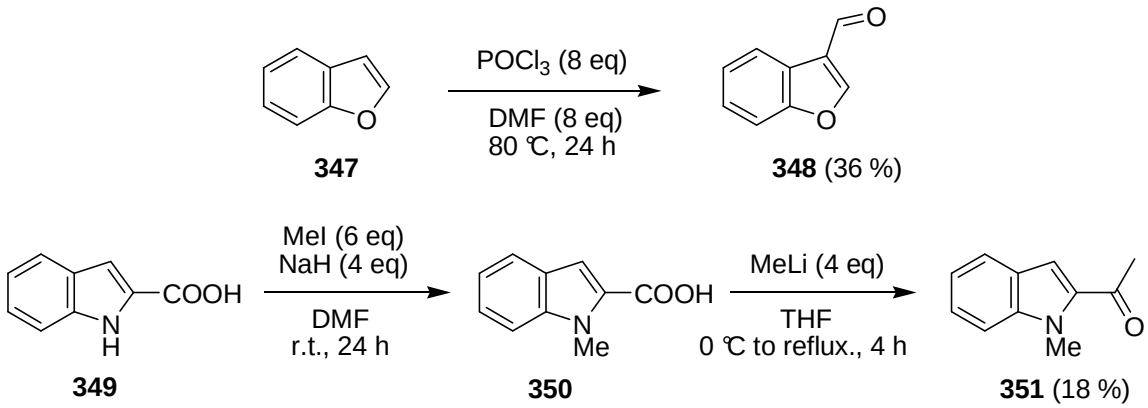
The 5-lithiated protected 2-acetylfuran[167] was also carboxylated using dry ice. It turned out that during the acid-base work-up of the crude acid, the dioxolane moiety was cleaved and produced the intermediate keto acid **345**. From practical reasons, the crude acid was transformed into ethyl ester **346** using the mixed anhydride method with ethyl chloroformate.[168]



Scheme 4.8. Carboxylation of Protected 2-Acetylfuran

For the group of Grignard addition reactions, only one aldehyde was synthesised,

the others were commercially available. The Vilsmeier-Haack formylation of benzo[*b*]furan produced selectively the 3-formyl isomer **348**, even if it was in only 36 % yield (Scheme 4.9).

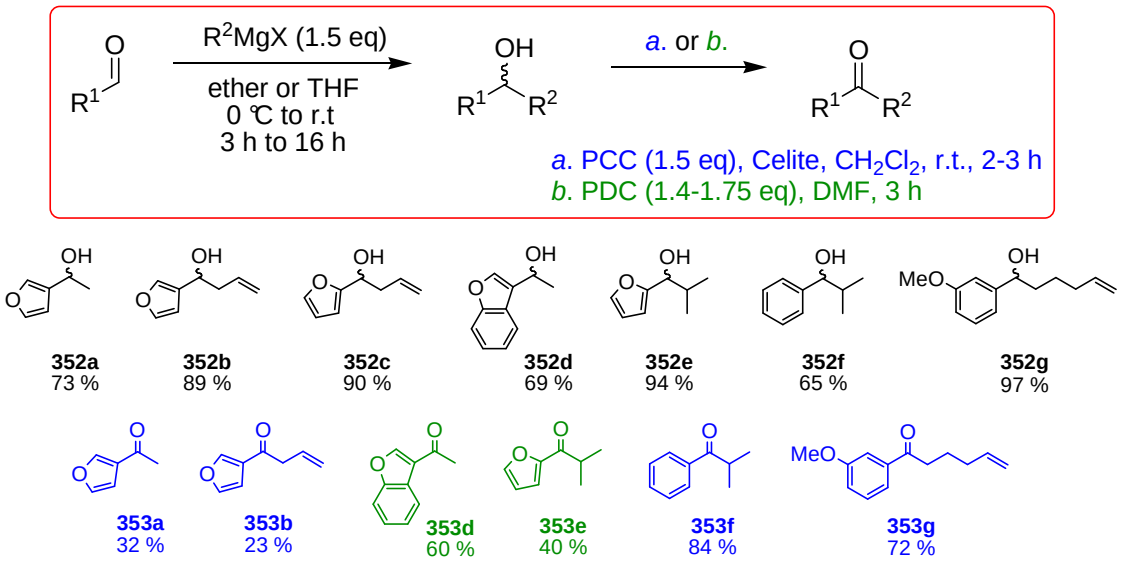


Scheme 4.9. Vilsmeier-Haack Formylation of Benzofuran and Preparation of 2-Acetylindole

N-Methylated 2-acetylindole was prepared by a two-step procedure from the *NH*-free acid **349** (Scheme 4.9). The mixture of *N*-methyl and/or *O*-methyl compounds resulting from the methylation of the acid **349** was unified by facile basic hydrolysis of the methyl ester. Addition of methyllithium to the *N*-methyl acid intermediate **350** afforded the 2-acetyl derivative **351** in 18 % overall yield.

4.1.2. Grignard Additions and Concomitant Oxidations

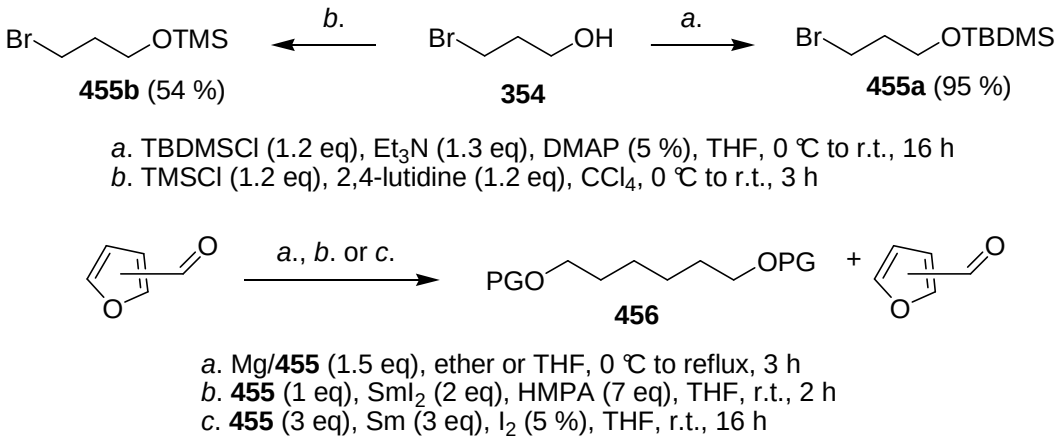
The addition of an appropriate Grignard reagent was the most common way for the preparation of the desired alcohols that were oxidised to the corresponding ketones.[169] The reactions were reliable and high-yielding (65-97 %). The oxidation with pyridinium chlorochromate[169] (PCC) was the method of choice for alcohols whose side chains were not sensitive to the acidic oxidative conditions. Thus, the furan-derived alcohols were oxidised preferentially with pyridinium dichromate[170] (PDC) which is less acidic.



Scheme 4.10. Grignard Additions and Concomitant Oxidations

Remarkably, furaldehydes did not undergo Grignard addition with silylether-protected 3-bromopropanol,[171] although this protocol was described in the literature.[172] Reaction conditions were varied:

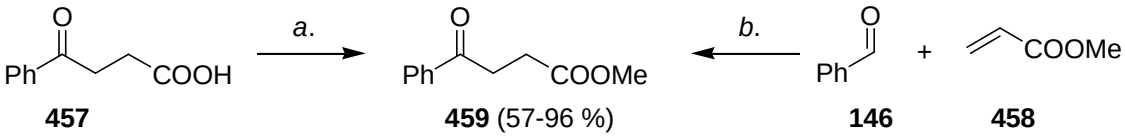
- reaction temperatures – from cooling to heating,
- dilution – to prevent undesired reactions of the initially formed magnesio-species,
- activation with iodine or 1,2-dibromoethane was expected to promote the formation of the Grignard reagent.



Scheme 4.11. Protection of Bromoalcohol and Its Attempted Grignard Addition

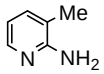
However, none to these attempts produced the desired alcohol; instead, only Wurtz coupling occurred and the silylated hexanediol was isolated in high yields (~80 %),

presumably because the Grignard magnesiohalide was not formed. The Grignard addition of an *O*-protected 3-bromoalcohol was problematic also with other protecting group (tetrahydropyranyl).[173] Another possible way for the preparation of the Grignard reagent was metal-halogen exchange with *iso*-propylmagnesium chloride[174] followed by standard addition of the aldehyde. However, this method provided only the products of *i*-PrMgCl addition to the aldehyde (30 %) and reduction of the aldehyde to a primary alcohol (50 %). The attempt to promote the formation of the correct magnesio-species by performing Barbier-version[175] with SmI_2 or Sm/I_2 afforded similar Wurtz-type product, if any (Scheme 4.11).



457 **459** (57-96 %) **146** **458**

a. H_2SO_4 (cat.), MeOH, reflux, 3 h

b. $[(PPh_3)_3Rh]Cl$ (5 %), PhCOOH (0.2 eq), 

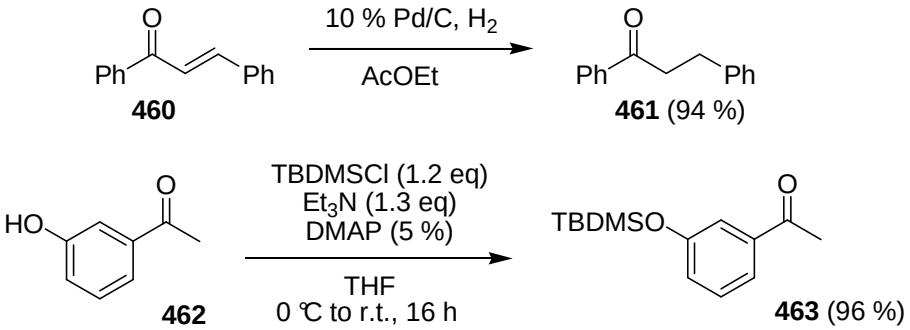
(0.4 eq), toluene, 130 ℃, 2 h

Scheme 4.12. Synthesis of γ-Keto Ester

Previously attempted synthesis of β,γ-functionalised ketones led us to an alternative γ-keto ester (Scheme 4.12) which could be reduced to alcohol for further applications. Besides the simple high-yielding esterification of the corresponding acid **457**, a Rh-catalysed addition of benzaldehyde to methyl acrylate[176] afforded the ester (57 % yield).

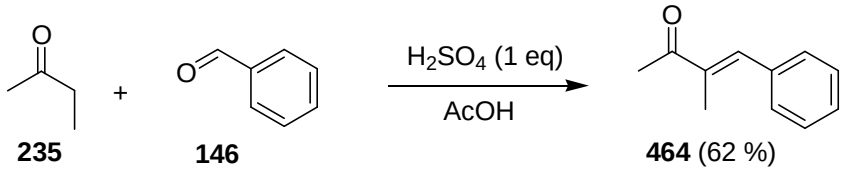
4.1.3. Aryl-alkyl or dialkyl ketones

Two model substrates were examined before embarking on the synthesis of colchinol (Chapter 7.2). Chalcone **460** was hydrogenated at an atmospheric pressure over palladium on charcoal (Scheme 4.13). This heterogenous hydrogenation provided selective reduction of the α,β-double bond, whereas its selectivity failed in the colchinol intermediate **562** and homogenous protocol was used (Scheme 7.19). Free-OH group was expected to have deleterious effect on the reduction of the corresponding imine, hence a silylether protecting group[171] was utilised for 3-hydroxyacetophenone (Scheme 4.13). Structurally analogous protected hydroxyl ketone **563** was applied in the synthesis of colchinol (Scheme 7.19).



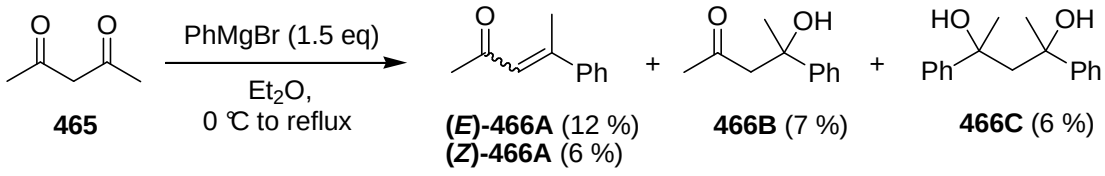
Scheme 4.13. Hydrogenation of Chalcone and Silylation of 3-Acetylphenol

Three α,β-unsaturated conjugated ketones were synthesised for investigating the effect of an extended conjugation on the reduction step. The easiest to prepare proved to be the (*E*)-3-methyl-4-phenylbut-3-en-2-one **464** (Scheme 4.14). Acid-catalysed aldol condensation[177] favoured the reaction of benzaldehyde with the thermodynamically more stable trisubstituted-enol (derived from **235**) and give rise to **464**.



Scheme 4.14. Synthesis of 3-Methyl-4-phenylbut-3-en-2-one

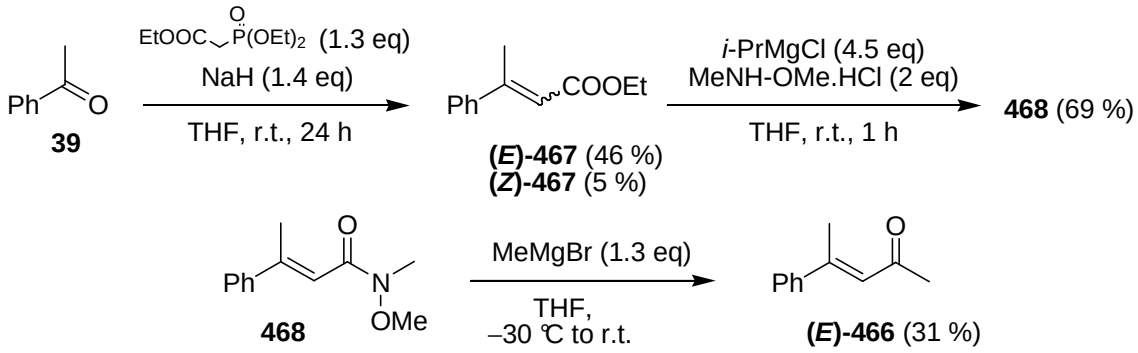
By contrast, the synthesis of the 2-methyl analogue **466A** proved tricky. Careful addition of phenylmagnesium bromide to acetylacetone[178] yielded a mixture of (at least) five products **466** in low yields (Scheme 4.15).



Scheme 4.15. Reaction of Acetylacetone with Phenylmagnesium Bromide

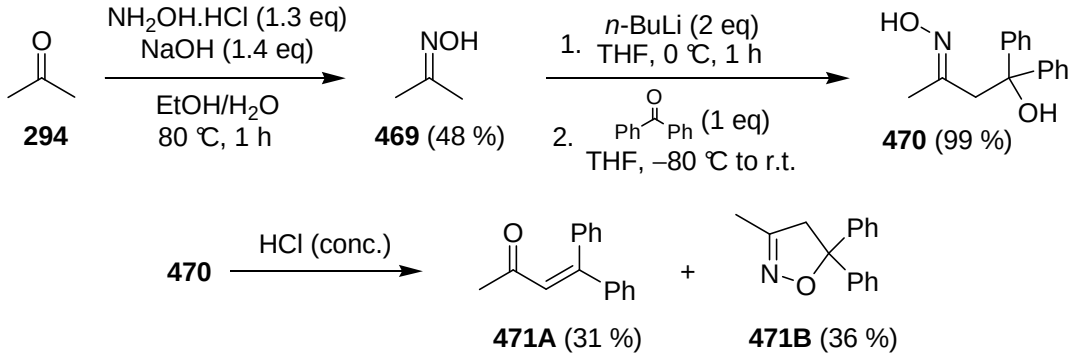
Hence, a three-step approach, lengthy but selective, was chosen[179] (Scheme 4.16). Horner-Wadsworth-Emmons reaction of acetophenone with triethyl phosphonoacetate afforded the (*E*)- and (*Z*)-α,β-unsaturated ester **467** in moderate yield and good 9:1 selectivity. These two isomers were separable by column chromatography and the starting material was also recovered. The (*E*)-ester was transformed into the Weinreb amide **468**

and subjected to the addition of methylmagnesium bromide to provide the desired 4-methyl-4-phenylbut-3-en-2-one **466** in 10 % overall yield. According to the literature,[179] the two latter reactions should have been almost quantitative.



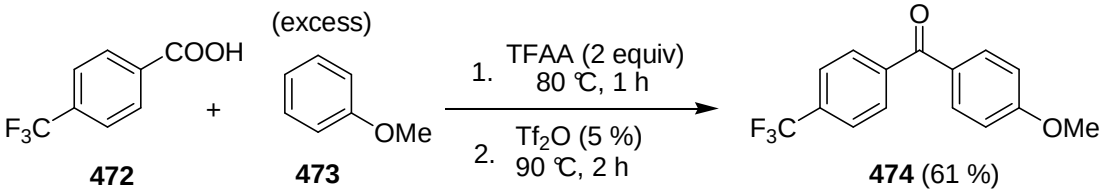
Scheme 4.16. Synthesis of 4-Methyl-4-phenylbut-3-en-2-one

4,4-Diphenyl analogue was prepared by condensation of dilithium salt of acetonoxime **469** and benzophenone[180] in nearly quantitative yield with no purification required (Scheme 4.17). Not surprisingly, the following oxime deprotection[181] and dehydration in concentrated HCl was non-selective and accompanied by closure of isoxazoline ring **471b**.



Scheme 4.17. Synthesis of 4,4-Diphenylbut-3-en-2-one

The *p,p'*-disubstituted benzophenone was synthesised by Friedel-Crafts acylation of anisole by the appropriate acid **472** (Scheme 4.18). Crystallisation of the product **474** from the solution was induced by addition of methanol.



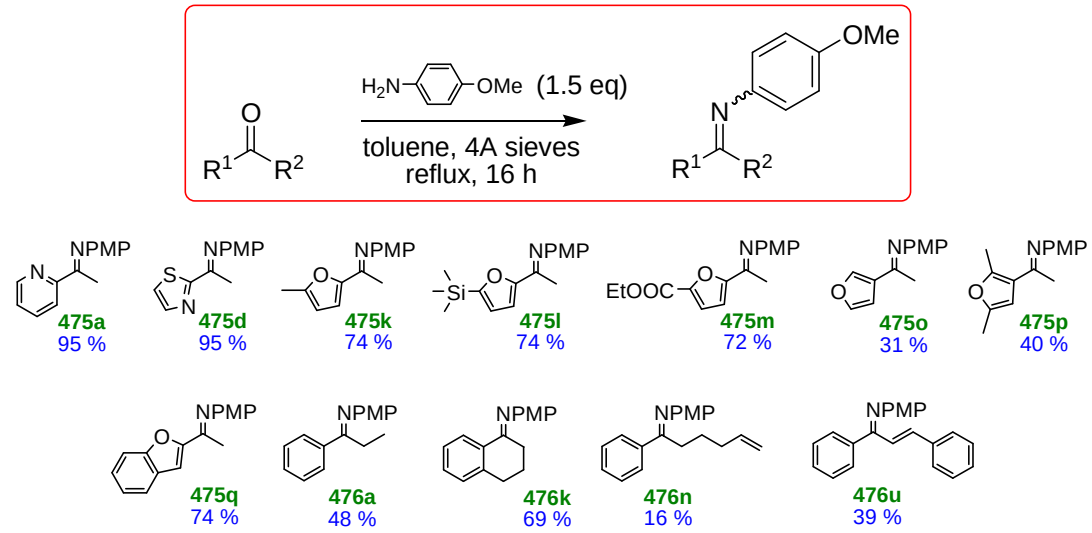
Scheme 4.18. Synthesis of Substituted Benzophenone

4.2. Formation of Imines

Four methods were used for the preparation of a library of imines and enamines, which differ in the way the reaction water is removed.

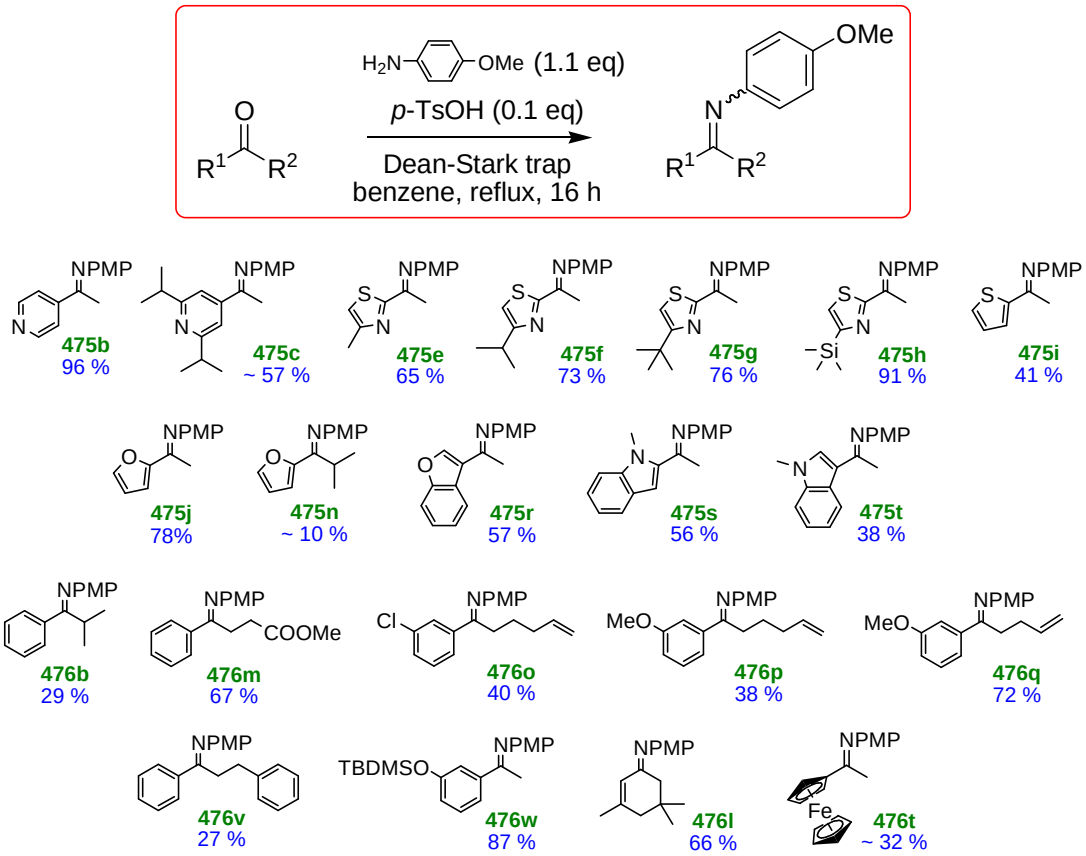
4.2.1. Prepared Imines

The first two methods required elevated temperatures. The first of them used 4Å molecular sieves as the water scavenger (Method A, Scheme 4.19.). The advantage of this method was that the imine solution was obtained by simple filtration from the sieves and, in general, it provided imines in good isolated yields.



Scheme 4.19. Imines Synthesised by Method A

However, in the cases where only small amounts of the ketone were available, the reaction became quite sensitive to the traces of water in the apparatus, the reaction components and the activity of the sieves. This rendered it inconvenient and unsuitable for imination of precious ketones.

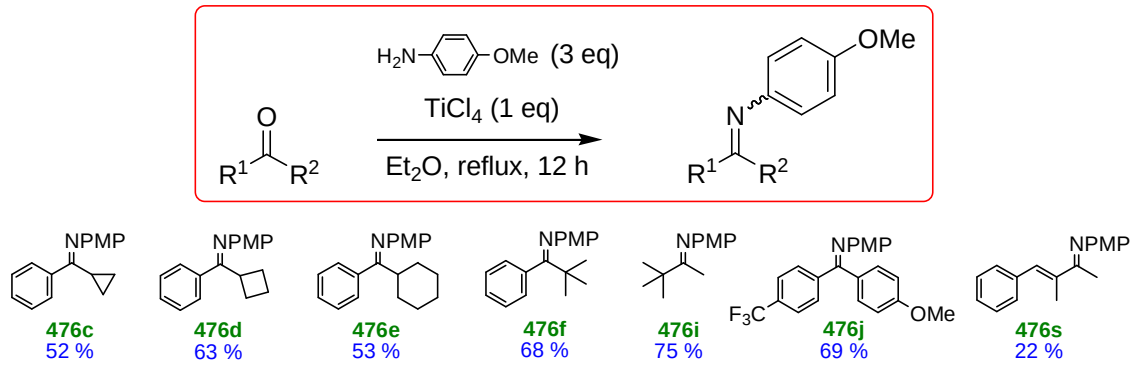


Scheme 4.20. Imines Synthesised by Method B

An alternative method used a Brønsted acid catalyst (*p*-toluenesulfonic acid) and a solvent that forms azeotropic mixtures with water, e.g., benzene or toluene (Method B, Scheme 4.20.). This method was efficient even for small quantities of ketones, provided a Dean-Stark trap of an adequate size was used. However, for obtaining pure imines, the removal the (*p*-TsOH)-(*p*-anisidine) salt and other polar components (e.g., residues of unreacted *p*-anisidine) by filtration on the triethylamine-treated silica proved beneficial, followed by crystallisation (typically from hexane).

Generally, either of the previously mentioned methods A or B was suitable for imines from methyl or other non-hindered ketones. However, when steric bulk was built around the carbonyl, conversion to imines became low (e.g. imines **475n**, **476b**). A third

method was chosen, a Lewis-acid-mediated imination[182] where the Lewis acidic titanium tetrachloride also served as a powerful dehydrating agent (Method C, Scheme 4.21.). This method proved to be the most efficient and was also used when the other methods failed or when a sensitive imine was formed (e.g., imine **476s**). This method required anhydrous conditions and large excess of the aniline (3 equiv.), but the imine was obtained essentially pure (in particular, containing no *p*-anisidine residues) by simple filtration from the precipitate.

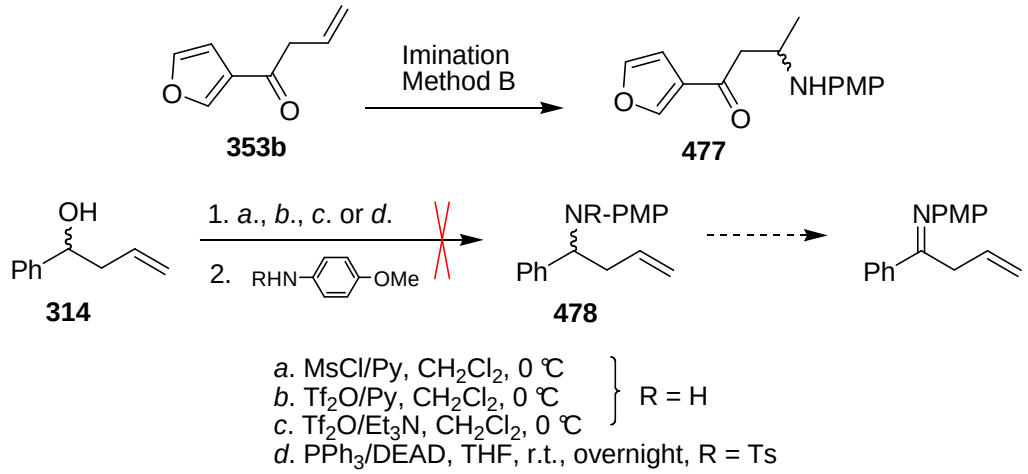


Scheme 4.21. Imines Synthesised by Method C

As revealed by ^{1}H NMR spectroscopy, the configuration at the imine double bond was predominantly (*E*)-, typically in 7:1-10:1 ratio when $R^2 \neq$ Me; otherwise, the imine adopted (*E*)-form exclusively. When the R^2 group became very bulky, in particular for **476c**-**f**, 5:2-5:3 mixtures of (*E*/*Z*)-isomers were isolated, whereas **476j** was a 3:2 mixture. However, this did not influence the enantioselectivity of the reduction, as shown later.

4.2.2. Attempted Syntheses of Imines

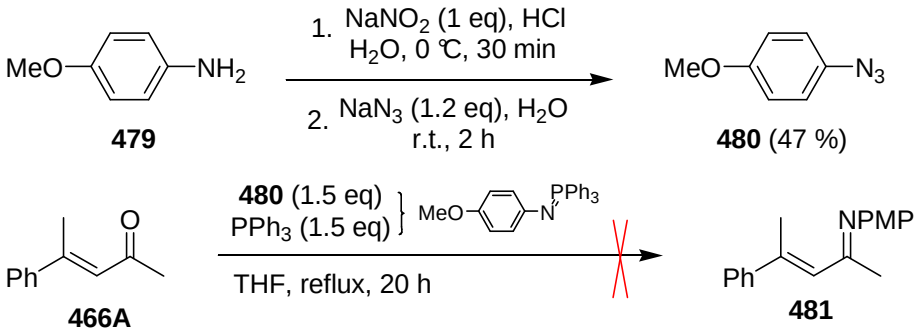
It is pertinent to note that some ketones did not produce the corresponding imines. One of these was the β,γ-unsaturated ketone **353b**, as it underwent isomerisation followed by Michael addition (Scheme 4.22). The standard imination is unsuitable for β,γ-unsaturated ketones; thus, other ways were tried.



Scheme 4.22. Michael Addition under Imination Conditions and Proposed Alternative Route

An easy-to-perform but lengthy approach would be the substitution-oxidation sequence (Scheme 4.22). A model homoallyl alcohol **314**, activated as mesylate,[183] triflate, tosylate, or via Mitsunobu conditions,[184] was subjected to nucleophilic substitution with *p*-anisidine. None of these reactions led to any reasonable product and this type of substrate was erased from the list.

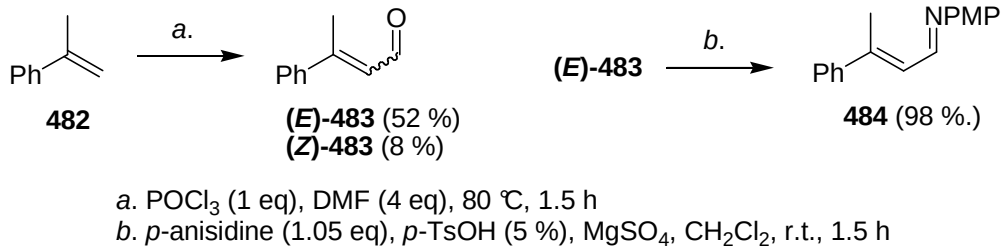
Interestingly, the α,β-unsaturated-β,β-disubstituted ketones were not suitable substrates for imination by any of the above-mentioned methods, including reductive amination. The only imine prepared was the α,β-disubstituted **476s**, the other two β,β-disubstituted analogues failed even if three alternative routes were investigated.



Scheme 4.23. Attempted Aza-Wittig reaction

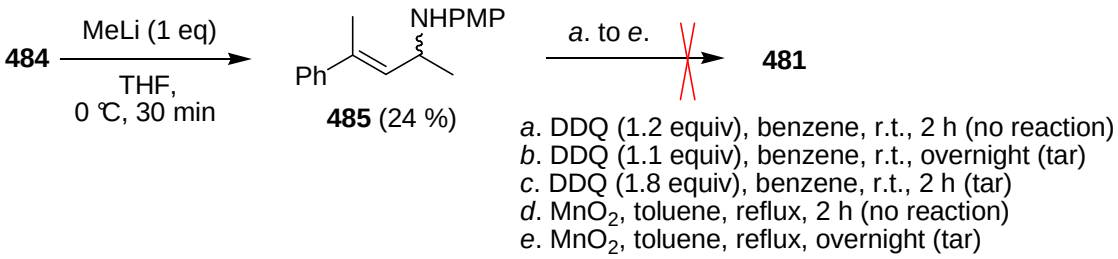
The first non-traditional method for introducing the imino group was an aza-Wittig reaction with the corresponding ketone, performed with *p*-azidoanisole **480** (Scheme 4.23) as the source of nitrogen. This method afforded only recovered starting ketone and *N*-

triphenylphosphino-*p*-anisidine adduct. This method was reported for β,γ-usaturated-α-imino esters[127] which are much more reactive than α,β-unsaturated ketones.



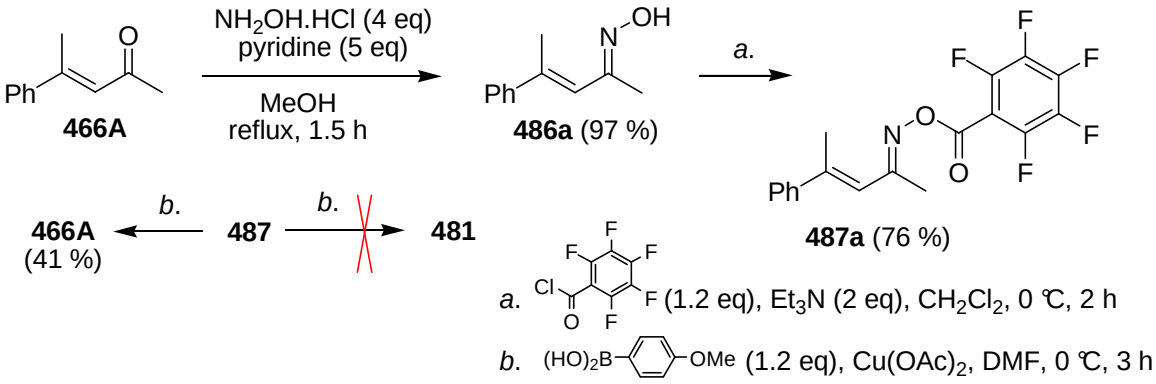
Scheme 4.24. Vilsmeier-Haack Formylation of Styrene and Imination of The Aldehyde

In parallel to the β,γ-unsaturated ketones, an alternative way was based on the idea of oxidation of the corresponding racemic amine. The synthesis of the amine started by Vilsmeier-Haack formylation of α-methylstyrene **482** which produced (*E*)- and (*Z*)-isomeric β-methylcinnamaldehyde **483** in good selectivity and moderate yield (Scheme 4.24). Separation by column chromatography afforded the (*E*)-α,β-unsaturated aldehyde in 52 % yield.



Scheme 4.25. Addition of MeLi on Aldimine to Produce Amine **485** and Attempts to Oxidise It

The aldehyde (*E*)-**483** was iminated in virtually quantitative yield and the product **484** was used for the addition of methyllithium to produce the racemic amine **485** in poor 24 % yield (Scheme 4.25). However, that was enough to carry out the following oxidation reactions and no optimisation was attempted. The oxidation was performed with DDQ[185] and freshly prepared manganese dioxide;[186] though, no success was achieved. Production of tar material or occasional isolation of acetophenone pointed at the instability of the possibly-formed imine.



Scheme 4.26. Copper(II)-catalysed Coupling Reaction

Much milder method of preparation of imine was needed. The nitrogen atom could be introduced in the form of oxime **486a**, because this is not an equilibrium reaction and coupling with an appropriate boronic acid would provide the imine. The final coupling precursor pentafluorobenzoate-*O*-oxime ester[187] **487a** (Scheme 4.26) was formed from the corresponding oxime in 76 % yield. Copper(II)-catalysed coupling of **487a** with 4-methoxyphenylboronic acid (Scheme 4.26) afforded only the ketone **466A** (41 % yield), which might have been a result of hydrolysis of imine **481** by traces of reaction water produced from the boronic acid.

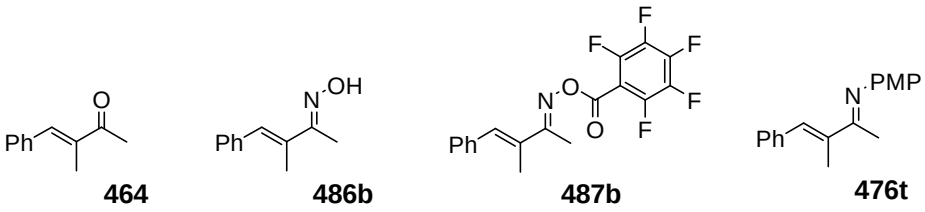


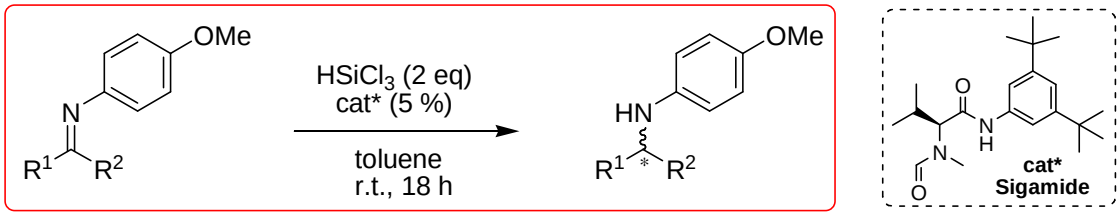
Figure 4.1. Reference Intermediates for Cu-catalysed Imine Formation

The whole synthesis was carried out in parallel (Figure 4.1) with 3-methyl-4-phenylbut-3-en-2-one **464** whose imine **476s** was prepared by imination Method C in 22 % yield. In this case, the coupling yielded a 1:1 mixture of the desired imine and the corresponding ketone (26 % each). It became apparent that the imine **481** would not be stable enough to bring it through to the next step. It is likely that the imine of ketone **471A** would be even less stable.

5. Reduction of Imines[188]

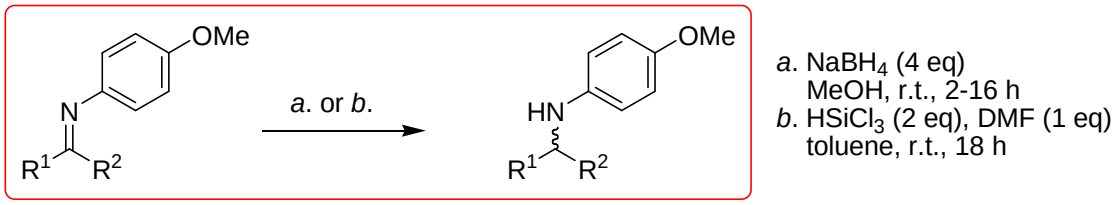
5.1. Preparation of Enantioenriched Amines

The reduction of all imines was carried out under our standard conditions at 0.2 mmol scale with 2 equivalents of trichlorosilane, 5 mol % of the catalyst Sigamide in toluene at ambient temperature for 18 hours under an argon atmosphere (Scheme 5.1). In some cases an additive was used to improve the reaction rate.



Scheme 5.1. Enantioselective Reduction of Imines

All enantioenriched amines were were also synthesised in their racemic forms (Scheme 5.2), either by reduction with sodium borohydride in methanol at ambient temperature or by a way analogous to the enantioselective one using DMF as the activator.



Scheme 5.2. Racemic Reduction of Imines

The typical isolated yields of the racemic amines were 65-95 %. These were prepared at 0.3 mmol scale to be used for characterisation and calibration of the HPLC conditions.

In the following text, only the formation of enantioenriched amines will be discussed, they are colour-coded: yields are in blue, enantiomeric excess in red.

5.1.1. Amines Containing N-; N,S- and S-heterocycles

In the previous study,[93,101-105] the method showed a good substrate generality, however only considering the electronically modified aromatic imines. Introduction of a heteroatom into the aromatic system of the model compounds was a natural step towards broader applicability in the view of the role of heterocyclic compounds in the pharmaceutical industry. At first, substrates containing an *N*- or *S*-heterocycle were investigated (Figure 5.1, Figure 5.2).

The pyridin-2-yl and pyridin-4-yl derivatives **488a**,**b** were reduced cleanly only with the addition of 1 equivalent of acetic acid (Figure 5.1); without it, these substrates reacted sluggishly. However, the products turned out to be almost racemic (7 and 21 % ee, respectively). In another study, it was shown that the pyridine nitrogen is capable of coordinating the silicon of trichlorosilane.[89,94] Hence, the lack of enantioselection can be attributed to this type of coordination, which is stoichiometric and non-chiral and can compete with the coordination to the chiral catalyst, which is present in only 5 mol %. To support this theory of the undesired coordination, steric bulk was built around the nitrogen of the substrate, as in the 2,6-di-*iso*-propyl analogue **488c** which was reduced with good enantioselectivity (78 % ee).

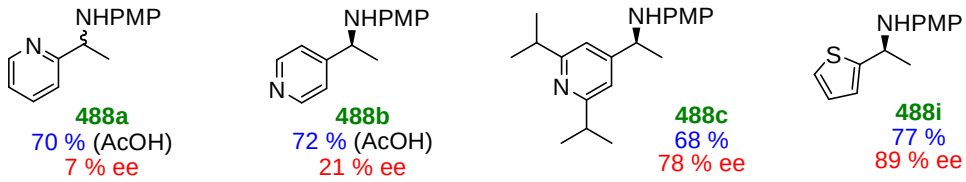


Figure 5.1. Amines Containing Pyridine and Thiophene Heterocycles

Thiazole is another heterocycle favoured in many pharmaceuticals (Figure 5.2). However, in its character it is similar to the pyridine nitrogen and its coordinating properties can account for the low observed enantioselectivity (13 %) of the amine **488d**. Introduction of increased bulk next to the nitrogen as Me < *i*-Pr < *t*-Bu improved the enantioselectivity in this series (31, 34, and 41 % ee, respectively); though, not as efficiently as in the case of pyridine. A drop of enantioselectivity (to 6 % ee) was caused by even bulkier, but more electron-donating 4-TMS group in derivative **488h**. The longer *C-Si* bond also might have caused overall smaller steric hindrance of the nitrogen.

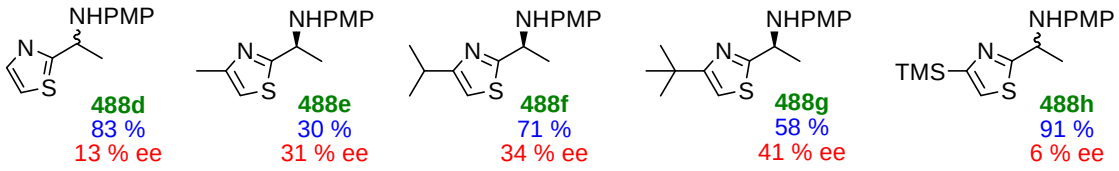
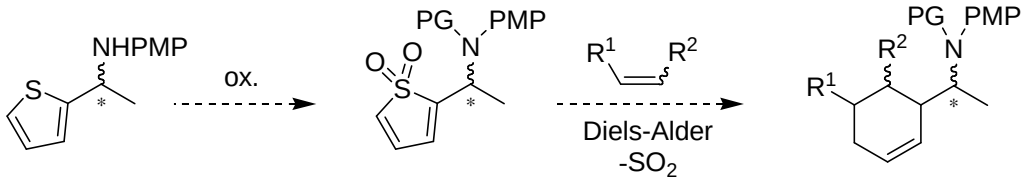


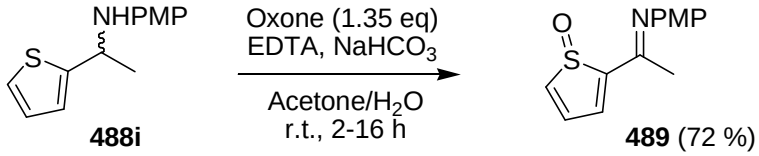
Figure 5.2. Amines Containing Thiazole Heterocycle

Sulfur as a heteroatom is free of negative effects, as shown by the thiophen-2-yl derivative **488i** (Figure 5.1), where the enantioselectivity (89 % ee) was close to that observed for the acetophenone-derived imines (91-94 % ee).



Scheme 5.3. Possible Use of Enantioenriched Thiophene-derived Amine

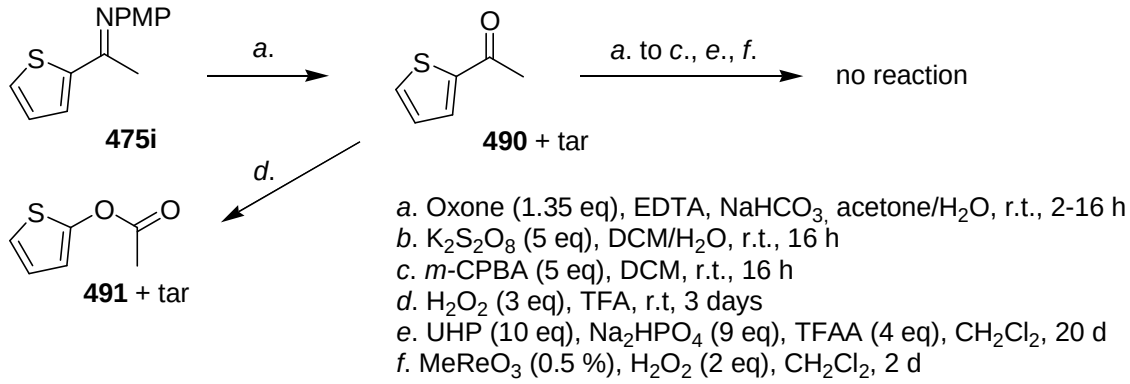
Thiophene in form of its 1,2-dioxide is known to be a good substrate for Diels-Alder reaction.[189] First attempt of oxidation of thiophene **488i** to thiophene-1,1-dioxide was performed with Oxone/acetone mixture[190] forming 3,3-dimethyldioxirane in situ. This produced thiophene-1-oxide **489** undesirably oxidised also at the *C-N* bond destroying the stereogenic centre previously formed (Scheme 5.4).



Scheme 5.4. Oxidation of Thiophene with Oxone

When Oxone was used with the imine **475i**, partial hydrolysis occurred (Scheme 5.5). Thus, more experiments were carried out with the corresponding ketone **490**. The mild oxidant as *m*-chloroperoxybenzoic acid[191] proved inefficient and the starting ketone was recovered. Stronger oxidising reagent potassium peroxydisulfate or aqueous hydrogen peroxide in trifluoroacetic acid was utilised, but again with no success. In the latter case, it is plausible that Baeyer-Villiger product was formed instead of the 1,1-dioxide.[192] Urea-hydrogen peroxide adduct[193] or catalytic methyltrioxorhenium with stoichiometric hydrogen peroxide[194] were reported to oxidise α,β-unsaturated ketones to lactones or

pyridines to their *N*-oxides, respectively, however they provided no product (at no conversion).

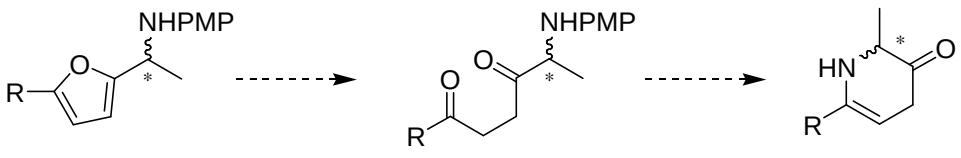


Scheme 5.5. Attempted Oxidation of Thiophene to Its 1,1-Dioxide

It was reported that in the cases where the common oxidants (Scheme 5.5) failed in oxidations of sulfides to sulfones, anhydrous conditions were found to be helpful. The literature[192] also describes how to avoid the Baeyer-Villiger reaction by using extremely strong oxidant as 95 % hydrogen peroxide in TFA; however this was not attempted for safety concerns.

5.1.2. Amines Containing O-heterocycles and N- or O-bicyclics

From the oxygen-containing heterocycles, furan is particularly interesting as it can be oxidatively opened to substituted 1,4-dicarbonyls and then further reactions can be performed (Scheme 5.6). Several furan-derived imines were prepared to study a library of substituted furans which then could undergo other transformations.



Scheme 5.6. Possible Trasformations of Furan

Furan-derived imines **488j-n** were found to be reduced with the efficiency laying between that of the sulfur and nitrogen heterocycles (45-77 % ee; Figure 5.3). Oxygen in the furan ring might also interact with trichlorosilane, which would explain the drop of

enantioselectivity in comparison with its thiophene analogue (from 89 to 56 % ee, structure **488j**). Decreased temperature helped to improve the enantioselectivity only marginally, to 62 % ee at –20 °C and at the expense of reactivity. The substitution in position-5 also influenced the enantioselectiviy, however, the results were rather confusing.

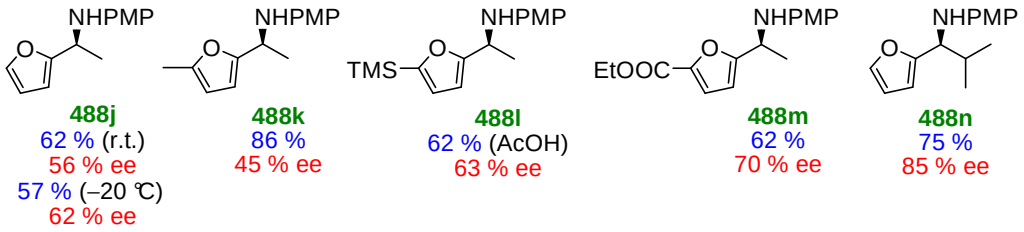


Figure 5.3. Amines Containing 2-Substituted Furan

Bulk at the position-5 caused drop *or* rise of enantioselectivity – the 5-methyl **488k** (drop to 45 % ee) and 5-TMS **488l** (increase to 63 % ee) analogues exhibited the opposite trend in comparison to the members of thiazole series (Figure 5.2). Trimethylsilyl group can be considered not only as a sterically hindering substituent, but also an electron-donating one. The effect of an electron-withdrawing group was shown on amine **488m**. Unfortunately, only marginal change of enantioselectivity was observed (62 %). Good enantioselectivity was achieved for the furyl-*iso*-propyl derivative **488n** (85 % ee). The effect of the bulk around the prochiral centre of the imine is discussed in Chapter 5.1.3.

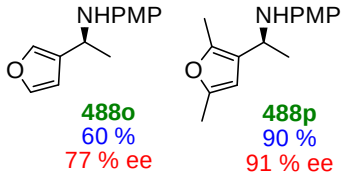


Figure 5.4. Amines Containing 3-Substituted Furan

The results obtained with the furan-2-yl series were slightly disappointing, therefore no further synthetic application of these substrates was provided. On the other hand, the furan-3-yl derivatives (Figure 5.4) exhibited a significantly higher level of asymmetric induction, the **488o** (77 % ee) than its 2-isomers **488h** (56 % ee). In their case, increasing the steric bulk in position-5 had clearly a positive effect, as documented by the 2,5-dimethyl derivative **488p** (91 % ee).

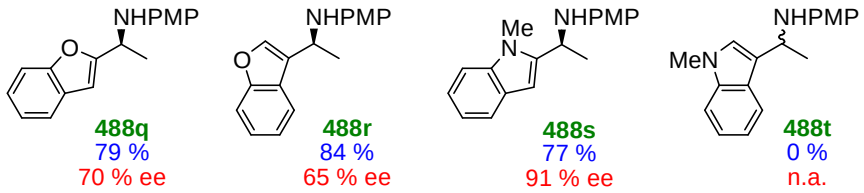


Figure 5.5. Amines Containing Benzo[*b*]furan and Indole Heterocycles

The benzo[*b*]furans **488q** (70 % ee) and **488r** (65 % ee) followed similar trends as the furans (Figure 5.5). *N*-Methylindol can be viewed as the benzo[*b*]furan nitrogen congener with a non-coordinating (protected) nitrogen atom (Figure 5.5). In contrast to the indol-2-yl **488s**, which was reduced in good yield and high enantioselectivity (91 % ee), the indol-3-yl analogue **488t** did not react at all, even with the addition of acetic acid or at elevated temperature (50 °C).

5.1.3. Aryl-alkyl Chain with Increasing Bulk or Functional Groups

The imines investigated so far were all derived from either electronically modified acetophenone or heteroaryl methyl ketones. Naturally, to present a complete study, it was of interest to vary the methyl group (Figure 5.6).

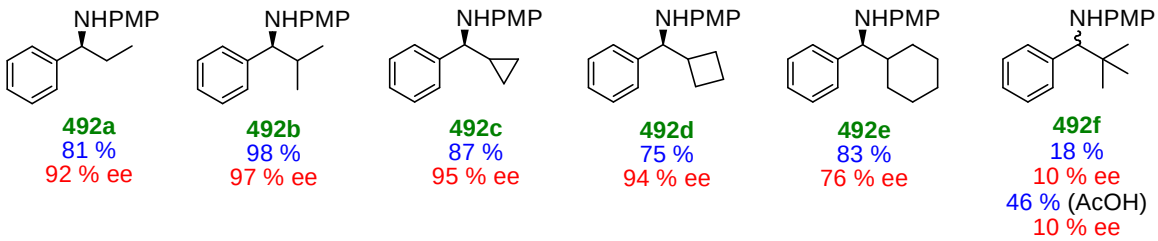


Figure 5.6. Aryl-alkyl Amines with Increasing Bulk

The ethyl analogue **492a** (92 % ee) turned out to behave in the same way as the acetophenone-derived counterpart. Branching in the R^2 group, as in the isopropyl **492b**, had a positive effect, in fact it was the "best-fitting" substrate (97 % ee). The structurally similar, but more rigid cyclopropyl **492c** and the cyclobutyl derivative **492d** were obtained in high enantiopurity (95 and 94 % ee, respectively). Moving to the bulkier cyclohexyl derivative **492e**, a drop of enantioselectivity was observed (76 % ee). Even more sterically congested *tert*-butyl substrate was reduced to **492f** in very sluggish and close-to-racemic fashion (10 % ee).

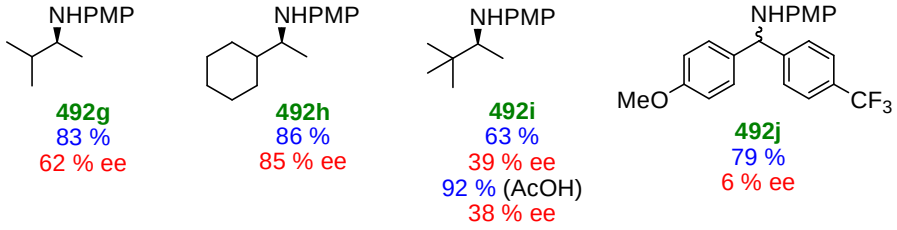


Figure 5.7. Dialkyl or Diaryl Amines

The dialkyl imines **492g-i** (Figure 5.7) showed a similar pattern as the phenyl-alkyl congeners. Good fit of the *cyclo*-hexyl group in substrate **492h** (85 % ee), but drop of enantioselectiviy in **492j** raised a question of what is the role of the aromatic moiety or the bulk of the group. As expected, the *iso*-propyl substrate was reduced in moderate (62 % ee) and *tert*-butyl-methyl in low enantioselectivity (38 % ee). Hydrolysis occurred partially when no additive (e.g. acetic acid) was used, similar to the case of **492f**. However, the yield was better as **492i** has at least one sterically non-hindered site. Furthermore, an imine with two electronically opposite aromatic groups was prepared to investigate the importance of the electronics in either of sterically identical sides (Figure 5.7). The corresponding amine **492j** was obtained readily but almost racemic (6 % ee). These results show that the electronics in the imine plays a negligible role during the reduction compared to the steric effects.

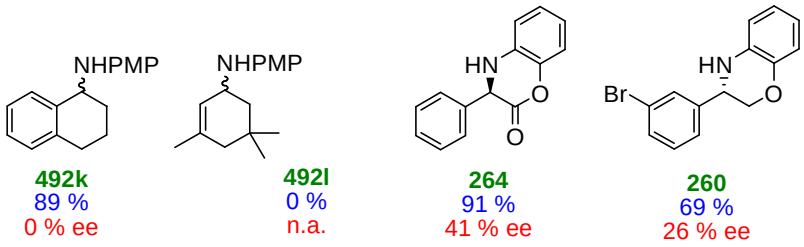


Figure 5.8. Cyclic Amines

Reduction of the cyclic exo-imines to amines **492k**,**l** (Figure 5.8) was briefly investigated. The tetralone-derived imine, which could be viewed as a cyclic analogue of **492a**, was reduced readily, but in a racemic fashion. On the other hand, the isophorone-derived imine was not reduced at all. The reduction to amines **264** and **260** carrying familiar structural features – *N*-aryl, *N*-*C*-phenyl group (R^1) and a functionalised carbon chain (R^2), also proceeded smoothly but in low enantioselectivities (41 and 26 % ee); noteworthy, in opposite configuration to each other. These results suggest that a highly

enantioselective reduction occurs in a conformation that is attainable by the non-cyclic imines but not available for the rigid cyclic structures (discussion in Chapter 5.2).

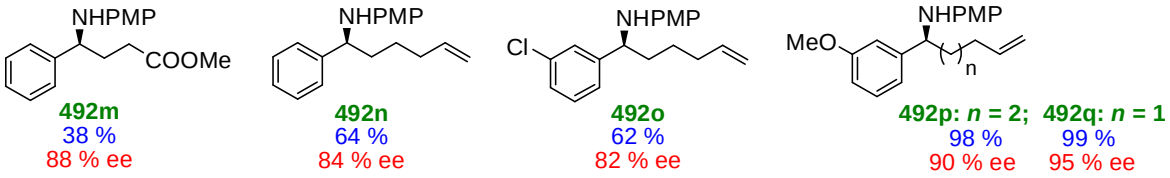


Figure 5.9. Aryl-alkyl Amines with Functionalised Side Chain

Further interest lied in functionalised side chain that would be available for synthetic transformations. Extension of the R^2-alkyl chain to a functionalised one with a double bond or a carboxylic acid was also successful in terms of yields and enantioselectivity (Figure 5.9). γ-Imino ester was reduced to **492m** in comparable enantioselectivity as the enamino ester **191**[105] (88 % ee). Terminal double bond was also tolerated well in **492n-p** (82-90 % ee) and proved very profitable in the reduction to amine **492q** (95 % ee).

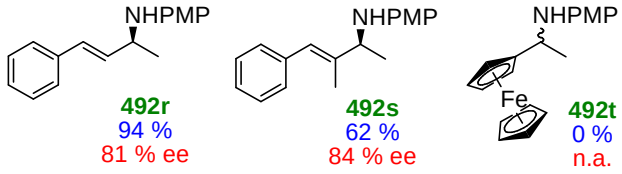


Figure 5.10. Cinnamyl-methyl and Ferrocene-derived Amines

Extended conjugation and distance between the aromatic nucleus and the imine moiety caused a minor decrease of the enantioselectivity (81 and 84 % ee) for the cinnamyl derivative **492r** and its more hindered α-methyl analogue **492s**, respectively (Figure 5.10). The ferrocene-based imine was not reduced under our reaction conditions.

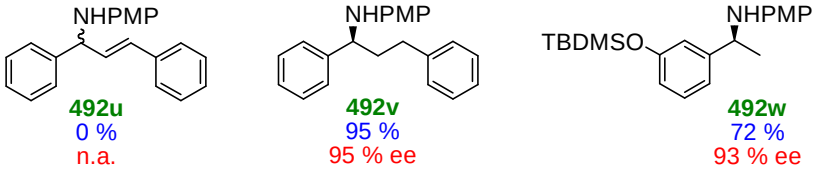


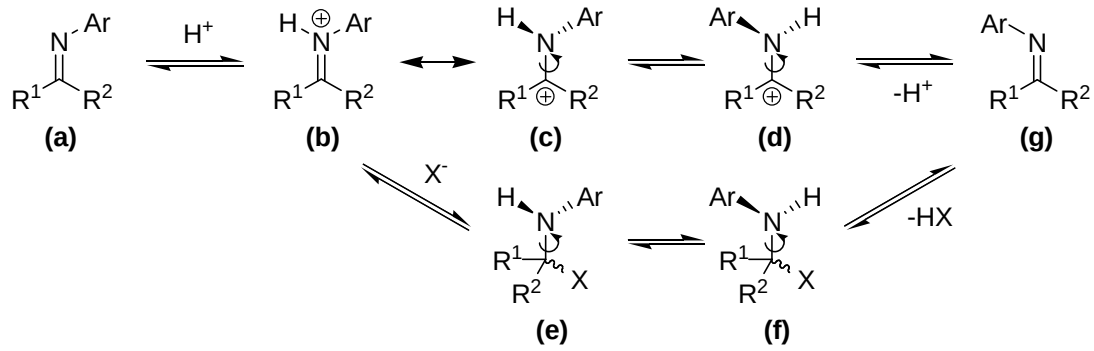
Figure 5.11. Targeting Colchinol

Amine **492v** containing the 1,3-diphenyl core was obtained in one of the highest enantioselectivities (95 % ee) which was exploited in the synthesis of the natural product *N*-acetylcolchinol (Chapter 7.2). Its conjugated analogue **492u** was not formed under our conditions, possibly because of the extensive conjugation of the imine **476u**. A silylether protecting group was also tolerated and the amine **492w** was prepared in high yield and enantiopurity (93 % ee); no desilylation occurred. It is noteworthy to say that the free phenol obstructed the reduction and a protecting group must be used.

5.2. Proposed Mechanism

5.2.1. The Impact of a Brønsted Acid and the Imine (E/Z)-isomerism

Bulkier imines were obtained in mixtures of (*E*/*Z*)-isomers, e.g., the phenyl-alkyl imines **492b-d** existed as up to 5:3 (*E*:*Z*) mixtures of isomers. However, the enantioselectivity of the Lewis base-catalysed imine reduction with trichlorosilane does not seem to be affected by the isomeric non-homogenity of the starting imines as the above-mentioned imines were reduced to the corresponding amines with 94-97 % ee.



Scheme 5.7. Brønsted-acid-catalysed Isomerisation of Imines

The Brønsted-acid-catalysed isomerisation of compounds containing *C=N* bonds is a well-known process (Scheme 5.7; also described in Chapter 2.1.2). The generally accepted mechanism involves the initial protonation of the imine nitrogen, generating trace amounts of the iminium ion **(b)**, followed by rotation around the *C-N* bond in the mesomeric carbocation **(c,d)** and loss of the proton. Alternatively, addition of the acid

counter-anion to the iminium **(b)** produces the corresponding tetrahedral intermediate **(e)** which also undergoes rotation to **(f)** and elimination of a molecule of acid yields the other isomer **(g)**.

Traces of hydrochloric acid, naturally present in the moisture-sensitive $HSiCl_3$, trigger an (*E*/*Z*)-equilibration of imines, which must be faster than the reduction. Apparently, the (*E*)-isomer is the more stable imine species and it is reduced from the *re*-face to give the (*S*)-amine. However, the absence of steric preference for (*E*)- or (*Z*)-isomer may account for the loss of enantioselectivity and formation of a racemic product in the case of imine **492j** (Figure 5.7).

However, protonation does not only catalyse the isomerisation process, but may also contribute to the non-selective background reaction by enhancing the electrophilicity of the imines in the form of iminium ions. To shed more light on the effect of the solution acidity on the rate and enantioselectivity of the reduction catalysed by Sigamide **152d**, a few common acidic and basic additives were briefly investigated (Table 5.1).

Reduction of imine **151** in the presence of triflic acid (0.1 equiv) led to a minor decrease of enantioselectivity (91 % ee; Table 5.1, entry 1; compare with 93 % ee, Table 2.17, entry 2 in Chapter 2.4.2). Addition of methanol caused partial hydrolysis of trichlorosilane producing HCl and the enantioselectivity of the reduction dropped to 84 % ee (Table 5.1, entry 2). In the case of enamino ester **191**, the addition of acetic acid was found to have a beneficial effect on reactivity at the slight expense of enantioselectivity, affording the β-amino ester **196** in 85-89 % ee (Table 5.1, entries 3 and 4). Reduction carried out in the presence of the stronger trifluoroacetic acid, afforded a racemic mixture of amine **154** (Table 5.1, entry 5).

Table 5.1. Reduction of Imines with Trochlorosilane in the Presence of Additives

Entry	Imine	Additive (equiv)	Yield (%) / ee (%)
1	**151**	CF_3SO_3H (0.1 equiv)	90 / 91
2	**151**	MeOH (1.0 equiv)	90 / 84
3	**191**	AcOH (1.5 equiv)	95 / 85
4	**191**	AcOH (1.0 equiv)	98 / 89
5	**191**	TFA (1.0 equiv)	89 / 0
6	**151**	*i*-Pr_2EtN (1.0 equiv)	trace / 0
7	**151**	Proton Sponge (1.0 equiv)	0 / n.a.
8	**151**	2,6-Lutidine (0.3 equiv)	73 / 92
9	**151**	Proton Sponge (1.0 equiv) + After 10 min AcOH (1.5 equiv)	92 / 87

By contrast, stoichiometric amounts of proton scavengers, such as *i*-Pr_2EtN (Hünig's base) or 1,8-bis(dimethylamino)naphthalene (proton sponge), were found to slow down the reaction dramatically and to ruin the enantioselectivity (Table 5.1, entries 6 and 7). An analogous effect of a stoichiometric amount of 2,6-lutidine has also been observed.[99] On the other hand, the reported beneficial effect of sub-stoichiometric amounts of this base on enantioselectivity,[99] was not noticed with our model imine (Table 5.1, entry 8; compare with Table 2.16, entries 5-8 in Chapter 2.4.2). The complete loss of reactivity in the presence of stoichiometric amounts of bases implies that the Brønsted acid is involved in the catalytic cycle. This hypothesis is supported by the observation that the addition of acetic acid (1.5 equiv) to the reaction mixture, first deactivated with proton sponge (1.0 equiv), restored the reactivity providing the amine in high yield and 87 % ee (Table 5.1, entry 9).

5.2.2. Impact of the Spatial Organisation

The key importance of low concentrations of H^+ for the reaction to occur suggests that protonated imines (the iminium ions), might be the actual species undergoing the reduction by trichlorosilane (Figure 5.12). It can be speculated that the protonated iminium interacts with the catalyst's secondary anilide carbonyl via hydrogen bonding and trichlorosilane is activated by coordination to the formamide carbonyl group to form a pentacoordinated silicon species (Figure 5.12, **(B)**). However, increasing the concentration of Brønsted acid in the reaction mixture leads to an erosion of enantioselectivity due to the competing non-selective background reduction (Figure 5.12, **(C)**).

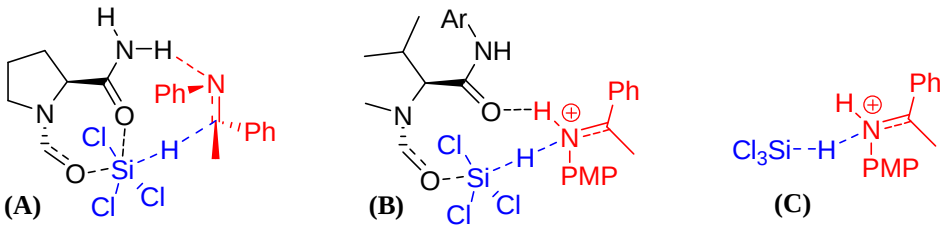
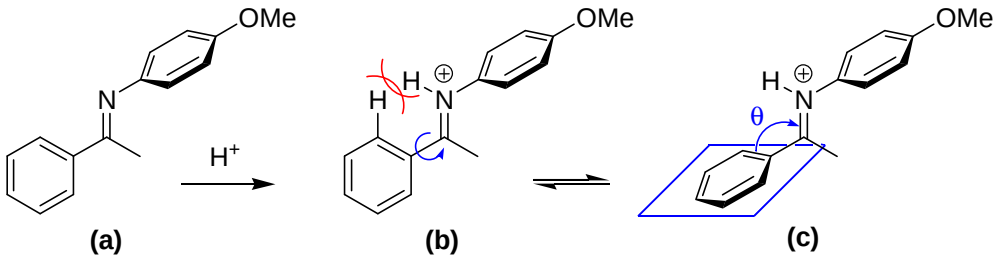


Figure 5.12. Proposed Calculated **(A)** and Our **(B)** Transition Structure and Non-selective Reduction **(C)**

A recent mechanistic and computational study on the reduction of imines with $HSiCl_3$, catalysed by a series of secondary amides,[112] suggests that the catalyst not only coordinates to the reagent (in hexacoordinate fashion), but also acts as a proton donor to

the imine in the transition structure [Figure 5.12, **(A)**]. However, the calculated structure does not take into account the role of the present Brønsted acid. Moreover, the calculations are performed with a model catalyst containing primary amide moiety instead of the secondary amides that were used experimentally.

Based on the experimental results, it is likely that the enantioselective reduction of imines proceeds smoothly only in cases when there is enough flexibility in the imine structure (Scheme 5.8). Aromatic imines usually attain conformation in which the aromatic ring (R^1 substituent) is coplanar with the *C=N* bond to maintain the conjugation, as in **(a)**. However, it is not rare that bulkier aromatic groups (or substituted phenyl rings) rotate to minimise the steric hindrance (also see Scheme 2.4, Chapter 2.1.2). Thus, it is expected that the steric bulk is even greater in the protonated form **(b)** and more prone to adopt a non-coplanar position of the R^1 aryl moiety in **(c)**, defined by dihedral angle θ (Scheme 5.8). The *N*-aryl group is typically close to perpendicular with respect to the *C=N-H* plane.



Scheme 5.8. Stereochemistry of a Model Imine and Its Protonated Iminium Form

The cases of cyclic imines strongly support the theory that highly enantioselective reduction occurs in a conformation attainable by the non-cyclic imines but not available for the rigid cyclic structures [Figure 5.13, **(A)**]. In the cyclic imines **476k** and **257**/**262**, the aromatic R^1 group is locked in coplanar arrangement and the steric congestion around the *C=N* bond prevents the catalyst from coordination and the background racemic reaction is the only feasible. Furthermore, the reduced conformational mobility of the *N*-aryl moiety, which is nearly coplanar with the *C=N* bond in imines **257** and **262** [Figure 5.13, **(A)**], has a similar effect; i.e. the reduction proceeds with much lower enantioselectivities than those observed for the acyclic imines.

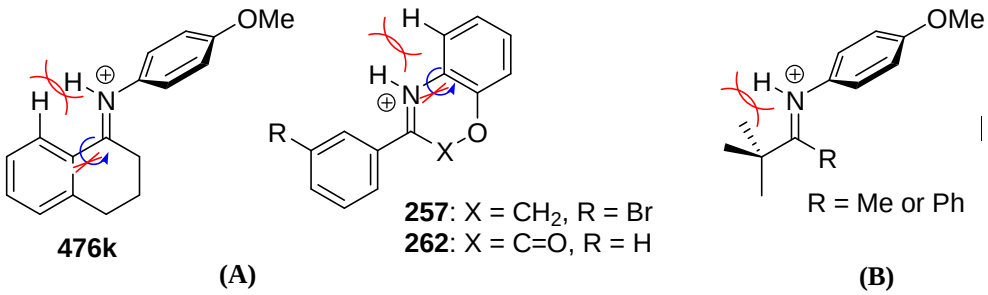


Figure 5.13. Problematic Substrates with: **(A)** Rigid Conformations and **(B)** Extreme Bulk

The effect of the steric hindrance is even more obvious in imines containing extremely bulky *tert*-butyl group, which impedes the protonation and/or coordination to the catalyst, resulting in low reactivity and enantioselectivity (Figure 5.13, **(B)**).

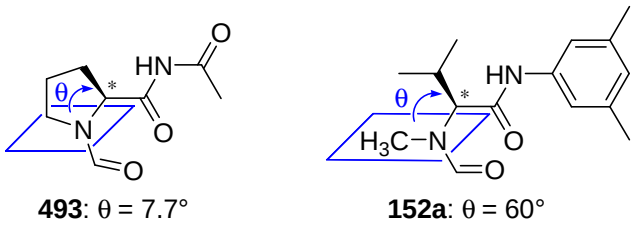


Figure 5.14. Dihedral Angle in Crystals of Selected Catalysts

It is pertinent to note that the proline-derived catalyst **149b**, which has the same absolute configuration as Sigamide **152c**, induced the formation of **(*R*)-35**, i.e. the opposite enantiomer to that produced by our catalysts **152a-d**. This result suggests that the two catalysts assume a different conformation on coordination of the silicon. This is partially supported by single crystal X-ray analysis of Kenamide **152a** and the acetamide **493**, an analogue of **149** which significantly differ in the dihedral angle of the CH_n-*N*-*C**-alkyl fragment[188] (*n* = 2 or 3; Figure 5.14). Note also that the L-alanine-derived (alkyl = Me) analogue of **152b** also affords (*R*)-configured amines (see Chapter 2.4.2). The flexibility of the valine-derived catalyst combined with the *N*-methyl moiety of the catalyst is crucial for the enantioselectivity, presumably by controlling the spatial orientation of the formamide group and relaying the stereochemical information from the chiral centre[93] and allow an optimal conformation in the transition state.

5.2.3. Conclusions

Trichlorosilane is a main building block of silicon industry (chips, solar cells), thus it is a cheap reducing agent, easily handled when techniques for moderately moisture-sensitive compounds are taken into account. Toluene as solvent represents lower environmental risk than the commonly used chlorinated solvents and aqueous work-up only produces non-toxic inorganic materials (NaCl and silica). Catalyst **152d** is a bench-stable compound synthesised in four steps from *N*-BOC-valine.[93b] Its reaction reliability and wide spectrum of substrates made it a suitable for commercial sale. It appeared under name *Sigamide* in the Aldrich catalogue from year 2008 (£120 per 100 mg).

A broad scope of the reduction of imines with trichlorosilane catalysed by the Lewis-basic Sigamide **152d** was demonstrated in this thesis. Current limitations are relatively few:

- the reaction exhibits very low enantioselectivity with imines derived from pyridine (containing a coordinating nitrogen atom), but a remedy to this flaw was found in the shape of steric bulk around the heteroatom,
- reduction of imines derived from diaryl ketones gives practically racemic products even if the two aryl groups differ in their electronics,
- the current system only works efficiently with imines derived from aromatic amines (e.g., aniline and anisidine), nevertheless, the anisidine-derived amines can be oxidatively deprotected to produce primary amines,
- imines derived from cyclic ketones exhibit low enantioselectivity.

Excluding the difficult types of substrates, high enantioselectivity (typically up to 90 % ee) was observed across the spectrum of aromatic, heteroaromatic, and aliphatic substrates, which may contain additional functional groups (protected hydroxyl, carboxyl or double bonds). The reaction proceeds in toluene at room temperature overnight with 5 mol % of the catalyst. Hence, our protocol compares competitively with its alternatives, such as catalytic hydrogenation, reduction with Hantzsch dihydropyridines catalysed by chiral acids or reduction with boranes.

6. Experimental Part

6.1. General

6.1.1. General Methods

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in $CHCl_3$ unless otherwise indicated, with an error of ≤(±0.1), the $[\alpha]_D$ values are given in 10^{-1} deg.cm^3.g^{-1}. The NMR spectra were recorded in $CDCl_3$, ^{1}H at 400.0 MHz and ^{13}C at 100.6 MHz with chloroform-d_1 (δ 7.26, ^{1}H; δ 77.0, ^{13}C) or TMS as internal standard unless otherwise indicated. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for a thin film of $CHCl_3$ solutions between NaCl plates unless otherwise stated. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. The enantiomeric excess values (ee) were determined by HPLC equipped with diode array detector and were calibrated with the corresponding racemic mixtures. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behaviour. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum.

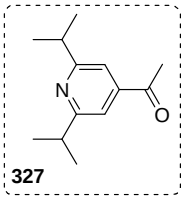
6.1.2. Materials

Some reactions, when needed, were performed under an atmosphere of dry, oxygen-free argon in oven-dried glassware three times evacuated and filled with the argon. Solvents and solutions were transferred by syringe-septum or cannula technique. Solvents for the anhydrous reactions were of reagent grade and were distilled immediately before use as follows: tetrahydrofuran (THF) from sodium/benzophenone; dichloromethane and triethylamine from calcium hydride, benzene was distilled from sodium and stored over 4Å molecular sieves and under argon, methanol (MeOH) was distilled from magnesium / magnesium methoxide, absolute ethanol (EtOH) from magnesium / magnesium ethoxide and stored over 4Å molecular sieves and under argon. Alternatively, THF, toluene and

dichloromethane were obtained from Pure-Solv™ Solvent Purification System (Innovative Technology). Aniline and *p*-anisidine were distilled prior to use. All other chemicals needed were used as received unless otherwise stated. Petroleum ether (PE) refers to the fraction boiling in the range of 40-60 ºC, AcOEt refers to ethyl acetate, AcOH refers to acetic acid, TsOH refers to *p*-toluenesulfonic acid and Py refers to pyridine. Saturated solutions of $NaHCO_3$ or NH_4Cl refer to aqueous solutions unless otherwise stated.

6.2. Precursors and Ketones

4-Acetyl-2,6-di-*iso*-propylpyridine (327), $C_{13}H_{19}NO$, FW = 205.33



Neat *tert*-butylhydroperoxide (11.3 mL, 61.9 mmol, 2.5 equiv) was added to a solution of 4-acetylpyridine (2.74 mL, 24.8 mmol, 1 equiv), *iso*-propyl iodide (3.42 mL, 99.0 mmol, 4 equiv), trifluoroacetic acid (1.84 mL, 24.8 mmol, 1 equiv) and ferric acetate (29 mg, 1.24 mmol, 5 mol %v) in acetic acid (250 mL) and the mixture was refluxed overnight. The reaction was quenched with NaOH (2.0 M, 600 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified on a silica gel column (75 mL) with a petroleum ether – ethyl acetate mixture (92:8) to afford **327** (355 mg, 1.73 mmol, 7 %): colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.28 (d, *J* = 6.9 Hz, 12H), 2.58 (s, 3H), 3.08 (sept, *J* = 6.9 Hz, 2H), 7.37 (s, 2H); **^{13}C NMR** δ 22.49 (4 × CH_3), 26.74 (2 × CH), 36.39 (CH_3), 115.17 (2 × CH), 143.83 (C), 167.83 (2 × C), 198.40 (C); **IR** ν 2964, 2929, 2871, 1697, 1564, 1468, 1409, 1359, 1283, 1202 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 206 [$(M+H)^+$, 100], 205 (33), 204 (90), 202 (33), 143 (10); **HRMS** (CI/isobutane) 206.1546 ($C_{13}H_{20}NO$ requires 206.1545).

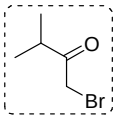
α-Bromination of Ketones:[195]

Neat bromine (5.12 mL, 16.0 g, 100 mmol, 1 equiv) was added drop-wise to a cooled (–30 ºC) solution of ketone (100 mmol, 1 equiv, see Table 6.1) in methanol (50 mL) over a

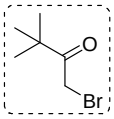
period of 30 min. The reaction mixture was allowed to warm to room temperature, at which time the solution became colourless and was immediately quenched with cold saturated $NaHCO_3$ (1 mL). After 5 min, water was added (50 mL) and extracted with petroleum ether (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to afford crude liquid product (strong lachrymatory!) which was used without further purification.

Table 6.1. Preparation of α-Bromoketones

Ketone	α-Bromoketone product
3-methylbutan-2-one (10.7 mL, 8.61 g)	**330** (10.5 g, 64 mmol, 64 %)
3,3-dimethylbutan-2-one (12.5 mL, 10.2 g)	**331** (17.4 g, 97.2 mmol, 97 %)



1-Bromo-3-methyl-butan-2-one (330),[196] **C_5H_9OBr, FW = 165.04**: greyish liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.9 Hz, 6H), 2.92 (sept d, *J* = 6.9, 0.7 Hz, 1H), 3.96 (br s, 2H).



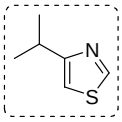
1-Bromo-3,3-dimethyl-butan-2-one (331),[195] **$C_6H_{11}OBr$, FW = 179.07**: colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.21 (s, 9H), 4.16 (s, 2H).

Cyclisation of Thiazoles:[162]

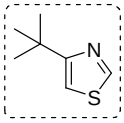
Solid diphosphorus pentasulfide (0.2 equiv) was added to a stirred mixture of α-ketone (1 equiv) and formamide (2 equiv) pre-cooled to 0 ºC (Table 6.2). The reaction mixture was allowed to warm to room temperature (highly exothermic reaction occurred when the temperature reached 5 ºC) and the slurry was heated to 90 ºC for 1 h. Then it was diluted with water (50 mL), basified with saturated aqueous ammonia and extracted with ethyl acetate. The combined organic layers were washed with brine (60 mL), dried over $MgSO_4$ and evaporated. Distillation of the crude mixture afforded pale yellow liquid of thiazole (stench!).

Table 6.2. Preparation of Thiazoles

α-Bromoketone	Formamide	P_2S_5	Alkylthiazole
330 (10.5 g, 64.0 mmol)	5.05 mL, 5.73 g, 127 mmol	5.65 g, 12.7 mmol	**332** (2.78 g, 21.9 mmol, 34 %)
331 (17.0 g, 94.9 mmol)	7.5 mL, 8.6 g, 189 mmol	8.44 g, 19.0 mmol	**333** (3.49 g, 24.7 mmol, 26 %)



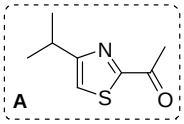
4-*iso*-Propylthiazole (332), C_6H_9NS, FW = 127.22: pale yellow liquid; **bp** 25 ºC (18 mbar); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.29 (d, *J* = 6.9 Hz, 6H), 3.12 (sept d, *J* = 6.9, 0.7 Hz, 1H), 6.88 (dd, *J* = 2.0, 0.9 Hz, 1H), 8.71 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** δ 22.32 (2 × CH_3), 30.63 (CH), 110.69 (CH), 152.11 (CH), 164.30 (C); **IR** ν 3116, 3083, 2964, 2928, 2873, 1702, 1508, 1409, 1280 cm^{-1}.



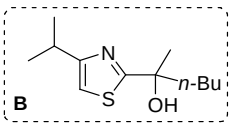
4-*tert*-Butylthiazole (333),[162] **$C_7H_{11}NS$, FW = 141.25**: pale yellow liquid; **bp** 55 ºC (60 mbar); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.37 (s, 9H), 6.95 (d, *J* = 2.0 Hz, 1H), 8.75 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** δ 30.13 (3 × CH_3), 34.67 (C), 110.14 (CH), 152.09 (CH), 167.42 (C).

Acetylation of 4-*iso*-propylthiazole:[163]

A solution of thiazole **332** (2.00 g, 15.7 mmol, 1 equiv) in anhydrous ether (0.2M, 79 mL) was added drop-wise to a solution of *n*-butyllithium (1.6M in pentane, 12.8 mL, 20.4 mmol, 1.3 equiv) in ether (13 mL) at –80 ºC and let to stir. After 1 h, a solution of ethyl acetate (3.08 mL, 2.77 g, 31.4 mmol, 2 equiv) in ether (0.2 M, 157 mL) was added drop-wise at –80 ºC. The mixture was let to stir at –80 ºC for 10 min and then let to warm to room temperature. Then it was quenched with saturated $NaHCO_3$ (100 mL) and extracted with ether (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and evaporated. The crude product was purified on a silica gel column (60 mL) with a gradient of petroleum ether to petroleum ether – ethyl acetate mixture (95:5) to afford the desired acetylthiazole **334A** and over-reacted alcohol **334B**.



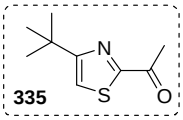
2-Acetyl-4-*iso*-propylthiazole (334A), $C_8H_{11}NOS$, FW = 169.26 (1.30 g, 7.65 mmol, 49 %): pale yellow liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.31 (d, *J* = 6.9 Hz, 6H), 2.67 (s, 3H), 3.13 (sept d, *J* = 6.9, 0.7 Hz, 1H), 7.22 (d, *J* = 0.8 Hz, 1H); **^{13}C NMR** δ 22.38 (2 × CH_3), 26.03 (CH_3), 31.00 (CH), 119.01 (CH), 166.08 (C), 166.15 (C), 191.93 (C); **IR** ν 3358, 3105, 2966, 2928, 2871, 1691, 1499, 1430, 1360, 1274 cm^{-1}; **MS** (EI) *m/z* (%) 169 ($M^{\bullet+}$, 38), 154 (50), 112 (35); **HRMS** (EI) 169.0558 ($C_8H_{11}NOS$ requires 169.0561).



2-(2'-Hydroxy-hex-2'-yl)-4-*iso*-propylthiazole (334B), $C_{12}H_{21}NOS$, FW = 227.39 (992 mg, 4.38 mmol, 28 %): yellow liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.2 Hz, 3H), 1.10-

1.41 (m, 4H), 1.27 (dd, J = 6.9, 0.6 Hz, 6H), 1.59 (s, 3H), 1.83-1.85 (m, 2H), 3.04 (sept d, J = 6.9, 0.9 Hz, 1H), 3.50 (br s, 1H), 6.76 (d, J = 0.9 Hz, 1H); **^{13}C NMR** δ 13.94 (CH_3), 22.17 (CH_3), 22.24 (CH_3), 22.77 (CH_2), 25.76 (CH_2), 29.48 (CH_3), 30.75 (CH), 43.56 (CH_2), 75.13 (C), 110.54 (CH), 162.80 (C), 177.44 (C); **IR** ν 33426, 3113, 2960, 2932, 2871, 1519, 1462, 1381, 1165 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 228 [$(M+H)^+$, 100], 210 (42), 170 (20); **HRMS** (CI/isobutane) 228.1416 ($C_{12}H_{22}NOS$ requires 228.1422).

2-Acetyl-4-*tert*-butylthiazole (335), $C_9H_{13}NOS$, FW = 183.29

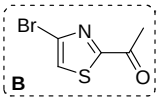


n-Butyllithium (7.43 mL, 2.0M in pentane, 14.9 mmol, 1.05 equiv) was added drop-wise to a solution of thiazole **333** (2.00 g, 14.2 mmol, 1 equiv) in anhydrous THF (30 mL, 0.2 M) under an argon atmosphere at –80 ºC.[164] After 1 h at this temperature, neat *N*-acetyl morpholine (2.13 mL, 2.38 g, 18.4 mmol, 1.3 equiv) was added drop-wise and the mixture was let to warm up to room temperature. The reaction mixture was diluted with ether (50 mL) and washed with a saturated $NaHCO_3$ solution (20 mL), dried over $MgSO_4$ and concentrated. The residue was purified on a silica gel column (120 mL) with a gradient of petroleum ether to petroleum ether – ethyl acetate mixture (97:3) to afford the desired acetylthiazole **335** (1.37 g, 7.47 mmol, 53 %): pale yellow liquid which solidified upon standing; **mp** 26-27 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.70 (s, 3H), 7.25 (s, 1H); **^{13}C NMR** δ 25.96 (CH_3), 30.06 (3 × CH_3), 35.02 (C), 118.17 (CH), 165.98 (C), 168.99 (C), 192.16 (C); **IR** (ATR) ν 3099, 2955, 1679, 1493, 1417, 1355, 1276, 1245 cm^{-1}; **MS** (EI) *m/z* (%) 183 ($M^{\bullet+}$, 30), 168 (100), 141 (15), 126 (55); **HRMS** (EI) 183.0721 ($C_9H_{13}NOS$ requires 183.0718).

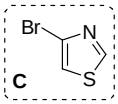
Acetylation of 2,4-Dibromothiazole:

Method A:[166a] A solution of *iso*-propylmagnesium chloride (2.06 mL, 4.12 mmol, 2.0 M in THF, 1 equiv) was added drop-wise to a solution of 2,4-dibromothiazole (1.00 g, 4.12 mmol, 1.0 equiv) in anhydrous THF (10 mL) at 0 ºC and let to stir for 1 h. Then neat acetonitrile (323 µL, 254 mg, 6.18 mmol, 1.5 equiv) was added drop-wise. The mixture was let to warm to room temperature and stirred additional 1 h after which it was quenched with water (10 mL) and extracted with ether (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified on a silica gel column (25 mL) with a petroleum ether – ethyl acetate

mixture (95:5) to afford the desired acetylthiazole **337A**, debrominated product **337B** resulting from the quenched unreacted 2-magnesiothiazole chloride and recovered starting material (151 mg).



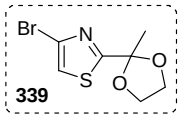
2-Acetyl-4-bromothiazole (337A),[197] **C_5H_4NOSBr, FW = 206.04** (122 mg, 0.592 mmol, 14 %): white crystals; **mp** 65-66 ºC (hexane, with sublimation); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.69 (s, 3H), 7.78 (s, 1H); **^{13}C NMR** δ 25.82 (CH_3), 125.03 (CH), 126.85 (C), 166.82 (C), 190.36 (C); **IR** ν 3080, 3019, 1691, 1458, 1386, 1274 cm^{-1}; **MS** (EI) *m/z* (%) 207 ($M^{\bullet+}$, 10), 205 ($M^{\bullet+}$, 10), 179 (10), 177 (10); **HRMS** (EI) 204.9196 ($C_5H_4NOS^{79}Br$ requires 204.9197), 206.9183 ($C_5H_4NOS^{81}Br$ requires 206.9176).



4-Bromothiazole (337B),[198] **C_3H_2NSBr, FW = 206.04** (197 mg, 01.20 mmol, 29 %): yellowish liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 2.3 Hz, 1H), 8.74 (d, *J* = 2.2 Hz, 1H).

Method B:[164] *n*-Butyllithium (6.80 mL, 2.0 M in pentane, 13.58 mmol, 1.1 equiv) was added drop-wise to a solution of 2,4-dibromothiazole (3.00 g, 12.35 mmol, 1.0 equiv) in THF (14 mL) under an argon atmosphere at –80 ºC. After 30 min at this temperature, neat *N*-acetyl morpholine (2.00 mL, 2.23 g, 17.29 mmol, 1.4 equiv) was added drop-wise and the mixture was stirred for 2 h at –80 ºC. The reaction mixture was diluted with ether (50 mL) and washed with a saturated $NaHCO_3$ solution (20 mL), dried over $MgSO_4$ and concentrated. The residue was purified on a silica gel column (60 mL) with a petroleum ether – ethyl acetate mixture (95:5) to afford the desired acetylthiazole **337B** (1.43 g, 6.94 mmol, 56 %).

2-Methyl-2-(4'-bromothiazol-2'-yl)-1,3-dioxolane (339), $C_7H_8NO_2SBr$, FW = 250.12

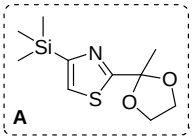


A solution of **337B** (1.55 g, 7.52 mmol, 1 equiv), ethyleneglycol (1.31 mL, 1.87 g, 30.1 mmol, 4 equiv) and *p*-toluenesulfonic acid (142 mg, 0.752 mmol, 10 mol %) in toluene was refluxed in a Dean-Stark apparatus for 10 hours.[167] The reaction mixture was cooled to room temperature, concentrated, loaded on a silica gel column (40 mL) and eluted with a petroleum ether – ethyl acetate mixture (99:1 to 90:10) to afford the dioxolane **339** (1.84 g,

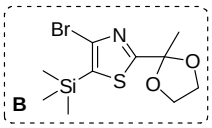
7.36 mmol, 98 %): pale yellow liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.81 (s, 3H), 3.97-4.13 (m, 4H), 7.19 (s, 1H); **^{13}C NMR** δ 25.25 (CH_3), 65.57 (2 × CH_2), 106.75 (C), 117.87 (CH), 125.46 (C), 173.31 (C); **IR** ν 3115, 2992, 2890, 1476, 1423, 1373, 1254, 1196 cm^{-1}; **MS** (EI) *m/z* (%) 251 ($M^{\bullet+}$, 10), 249 ($M^{\bullet+}$, 10), 236 (32), 234 (32), 208 (20), 206 (20), 192 (18), 190 (18), 87 (100); **HRMS** (EI) 250.9436 ($C_7H_8NO_2{}^{81}Br$ requires 250.9438), 248.9460 ($C_7H_8NO_2{}^{79}Br$ requires 248.9459);

Silylation of Bromothiazole:[167]

n-Butyllithium (4.30 mL, 2.0 M in pentane, 8.64 mmol, 1.2 equiv) was added drop-wise to a solution of **339** (1.80 g, 7.20 mmol, 1.0 equiv) in THF (14 mL) under an argon atmosphere at –80 ºC and the mixture was stirred at this temperature for 30 min. Then neat trimethylsilyl chloride (1.66 mL, 1.41 g, 13.0 mmol, 1.8 equiv) was added drop-wise to the resulting red slurry and it was stirred at this temperature for 1 h. The solution was then let to warm to room temperature and quenched with water (20 mL). The aqueous layer was extracted with ether (2 × 15 mL), the combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified on a silica gel column (60 mL) with a solvent gradient from petroleum ether to a mixture of petroleum ether – ethyl acetate (90:10) affording three products.

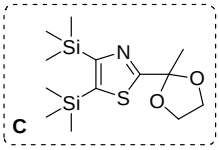


2-Methyl-2-(4'-trimethylsilylthiazol-2'-yl)-1,3-dioxolane (341A), $C_{10}H_{17}NO_2SSi$, FW = 243.43 (882 mg, 3.62 mmol, 49 %): pale yellow liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.32 (s, 9H), 1.83 (s, 3H), 3.97-4.15 (m, 4H), 7.75 (s, 1H); **^{13}C NMR** δ –0.11 (3 × CH_3), 25.50 (CH_3), 65.37 (2 × CH_2), 107.23 (C), 133.50 (C), 148.91 (CH), 176.72 (C); **IR** ν 2991, 2956, 2894, 1498, 1372, 1252, 1201 cm^{-1}; **MS** (CI/isobutane) 244 [$(M+H)^+$, 100], 113 (20), 85 (38); **HRMS** (CI/isobutane) 244.0832 ($C_{10}H_{18}NO_2SSi$ requires 244.0828).



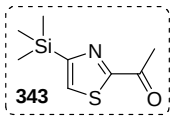
2-Methyl-2-(4'-bromo-5'-trimethylsilylthiazol-2'-yl)-1,3-dioxolane (341B), $C_{10}H_{16}NO_2SBrSi$, FW = 322.32 (1.03 g, 3.18 mmol, 43 %): thick pale yellow oil which solidified upon standing; **mp** 55-56 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.39 (s, 9H), 1.81 (s, 3H), 4.00-4.12 (m, 4H); **^{13}C NMR** δ –0.84 (3 × CH_3), 25.27 (CH_3), 65.48 (2 × CH_2), 106.82 (C), 129.35 (C), 131.05 (C), 175.98 (C); **IR** ν 2991, 2957, 2895, 1473, 1403, 1372, 1253, 1203 cm^{-1}; **MS** (EI) *m/z* (%) 323 ($M^{\bullet+}$, 18), 321 ($M^{\bullet+}$, 18), 308 (70), 306 (70), 280 (80), 278 (80), 264 (10), 262

(10), 87 (100); **HRMS** (EI) 322.9832 ($C_{10}H_{16}NO_2S^{81}BrSi$ requires 322.9834), 320.9850 ($C_7H_8NO_2S^{79}BrSi$ requires 320.9854).



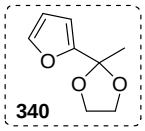
2-Methyl-2-[4',5'-bis(trimethylsilyl)thiazol-2'-yl]-1,3-dioxolane (341C), $C_{13}H_{25}NO_2SSi_2$, FW = 315.63 (181 mg, 0.573 mmol, 7 %): pale yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.36 (s, 9H), 0.38 (s, 9H), 1.86 (s, 3H), 4.10 (s, 4H).

2-Acetyl-4-trimethylsilylthiazole (343), $C_8H_{13}NOSSi$, FW = 199.37



A solution of **341A** (730 mg, 3.00 mmol, 1 equiv) and pyridinium tosylate (113 mg, 0.450 mmol, 15 mol %) in an acetone (17 mL) / water (3 mL) mixture was refluxed for 4 days.[199] The reaction mixture was concentrated *in vacuo*, the residue was dissolved in ether, and the resulting solution was washed with water (2 × 30 mL) and evaporated. The residue was purified by flash chromatography on a silica gel column (30 mL) with a petroleum ether – ethyl acetate mixture (98:2) to afford **343** (394 mg, 1.98 mmol, 66 %): colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.37 (s, 9H), 2.72 (s, 3H), 4.01-4.14 (m, 4H), 7.97 (s, 1H); **^{13}C NMR** δ –0.26 (3 × CH_3), 26.33 (CH_3), 142.04 (C), 149.85 (CH), 171.08 (C), 191.46 (C); **IR** ν 2958, 1688, 1479, 1387, 1358, 1267, 1254 cm^{-1}; **MS** (EI) *m/z* (%) 199 ($M^{\bullet+}$, 45), 184 (90), 142 (38), 115 (50); **HRMS** (EI) 199.0489 ($C_8H_{13}NOSSi$ requires 199.0487).

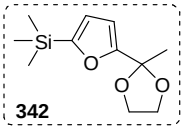
2-(Furan-2'-yl)-2-methyl-1,3-dioxolane (340), $C_8H_{10}O_3$, FW = 154.18



A solution of 2-acetylfuran (2.20 g, 20.0 mmol, 1 equiv), ethyleneglycol (3.13 mL, 4.47 g, 72.0 mmol, 3.6 equiv) and *p*-toluenesulfonic acid (38 mg, 0.200 mmol, 1 mol %) in toluene was refluxed in a Dean-Stark apparatus for 10 hours.[167] The reaction mixture was cooled to room temperature and washed with a saturated $NaHCO_3$ solution (50 mL), water (2 × 50 mL) and concentrated *in vacuo*. The residue was filtered through a short silica gel column (35 mL) with petroleum ether to obtain **340** (1.13 g, 7.33 mmol, 37 %): colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.72 (s, 3H), 3.96-4.06 (m, 4H), 6.29 (dd, *J* = 3.2, 1.7 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.0 Hz, 1H), 7.35 (dd, *J* = 1.7, 1.0 Hz, 1H); **^{13}C NMR** δ

24.33 (CH_3), 65.12 (2 × CH_2), 104.71 (C), 106.49 (CH), 109.86 (CH), 142.35 (CH), 154.44 (C); **IR** ν 3121, 2993, 2891, 1373, 1258, 1199, 1039 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 155 [$(M+H)^+$, 100], 139 (30), 111 (12), 109 (11), 87 (14); **HRMS** (CI/isobutane) 155.0710 ($C_8H_{11}O_3$ requires 155.0708).

2-Methyl-2-(5'-Trimethylsilylfuran-2'-yl)-1,3-dioxolane (342), $C_{11}H_{18}O_3Si$, FW = 226.38



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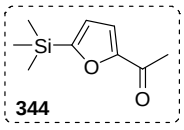
n-Butyllithium (1.6 M in hexane, 3.04 mL, 4.87 mmol, 1.5 equiv) was added to a solution of **340** (500 mg, 3.24 mmol, 1 equiv) in THF (3 mL) under an argon atmosphere at –80 ºC and the mixture was stirred at this temperature for 2 h.[167] Then trimethylsilyl chloride (829 µL, 705 mg, 6.49 mmol, 2 equiv) was added drop-wise to the resulting red solution and the solution was let to warm to room temperature and to stir for 3 h. Then the mixture was diluted with CH_2Cl_2 (2 mL) and quenched with water (3 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), the combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography on a silica gel column (25 mL) with petroleum ether to afford **342** (562 mg, 2.48 mmol, 77 %): colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.25 (s, 9H), 1.74 (s, 3H), 3.98-4.06 (m, 4H), 6.28 (d, *J* = 3.2 Hz, 1H), 6.52 (d, *J* = 3.2 Hz, 1H); **^{13}C NMR** δ –1.71 (3 × CH_3), 24.15 (CH_3), 64.99 (2 × CH_2), 104.72 (C), 106.25 (CH), 119.65 (CH), 158.60 (C), 160.21 (C); **IR** ν 2960, 2896, 1374, 1251, 1185, 1040 cm^{-1}; **MS** (EI) *m/z* (%) 226 ($M^{\bullet+}$, 20), 212 (38), 211 (100), 167 (82), 87 (32); **HRMS** (EI) 226.1026 ($C_{11}H_{18}O_3Si$ requires 226.1025).

2-Acetyl-5-trimethylsilylfuran (344), $C_9H_{14}O_2Si$, FW = 182.32



344

A solution of **342** (500 mg, 2.21 mmol, 1 equiv) and pyridinium tosylate (83 mg, 0.330 mmol, 15 mol %) in an acetone (13 mL) – water (2 mL) mixture was refluxed for 3 h and then stirred overnight at room temperature overnight.[199] The reaction mixture was concentrated *in vacuo*, the residue was dissolved in ether, and the resulting solution was washed with water (2 × 20 mL) and evaporated. The residue was purified on a silica gel column (25 mL) with a petroleum ether – ethyl acetate mixture (99:1) to afford **344**[200]

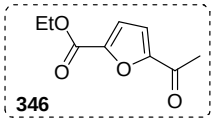
(355 mg, 1.94 mmol, 88 %): colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.30 (s, 9H), 2.47 (s, 3H), 6.68 (d, *J* = 3.5 Hz, 1H), 7.14 (d, *J* = 3.5 Hz, 1H); **^{13}C NMR** δ –1.96 (3 × CH_3), 26.14 (CH_3), 117.00 (CH), 121.24 (CH), 156.45 (C), 166.45 (C), 189.97 (C); **IR** ν 2960, 1689, 1563, 1453, 1360, 1252, 1118 cm^{-1}; **MS** (EI) *m/z* (%) 182 ($M^{\bullet+}$, 44), 167 (100), 151 (23); **HRMS** (EI) 182.0767 ($C_9H_{14}O_2Si$ requires 182.0763).

Two-step Procedure for Preparation of Ethyl 5-acetylfuran-2-carboxylate:

n-Butyllithium (1.6 M in hexane, 4.30 mL, 6.81 mmol, 1.5 equiv) was added to a solution of **340** (700 mg, 4.54 mmol, 1 equiv) in THF (3.5 mL) under an argon atmosphere at –80 ºC and the mixture was stirred at this temperature for 2 h.[167] The resulting red solution was transferred by cannula technique onto a large excess of dry ice continuously cooled to –80 ºC. After 3 h (or when all the dry ice was consumed) the suspension was dissolved in water (15 mL) and extracted with ether (3 × 20 mL). Then the aqueous layer was acidified to pH 3 and extracted with ether (3 × 20 mL); the combined organic layers (of the latter extraction) were washed with water, dried over $MgSO_4$ and evaporated. The crude acid **345** thus obtained was considered pure enough to be used directly in the next step.

Triethylamine (484 µL, 308 mg, 3.20 mmol, 1.05 equiv) was added to a solution of the crude acid (470 mg, approximated as 3.05 mmol, 1 equiv) in CH_2Cl_2 (14 mL).[168] The mixture was cooled to 0 ºC and ethyl chloroformate (310 µL, 316 mg, 3.05 mmol, 1 equiv) was added dropwise. The mixture was let to warm to room temperature, then refluxed for 2 h and let to stir at room temperature overnight. The reaction was quenched with water (10 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), the organic layers were combined, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on a silica gel column (60 mL) with a petroleum ether – ethyl acetate mixture (85:15) to obtain white crystalline solid **346** (317 mg, 1.74 mmol, 38 % over two steps).

Ethyl 5-acetylfuran-2-carboxylate (346), $C_9H_{10}O_4$, FW = 182.19



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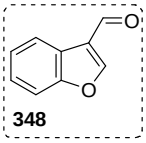
346:[201] white crystals; **mp** 69-70 ºC (hexane/CH_2Cl_2), [lit.[201] gives 77 ºC (EtOH)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.1 Hz, 3H), 2.55 (s, 3H), 4.39 (q, *J* = 7.1 Hz, 2H), 7.18 (d, *J* = 3.7 Hz, 1H), 7.20 (d, *J* = 3.7 Hz, 1H); **^{13}C NMR** δ 14.29 (CH_3), 26.41 (CH_3),

61.71 (CH_2), 116.69 (CH), 118.63 (CH), 146.55 (C), 154.16 (C), 158.21 (C), 187.65 (C); **IR** ν 3020, 1725, 1686, 1575, 1298, 1263, 1217 cm^{-1}; **MS** (EI) *m/z* (%) 182 ($M^{\bullet+}$, 54), 169 (82), 154 (32), 139 (100), 137 (50), 95 (52), 86 (40), 84 (61); **HRMS** (EI) 182.0582 ($C_9H_{10}O_4$ requires 182.0579).

Benzo[*b*]furan-3-carbaldehyde (348), $C_9H_6O_2$, FW = 146.15



348

Freshly distilled phosphous oxytrichloride (12.6 mL, 20.8 g, 135 mmol, 8 equiv) was added drop-wise to a stirred solution of benzofuran (1.87 mL, 2.00 g, 16.9 mmol, 1 equiv) in anhydrous DMF (10.5 mL, 9.90 g, 135 mmol, 8 equiv) at 80 ºC and the to stir for 24 h at this temperature.[202] After cooling to room temperature, the reaction was quenched with water (150 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and evaporated. The crude product was purified on a silica column (30 mL) with a gradient of petroleum ether to petroleum ether – ethyl acetate mixture (95:5) to furnish yellowish liquid aldehyde **348**[202] (897 mg, 6.14 mmol, 36 %): yellowish liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H), 7.50 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.55 (d, *J* = 1.0 Hz, 1H), 7.58 (ddd, *J* = 8.5, 1.7, 0.9 Hz, 1H), 7.73 (ddd, *J* = 7.9, 1.2, 0.8 Hz, 1H), 9.85 (s, 1H); **^{13}C NMR** δ 112.56 (CH), 117.82 (CH), 123.56 (CH), 124.10 (CH), 126.53 (C), 129.12 (CH), 152.55 (C), 156.15 (C), 179.65 (CH); **IR** ν 3123, 3092, 2835, 1685, 1611, 1557, 1448, 1328, 1289 cm^{-1}; **MS** (EI) *m/z* (%) 116 ($M^{\bullet+}$, 100), 145 (90), 118 (17), 89 (70); **HRMS** (EI) 146.0369 ($C_9H_6O_2$ requires 146.0368).

General Procedure for Grignard Addition:[169]

Grignard reagents were commercial solutions (methylmagnesium bromide, *iso*-propylmagnesium chloride) or freshly prepared from the corresponding alkyl halogenide (methyl iodide, allyl bromide, 5-bromopent-1-ene) and magnesium (1:1 equiv) as follows:

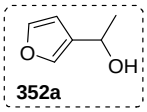
The alkyl halogenide was added drop-wise to magnesium turnings in ether in a three-necked flask under an argon atmosphere and the reaction mixture was heated to maintain the reflux. When all the magnesium was consumed, the mixture was cooled to 0 ºC and neat aldehyde (1 equiv for 1.5 equiv of the Grignard reagent; Table 6.3) was added drop-

wise. The reaction was monitored by TLC and when complete, it was quenched with a saturated aqueous NH_4Cl solution and the aqueous layer was extracted with ether (2 × one fold volume). The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was used without further purification or distilled on Kugelrohr apparatus at 5 mbar (3.75 mmHg, temperature in Table 6.3) to obtain pure alcohols as colourless oils.

Table 6.3. Addition of Grignard Reagents onto Aldehydes

Alkylhalogenide or Grignard reagent	**Aldehyde / Reaction time**	**Purif.**	**Alcohol**
MeI (467 µL, 1.07 g, 7.50 mmol), ether 10 mL	**3-Furaldehyde** (433 µL, 481 mg, 5.00 mmol) / 1 h	-	**352a** (500 mg, 4.46 mmol, 89 %)
AllylBr (1.04 mL, 1.45 g, 12.0 mmol), ether 20 mL	**3-Furaldehyde** (692 µL, 769 mg, 8.00 mmol) / 2 h	dist. 60 °C	**352b** (996 mg, 7.21 mmol, 90 %)
AllylBr (2.60 mL, 3.63 g, 30.0 mmol), ether 50 mL	**2-Furaldehyde** (1.66 mL, 1.92 g, 20.0 mmol) / 4 h	dist. 75 °C	**352c** (1.92 g, 13.89 mmol, 69 %)
MeMgBr (3.0 M in ether, 3.04 mL, 9.13 mmol), ether 24 mL	**Benzo[*b*]furan-3-carbaldehyde** (890 mg, 6.09 mmol, 1 equiv) / 3 h	20 mL SiO_2, PE – EA (90:10)	**352d** (927 mg, 5.72 mmol, 94 %).
***i*-PrMgCl** (2.0 M in THF, 13 mL, 25.0 mmol), THF 10 mL	**2-Furaldehyde** (1.66 mL, 1.93 g, 20.0 mmol) / 18 h	-	**352e** (2.04 g, 14.6 mmol, 73 %)
***i*-PrMgCl** (2.0 M in THF, 4.06 mL, 40.0 mmol), THF 20 mL	**Benzaldehyde** (4.06 mL, 40.0 mmol) / 18 h	75 mL SiO_2, PE – EA (95:5)	**352f** (3.88 g, 25.8 mmol, 65 %)
5-Bromopent-1-ene (3.55 mL, 4.47 g, 30.0 mmol), ether 50 mL	**3-Methoxybenzaldehyde** (2.43 mL, 2.72 g, 20.0 mmol) / 2.5 h	-	**352g** (4.03 g, 19.5 mmol, 97 %)

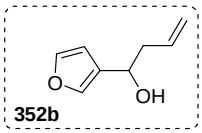
1-(Furan-3'-yl)ethanol, 3-(1'-hydroxyethyl)furan (352a), $C_6H_8O_2$, FW = 112.14



352a

352a:[203] colourless liquid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.49 (d, *J* = 6.4 Hz, 3H), 1.71 (br s, 1H), 4.87 (q, *J* = 6.3 Hz, 1H), 6.42 (dd, *J* = 1.4, 1.2 Hz, 1H), 7.38 (s, 1H), 7.39 (s, 1H); **^{13}C NMR** δ 22.97 (CH_3), 62.02 (CH), 107.48 (CH), 129.28 (C), 137.50 (CH), 142.35 (CH); **IR** ν 3357, 2975, 1503, 1371, 1160 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 112 ($M^{\bullet+}$, 14), 95 (100).

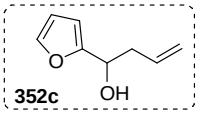
1-(Furan-3'-yl)but-3-en-1-ol, 3-(1'-Hydroxybut-3'-en-1'-yl)furan (352b), $C_8H_{10}O_2$, FW = 138.18



352b

352b:[169c] colourless liquid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.45-2.49 (m, 2H), 2.52 (br s, 1H), 4.66 (t, *J* = 6.4 Hz, 1H), 5.09-5.12 (m, 1H), 5.13 (ddd, *J* = 17.1, 3.3, 1.4 Hz, 1H), 5.78 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 6.38 (dd, *J* = 1.4, 0.9 Hz, 1H), 7.34-7.35 (m, 1H), 7.36 (dd, *J* = 3.4, 1.6 Hz, 1H); **^{13}C NMR** δ 42.41 (CH_2), 66.10 (CH), 108.63 (CH), 118.38 (CH_2), 128.51 (C), 134.22 (CH), 139.08 (CH), 143.27 (CH); **IR** ν 3375, 3077, 2908, 1642, 1502, 1160 cm^{-1}; **MS** (EI) *m/z* (%) 138 ($M^{\bullet+}$, 10), 97 (100), 95 (12); **HRMS** (EI) 138.0679 ($C_8H_{10}O_2$ requires 138.0681).

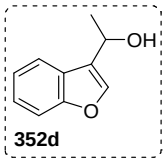
1-(Furan-2'-yl)but-3-en-1-ol, 2-(1'-Hydroxybut-3'-en-1'-yl)furan (352c), $C_8H_8O_2$, FW = 138.18



352c

352c:[204] colourless liquid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.54-2.64 (m, 2H), 3.02 (br s, 1H), 4.68-4.71 (m, 1H), 5.09-5.17 (m, 2H), 5.78 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 6.22-23 (m, 1H), 6.32 (dd, *J* = 3.1, 1.7 Hz, 1H), 7.36-7.37 (m, 1H); **^{13}C NMR** δ 40.03 (CH_2), 66.92 (CH), 106.13 (CH), 110.14 (CH), 118.19 (CH_2), 133.90 (CH), 141.88 (CH), 156.19 (C); **IR** ν 3375, 3078, 2912, 1642, 1505, 1149 cm^{-1}; **MS** (EI) *m/z* (%) 138 ($M^{\bullet+}$, 5), 97 (100); **HRMS** (EI) 138.0680 ($C_8H_{10}O_2$ requires 138.0681).

1-(Benzo[*b*]furan-3'-yl)ethanol, 3-(1'-Hydroxyethyl)benzo[*b*]furan (352d), $C_{10}H_{10}O_2$, FW = 162.20

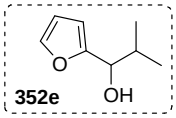


352d

352d:[205] yellowish oil which solidified upon standing; mp 36-37 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.50 (d, *J* = 6.6 Hz, 3H), 2.56 (br s, 1H), 4.88 (q, *J* = 6.6 Hz, 1H), 6.47 (s, 1H), 7.10 (ddd, *J* = 7.4, 7.4, 0.9 Hz, 1H), 7.16 (ddd, *J* = 7.8, 7.3, 1.3 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.42 (dd, *J* = 7.0, 1.2 Hz, 1H); **^{13}C NMR** δ 21.30 (CH_3), 64.01 (CH), 101.69 (CH), 111.10 (CH), 120.97 (CH), 122.66 (CH), 124.05 (CH), 128.04 (C), 154.64 (C),

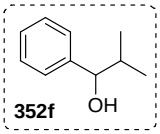
160.13 (C); **IR** ν 3347, 3066, 2981, 2928, 1454, 1254 cm^{-1}; **MS** (EI) *m/z* (%) 162 ($M^{\bullet+}$, 42), 147 (100), 145 (20), 91 (47); **HRMS** (EI) 162.0682 ($C_{10}H_{10}O_2$ requires 162.0681).

1-(Furan-2'-yl)-2-methylpropan-1-ol (352e), $C_8H_{12}O_2$, FW = 140.20



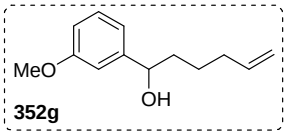
352e:[206] colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.83 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 2.08 (oct, *J* = 6.8 Hz, 1H), 2.40 (br s, 1H), 4.34 (br d, *J* = 6.9 Hz, 1H), 6.20 (dd, *J* = 3.2, 0.5 Hz, 1H), 6.31 (dd, *J* = 3.2, 1.8 Hz, 1H), 7.34 (dd, *J* = 1.8, 0.8 Hz, 1H); **^{13}C NMR** δ 18.26 (CH_3), 18.68 (CH_3), 33.32 (CH), 73.43 (CH), 106.43 (CH), 110.02 (CH), 141.60 (CH), 156.25 (C); **IR** ν 3389, 2962, 2873, 1505, 1468, 1386, 1150 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 141 [$(M+H)^+$, 10], 123 (100), 97 (20); **HRMS** (CI/isobutane) 141.0923 ($C_8H_{13}O_2$ requires 141.0916).

2-Methyl-1-phenylpropan-1-ol (352f), $C_{10}H_{14}O$, FW = 150.24



352f:[207] colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.79 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 1.94 (octet, *J* = 6.8 Hz, 1H), 2.47 (br s, 1H), 4.31 (br d, *J* = 6.9 Hz, 1H), 7.25-7.36 (m, 5H); **^{13}C NMR** δ 18.12 (CH_3), 18.73 (CH_3), 34.97 (CH), 79.68 (CH), 126.38 (2 × CH), 127.08 (CH), 127.87 (2 × CH), 143.43 (C); **IR** ν 3388, 2959, 2872, 1453, 1383 cm^{-1}; **MS** (EI) *m/z* (%) 150 ($M^{\bullet+}$, 12), 107 (100); **HRMS** (EI) 150.1046 ($C_{10}H_{14}O$ requires 150.1045).

1-(3'-Methoxyphenyl)hex-5-en-1-ol (352g), $C_{13}H_{18}O_2$, FW = 206.31



352g:[208] colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.21-1.35 (m, 1H), 1.35-1.48 (m, 1H), 1.55-1.73 (m, 2H), 1.97 (tdt, *J* = 7.3, 6.8, 1.3 Hz, 2H), 2.19 (br s, 1H), 3.70 (s, 3H), 4.51 (dd, *J* = 7.1, 6.1 Hz, 1H), 4.85 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 4.90 (ddt, *J* = 17.1, 3.6, 1.6 Hz, 1H), 5.69 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 6.71 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.79-6.81 (m, 2H), 7.15 (dd, *J* = 8.2, 8.0 Hz, 1H); **^{13}C NMR** δ 25.09 (CH_2), 33.63 (CH_2),

38.67 (CH_2), 55.22 (CH_3), 74.38 (CH), 111.40 (CH), 112.89 (CH), 114.22 (CH_2), 118.27 (CH), 129.46 (CH), 138.64 (CH), 146.67 (C), 159.71 (C); **IR** ν 3392, 3075, 2937, 2837, 1640, 1602, 1488, 1457, 1436, 1318, 1259, 1156 cm^{-1}; **MS** (EI) *m/z* (%) 206 ($M^{\bullet+}$, 80), 163 (90), 150 (81), 138 (80), 137 (100), 135 (60), 134 (44), 109 (100), 94 (93); **HRMS** (EI) 206.1306 ($C_{13}H_{18}O_2$ requires 206.1307).

General Procedures for Oxidation of Alcohols to the Corresponding Ketones:

Method A: A mixture of pyridinium chlorochromate (PCC, 1.5 equiv) and Celite (1:1 w/w) was added in several portions to a solution of alcohol (1 equiv) in CH_2Cl_2.[169] The reaction was monitored by TLC. When no starting material was observed (approximately 2 h), the mixture was diluted with ether (one fold volume) and let to stir for 15 min. Then the suspension was filtered through a pad of silica gel, washed with ether, and the filtrate was evaporated. The crude ketone was filtered on a silica gel column (10 fold weight of the crude) with a petroleum ether – ethyl acetate mixture (95:5) (Table 6.4).

Table 6.4. Oxidation of Alcohols the Corresponding Ketones with PCC

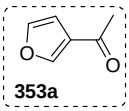
Alcohol / CH_2Cl_2	**PCC**	**Ketone**
352a (500 mg, 4.50 mmol) / 20 mL	1.50 g, 6.75 mmol	**353a** (161 mg, 1.46 mmol, 32 %)
352b (700 mg, 5.07 mmol) / 14 mL	1.64 g, 7.60 mmol	**353b** (157 mg, 1.15 mmol, 23 %)
352e (1.65 g, 8.00 mmol) / 30 mL	2.59 g,12.0 mmol	**353e** (1.37 g, 6.71 mmol, 84 %)
352f (2.50 g, 16.6 mmol) / 75 mL	5.38 g, 25.0 mmol	**353f** (1.78 g, 12.0 mmol, 72 %)

Method B:[170] A solution of pyridinium dichromate (PDC, 1.4 to 1.75 equiv) in anhydrous DMF was added drop-wise to the neat alcohol (1 equiv) and the reaction was let to stir overnight at room temperature for 3 h. The mixture was diluted with ether (60 mL) and quenched with water (300 mL). The layers were separated and the aqueous layer was extracted with ether (3×60 mL). The combined organic layers were washed with brine (60 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude ketone was purified on a silica gel column with a petroleum ether – ethyl acetate mixture (Table 6.5).

Table 6.5. Oxidation of Alcohols the Corresponding Ketones with PDC

Alcohol / DMF	**PDC**	**SiO_2 PE – EA**	**Ketone**
352d (900 mg, 5.55 mmol) / 6 mL	2.92 g, 7.78 mmol, 1.4 equiv	20 mL, 98:2	**353d** (534 mg, 3.33 mmol, 60 %)
352g (800 mg, 5.70 mmol) / 7.5 mL	9.98 mmol, 3.75 g, 1.75 equiv	35 mL, 97:3	**353g** (319 mg, 3.31 mmol, 40 %)

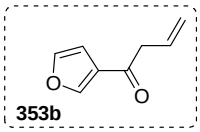
3-Acetylfuran (353a), $C_6H_6O_2$, FW = 110.12



353a

353a:[209] white crystals: mp 47-48 ºC (hexane) [lit. 48.5-49.5 ºC (pentane)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.37 (d, *J* = 0.9 Hz, 3H), 6.69-6.70 (m, 1H), 7.36-7.37 (m, 1H), 7.95-7.96 (m, 1H); **^{13}C NMR** δ 27.85 (CH_3), 108.59 (CH), 128.12 (C), 144.32 (CH), 147.59 (CH), 192.49 (C); **IR** ν 3122, 1658, 1562, 1311, 1161 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 111 [$(M+H)^+$, 100]; **HRMS** (CI/isobutane) 111.0442 ($C_6H_7O_2$ requires 111.0446).

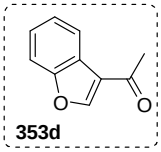
1-(Furan-3'-yl)but-3-en-1-one, 3-(1'-Oxobut-3'-en-1'-yl)furan (353b), $C_8H_8O_2$, FW = 136.16



353b

353b: colourless liquid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.51 (dt, *J* = 6.8, 1.4 Hz, 2H), 5.16-5.22 (m, 2H), 6.01 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 6.76 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.42 (dd, *J* = 1.8, 1.5 Hz, 1H), 8.04 (dd, *J* = 1.4, 0.8 Hz, 1H); **^{13}C NMR** δ 20.99 (CH_3), 46.34 (CH_2), 46.97 (CH), 108.54 (CH), 114.84 (CH_2), 127.27 (C), 130.71 (CH), 144.25 (CH), 147.46 (CH), 192.66 (C); **IR** ν 3134, 1678, 1562, 1511, 1390, 1333, 1157 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 137 [$(M+H)^+$, 100], 95 (55); **HRMS** (CI/isobutane) 137.0601 ($C_8H_9O_2$ requires 137.0603).

3-Acetyl-benzo[*b*]furan (353d), $C_{10}H_8O_2$, FW = 160.18

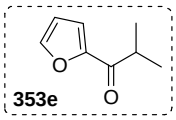


353d

353d:[205] off-white crystals; **mp** 58-59 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.60 (s, 3H), 7.30 (ddd, *J* = 7.8, 7.2, 0.8 Hz, 1H), 7.47 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.49 (d, *J* =

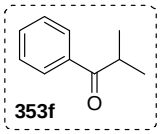
0.9 Hz, 1H), 7.57 (ddd, *J* = 8.4, 1.8, 0.9 Hz, 1H), 7.70 (dd, *J* = 7.9, 1.1, 0.8 Hz, 1H); **^{13}C NMR** δ 26.47 (CH_3), 112.49 (CH), 113.05 (CH), 123.31 (CH), 123.93 (CH), 127.08 (C), 128.29 (CH), 152.67 (C), 155.69 (C), 188.64 (C); **IR** ν 3121, 3086, 3019, 1678, 1613, 1556, 1362, 1295 cm^{-1}; **MS** (EI) *m/z* (%) 160 ($M^{\bullet+}$, 52), 144 (100), 89 (27), 86 (32), 84 (48); **HRMS** (EI) 160.0526 ($C_{10}H_8O_2$ requires 160.0524).

1-(Furan-2'-yl)-2-methylpropan-1-one (353e), $C_8H_{10}O_2$, FW = 138.18



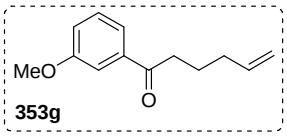
353e: colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6.9 Hz, 6H), 3.33 (sept, *J* = 6.9 Hz, 1H), 6.52 (dd, *J* = 3.5, 1.7 Hz, 1H), 7.18 (dd, *J* = 3.5, 0.6 Hz, 1H), 7.57 (dd, *J* = 1.6, 0.7 Hz, 1H); **^{13}C NMR** δ 18.80 (2 × CH_3), 36.25 (CH), 112.11 (CH), 117.15 (CH), 146.24 (CH), 152.13 (C), 193.69 (C); **IR** ν 3131, 2973, 2935, 2875, 1671, 1567, 1468, 1396, 1255 cm^{-1}; **MS** (EI) *m/z* (%) 138 ($M^{\bullet+}$, 10), 95 (30), 86 (62), 84 (100); **HRMS** (EI) 138.0679 ($C_8H_{10}O_2$ requires 138.0681).

2-Methyl-1-phenylpropan-1-one (353f), $C_{10}H_{12}O$, FW = 148.22



353f:[210] colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.11 (d, *J* = 6.9 Hz, 6H), 3.44 (sept, *J* = 6.8 Hz, 1H), 7.32-7.36 (m, 2H), 7.43 (dddd, *J* = 8.2, 6.5, 1.3, 1.3 Hz, 1H), 7.84-7.87 (m, 2H); **^{13}C NMR** δ 18.98 (2 × CH_3), 35.14 (CH), 128.12 (2 × CH), 128.43 (2 × CH), 132.62 (CH), 135.98 (C), 204.45 (C); **IR** ν 2972, 2933, 2873, 1682, 1597, 1465, 1384, 1224 cm^{-1}; **MS** (EI) *m/z* (%) 148 ($M^{\bullet+}$, 16), 147 (10), 105 (100); **HRMS** (EI) 148.0889 ($C_{10}H_{12}O$ requires 148.0888).

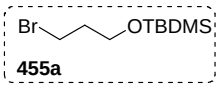
1-(3'-Methoxyphenyl)hex-5-en-1-one (353g), $C_{13}H_{16}O_2$, FW = 204.29



353g:[208] colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.81 (tt, *J* = 7.5, 7.2 Hz, 2H), 2.12 (ddt, *J* = 7.3, 6.8, 1.2 Hz, 2H), 2.92 (t, *J* = 7.3 Hz, 2H), 3.80 (s, 3H), 4.97 (ddt, *J* = 10.2, 2.1, 1.2 Hz, 1H), 5.02 (ddt, *J* = 17.1, 3.6, 1.6 Hz, 1H), 5.79 (ddt, *J* = 17.1, 10.3, 6.8

Hz, 1H), 7.05 (ddd, *J* = 8.2, 2.7, 0.9 Hz, 1H), 7.32 (dd, *J* = 8.0, 7.9 Hz, 1H), 7.45 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.49 (ddd, *J* = 7.6, 1.4, 1.0 Hz, 1H); **^{13}C NMR** δ 23.33 (CH_2), 33.19 (CH_2), 37.79 (CH_2), 55.36 (CH_3), 112.31 (CH), 115.29 (CH_2), 119.26 (CH), 120.65 (CH), 129.54 (CH), 138.05 (CH), 138.39 (C), 159.80 (C), 199.93 (C); **IR** ν 3076, 2940, 2837, 1685, 1640, 1598, 1583, 1486, 1452, 1431, 1260 cm^{-1}; **MS** (EI) *m/z* (%) 204 ($M^{\bullet+}$, 45), 150 (100), 135 (96), 122 (18), 107 (68), 92 (40); **HRMS** (EI) 204.1152 ($C_{13}H_{16}O_2$ requires 204.1150).

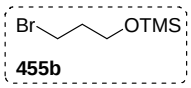
3-Bromo-1-(*tert*-butyldimethylsilyloxy)propane (455a), $C_9H_{21}OSiBr$, FW = 253.29



455a

3-Bromopropan-1-ol (2.71 mL, 4.17 g, 30.0 mmol) was added to a solution of *t*-butyldimethylsilyl chloride (5.44 g, 36.0 mmol, 1.2 equiv), triethylamine (5.90 mL, 3.75 g, 39.0 mmol, 1.3 equiv) and 4-(*N*,*N*-dimethylamino)pyridine (183 mg, 1.50 mmol, 5 mol %) in THF (45 mL) at 0 °C.[171] The mixture was let to warm to room temperature and to stir overnight. The reaction was quenched with a saturated aqueous NH_4Cl solution (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to afford a colourless oil **455a**[171] (7.24 g, 28.57 mmol, 95 %). The residue was used in the next step without further purification: colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.89 (s, 9H), 2.02 (tt, *J* = 6.2, 5.9 Hz, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 3.73 (t, *J* = 5.7 Hz, 2H); **^{13}C NMR** δ -6.53 (2 × CH_3), 17.14 (C), 24.76 (3 × CH_3), 29.48 (CH_2), 34.39 (CH_2), 59.22 (CH_2); **IR** ν 3360, 2961, 2832, 1670, 1511, 1155 cm^{-1}; **MS** (FAB/NOBA) *m/z* (%), 221 (21), 207 (19), 148 (56), 75 (100).

3-Bromo-1-(trimethylsilyloxy)propanol (455b), $C_6H_{15}OSiBr$, FW = 211.20



455b

Trimethylsilyl chloride (8.18 mL, 7.82 g, 72 mmol, 1.2 equiv) was added to a solution of 3-bromopropan-1-ol (5.43 mL, 8.34 g, 60 mmol) and 2,6-lutidine (8.39 mL, 7.72 g, 72 mmol, 1.2 equiv) in CCl_4 (60 mL) at 0 °C.[171] The mixture was let to warm to room temperature and to stir for 3 h. The resulting suspension was filtered and the solvent was distilled off at atmospheric pressure. The residue was distilled at 5 mbar (3.75 mmHg) at 70 °C to afford **455b** as a colourless oil (6.87 g, 32.50 mmol, 54%): colourless liquid; **^{1}H**

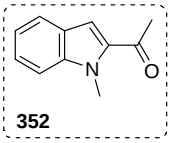
NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 9H), 2.04 (tt, *J* = 6.2, 6.0 Hz, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 3.70 (t, *J* = 5.7 Hz, 2H); **^{13}C NMR** δ -0.62 (3 × CH_3), 31.11 (CH_2), 35.89 (CH_2), 60.83 (CH_2); **IR** ν 2957, 1251, 1100 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 213 [$(M+H)^+$, 100], 211 [$(M+H)^+$, 100], 197 (15), 195 (15), 167 (15), 85 (24); **HRMS** (CI/isobutane) 211.0144 ($C_6H_{16}Osi^{79}Br$ requires 211.0154), 213.0114 ($C_6H_{16}Osi^{81}Br$ requires 213.0133).

Two-step Procedure for Preparation of 2-Acetyl-1-methyl-1*H*-indol:

A solution of 1*H*-indol-2-carboxylic acid (2.42 g, 15 mmol, 1 equiv) in anhydrous DMF (24 mL) was added drop-wise to a suspension of sodium hydride (neat, 1.44 g, 60 mmol, 4 equiv) in THF (12 mL) at 0 ºC and the mixture was let to stir for 1 h. Then methyl iodide (5.61 mL, 12.8 g, 90.0 mmol, 6 eq) was added and the reaction was left overnight at room temperature. The reaction was quenched with ethyl acetate (10 mL) and water (100 mL) and extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and evaporated. The crude contained mixture of compounds and was subjected to hydrolysis of the residual methyl ester as follows: a solution of potassium hydroxide (30 %, 30 mL) was added to a suspension of the crude material in toluene (30 mL) and refluxed for 2 h. The cooled mixture was diluted with water (100 mL) and the basic aqueous layer was extracted with ether (3 × 40 mL). Then the aqueous layer was acidified to pH = 1 and extracted with ether (3 × 50 mL). The second etheric extracts were combined, washed with brine (20 mL), dried over $MgSO_4$ and evaporated. The crude after hydrolysis (1.57 g) was used for the next step without further purification.

A solution of methyllithium (1.6 M in ether, 11.2 mL, 18.0 mmol, 2 equiv) was added drop-wise to a cooled solution (0 ºC) of crude acid (1.57 g, approximated as 9.00 mmol, 1 equiv).[211] The solution was let to warm to room temperature and stir for 1 h, then another portion of methyllithium was added (1.6 M in ether, 11.2 mL, 18.0 mmol, 2 equiv) and the mixture was refluxed for 4 h. After cooling to 0 ºC, the reaction was quenched with water (20 mL) and extracted with ether (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated. The crude mixture was purified on a silica gel column (75 mL) in a petroleum ether – ethyl acetate mixture (85:15) to obtain white crystalline solid of ketone **352** (469 mg, 2.71 mmol, 18 % from 1*H*-indol-2-carboxylic acid).

2-Acetyl-1-methyl-1*H*-indol (352), $C_{11}H_{11}NO$, FW = 173.23



352

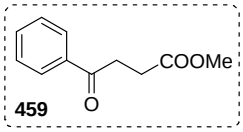
352:[211] off-white crystals; **mp** 54-55 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.62 (s, 3H), 4.08 (s, 3H), 7.16 (ddd, *J* = 8.0, 4.4, 3.5 Hz, 1H), 7.29 (s, 1H), 7.38-7.39 (m, 2H), 7.70 (ddd, *J* = 8.0, 0.9, 0.9 Hz, 1H); **^{13}C NMR** δ 27.90 (CH_3), 32.10 (CH_3), 110.31 (CH), 111.91 (CH), 120.63 (CH), 122.81 (CH), 125.72 (C), 125.84 (CH), 134.85 (C), 140.02 (C), 191.56 (C); **IR** ν 3017, 2935, 1656, 1513, 1465, 1392, 1352, 1219 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 174 [$(M+H)^+$, 100], 173 (15), 85 (27); **HRMS** (CI/isobutane) 174.0918 ($C_{11}H_{12}NO$ requires 174.0919).

Procedures for Preparation of Methyl 4-oxo-4-phenylbutanoate:

Method A: A Schlenk flask loaded with a solution of benzaldehyde (105 mg, 100 µL, 1.00 mmol, 1 equiv), methyl acrylate (172 mg, 180 µL, 2.00 mmol, 2 equiv), Wilkinson catalyst (48.4 mg, 0.050 mmol, 5 mol %), 2-amino-3-picoline (43 mg, 40 µL, 0.400 mmol, 0.4 equiv) and benzoic acid (24 mg, 0.200 mmol, 0.2 equiv) in anhydrous toluene (0.4 mL) under an inert atmosphere was put into an oil bath preheated to 130 ºC and was let to stir at this temperature for 2 h.[176] After cooling down, the reaction was diluted with ether and washed with water (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and evaporated. The crude product was purified on a silica gel column (40 mL) in a petroleum ether – ethyl actetate mixture (95:5) to obtain the γ-keto ester **167** (110 mg, 0.572 mmol, 57 %).

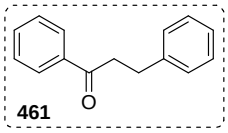
Method B: A solution of 4-oxo-4-phenylbutanoic acid (5 g, 28.1 mmol) and concentrated sulphuric acid (3 drops from Pasteur pipette) was was refluxed in methanol (50 mL) for 3 h after which the mixture was let to cool down and concentrated *in vacuo*. The residue was then dissolved in ether (50 mL) and washed with saturated $NaHCO_3$ (2 × 50 mL), water (50 mL), brine (50 mL), dried over $MgSO_4$ and evaporated. The crude methyl ester **459** (5.20 g, 27.1 mmol, 96 %) was used without further purification.

Methyl 4-oxo-4-phenylbutanoate (459), $C_{11}H_{12}O_3$, FW = 192.23



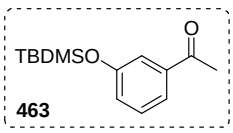
459:[176] colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.73 (t, *J* = 6.6 Hz, 2H), 3.29 (t, *J* = 6.6 Hz, 2H), 3.67 (s, 3H), 7.43 (dd, *J* = 7.8, 7.4, 2H), 7.53 (dd, *J* = 7.4, 7.1, 1H), 7.95 (dd, *J* = 7.8, 0.5, 2H); **^{13}C NMR** δ 23.88 (CH_2), 27.99 (CH_2), 51.84 (CH_3), 128.04 (2 × CH), 128.63 (2 × CH), 133.27 (CH), 136.48 (C), 173.39 (C), 198.07 (C); **IR** ν 3061, 1737, 1686, 1597, 1449, 1438, 1221 cm^{-1}; **MS** (EI) *m/z* (%) 192 ($M^{\bullet+}$, 10), 161 (14), 105 (100); **HRMS** (EI) 192.0785 ($C_{11}H_{12}O_3$ requires 192.0786).

1,3-Diphenylpropan-1-one (461), $C_{15}H_{14}O$, FW = 210.29



A suspension of 10 % palladium on carbon (514 mg) and chalcone **460** (4.17 g, 20.0 mmol) in ethyl acetate was placed under an atmosphere of H_2 (balloon). The reaction was monitored by TLC and when the starting material was consumed (ca. 60 h), the suspension was filtered through a Celite pad and the adsorbent was washed with ethyl acetate. The filtrate was evaporated to afford **461**[212] as a crystalline residue (3.95 g, 18.8 mmol, 94 %), which was used without further purification: white crystals; **mp** 70-71 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.00 (dd, *J* = 8.0, 7.4 Hz, 2H), 3.23 (dd, *J* = 8.0, 7.4 Hz, 2H), 7.14 (dddd, *J* = 7.1, 7.0, 1.8, 1.5 Hz, 1H), 7.18-7.25 (m, 4 H), 7.38 (dd, *J* = 8.5, 7.5 Hz, 2H), 7.45 (ddd, *J* = 8.0, 1.3, 1.3 Hz, 1H), 7.89 (ddd, *J* = 8.2, 1.7, 1.1 Hz, 2H); **^{13}C NMR** δ 30.15 (CH_2), 40.51 (CH_2), 126.18 (CH), 128.08 (2 × CH), 128.48 (2 × CH), 128.58 (2 × CH), 128.65 (2 × CH), 133.13 (CH), 136.85 (C), 141.33 (C), 199.28 (C); **MS** (EI) *m/z* (%) 210 ($M^{\bullet+}$, 42), 105 (92), 87 (38), 85 (100); **HRMS** (EI) 210.1046 ($C_{15}H_{14}O$ requires 210.1045).

3'-(*tert*-Butyldimethylsilyloxy)acetophenone (463), $C_{14}H_{22}O_2Si$, FW = 250.45



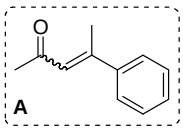
A solution of *tert*-butyldimethylsilyl chloride (907 mg, 6.00 mmol, 1.2 equiv) in anhydrous THF (2.5 mL) was added to a mixture of 3-hydroxyacetophenone (681 mg, 5.00 mmol),

triethylamine (983 µL, 625 mg, 6.50 mmol, 1.3 equiv) and 4-(*N*,*N*-dimethylamino)pyridine (31 mg, 0.250 mmol, 5 mol %) in THF (5 mL) at 0 ºC.[171] The mixture was let to warm to room temperature and to stir overnight. Then it was quenched with a saturated aqueous NH_4Cl solution (50 mL) and the aqueous layer was extracted with ether (2 × 40 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to afford **463** (1.20 g, 4.79 mmol, 96 %) as a colourless oil, which was used in the next step without further purification: colourless liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.21 (s, 6H), 0.99 (s, 9H), 2.57 (s, 3H), 7.04 (ddd, *J* = 8.1, 2.5, 1.0 Hz, 1H), 7.31 (dd, *J* = 7.9, 7.8 Hz, 1H), 7.41 (dd, *J* = 2.2, 1.8 Hz, 1H), 7.54 (ddd, *J* = 7.7, 1.6, 1.0 Hz, 1H); **^{13}C NMR** δ –4.40 (2 × CH_3), 18.22 (C), 25.67 (3 × CH_3), 26.78 (CH_3), 119.49 (CH), 121.59 (CH), 125.00 (CH), 129.58 (CH), 138.60 (C), 155.98 (C), 197.96 (C); **IR** ν 2956, 2931, 2859, 1687, 1582, 1483, 1436, 1359, 1283 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 251 [$(M+H)^+$, 100], 193 (5), 137 (5); **HRMS** (CI/isobutane) 251.1462 ($C_{14}H_{23}O_2Si$ requires 251.1467).

Reaction of acetylacetone with phenylmagnesium bromide:[178]

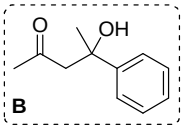
Freshly prepared etheral solution of phenylmagnesium bromide [3.0 M, prepared from bromobenzene (15.8 mL, 23.6 g, 150 mmol, 1.5 equiv) and magnesium turnings (3.45 g, 150 mmol, 1.5 equiv) in ether (50 mL), see general procedure stated previously] was added drop-wise (ca 30 min) to a solution of freshly distilled acetylacetone (10.3 mL, 10.0 g, 100 mmol, 1 equiv) in anhydrous ether (100 mL) at 0 ºC. The resulting suspension was let to warm to room temperature, to stir for 1 h at this temperature and refluxed for an additional 1 h. The mixture was the cooled to 0 ºC and quenched with saturated NH_4Cl (100 mL). The aqueous layer was extracted with ether (3 × 60 mL), washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified on a silica gel column (200 mL) with gradient of petroleum ether to a petroleum ether – ethyl acetate mixture (80:20) to obtain five distinguished fractions.

4-Phenylpent-3-en-2-one (466A), $C_{11}H_{12}O$, FW = 160.23

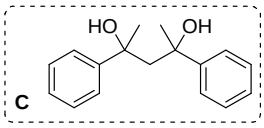


(*E*)-466A (1.94 g, 12.1 mmol, 12 %):[179] yellowish oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.45 (d, *J* = 1.2 Hz, 3H), 6.42 (q, *J* = 0.9 Hz, 1H), 7.27-7.30 (m, 3H), 7.38-7.40 (m, 2H); **(*Z*)-466A** (883 mg, 5.51 mmol, 5.5 %):[213] yellowish oil; **^{1}H NMR** (400 MHz, $CDCl_3$)

δ 1.81 (s, 3H), 2.20 (d, *J* = 1.4 Hz, 3H), 6.13 (q, *J* = 1.3 Hz, 1H), 7.19-7.22 (m, 2H), 7.35-7.44 (m, 3H).



4-Hydroxy-4-phenylpentan-2-one (466B),[214] **$C_{11}H_{14}O_2$, FW = 178.25,** (1.28 g, 7.18 mmol, 7 %); yellowish oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.52 (s, 3H), 2.08 (s, 3H), 2.85 (d, *J* = 17.1 Hz, 1H), 3.20 (d, *J* = 17.1 Hz, 1H), 4.53 (s, 1H), 7.21-7.25 (m, 1H), 7.31-7.35 (m, 2H), 7.41-7.43 (m, 2H).

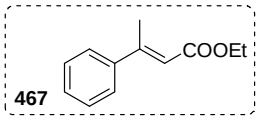


2,4-Diphenylpentan-2,4-diol (466C),[215] **$C_{17}H_{20}O_2$, FW = 256.37,** (1.62 g, 6.32 mmol, 6 %); yellowish oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.26 (s, 6H), 2.40 (s, 2H), 3.77-3.79 (m, 2H), 7.23-7.27 (m, 2H), 7.34-7.38 (m, 4H), 7.47-7.49 (m, 4H).

Biphenyl (466D), $C_{12}H_{10}$, FW = 154.22, (775 mg, 5.03 mmol, 5 %); white crystals; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33-7.38 (m, 2H), 7.43-7.47 (m, 4H), 7.59-7.62 (m, 2H).

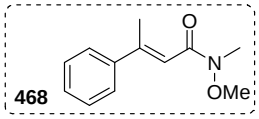
Three-step Procedure for Clean Preparation of (*E*)-alkene 466A:[179]

(*E*)-Ethyl 3-phenylbut-2-enoate (467), $C_{12}H_{14}O_2$, FW = 190.26



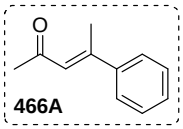
A solution of triethyl phosphonoacetate (10.7 mL, 12.1 g, 54.1 mmol, 1.3 equiv) in anhydrous THF (10 mL) was added drop-wise to a suspension of NaH (neat, 1.4 g, 58.2 mmol, 1.4 equiv) in anhydrous THF (10 mL) cooled to 0 ºC and the mixture was let to stir at room temperature for 30 min. Then, acetophenone (4.85 mL, 5.0 g, 41.6 mmol, 1 equiv) was added at 0 ºC, and the mixture was let to stir at room temperature for 24 h. The reaction was quenched with saturated $NaHCO_3$ (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified on a silica gel column (300 mL) with a petroleum ether – ethyl acetate mixture (96:4) to give (*E*)-ester **467** (3.63 g, 19.1 mmol, 46 %): colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.1 Hz, 3H), 2.58 (d, *J* = 1.3 Hz, 3H), 4.22 (q, *J* = 7.1 Hz, 2H), 6.13 (q, *J* = 1.3 Hz, 1H), 7.35-7.40 (m, 3H), 7.47-7.49 (m, 2H).

(*E*)-*N*-methoxy-*N*-methyl-3-phenylbut-2-enamide (468), $C_{12}H_{15}NO_2$, FW = 205.28



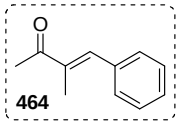
A solution of *iso*-propylmagnesium chloride (2.0M in THF, 36.0 mL, 72 mmol, 4.5 equiv) was added drop-wise at 0 ºC to a solution of **(*E*)-467** (3.04 g, 16.0 mmol, 1 equiv) and *N*,*O*-dimethylhydroxylamine hydrochloride (3.12 g, 32.0 mmol, 2 equiv) in anhydrous THF (40 mL). The mixture was let to stir for 1h at room temperature, after which the reaction was quenched with saturated NH_4Cl (40 mL) and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$ and evaporated. The residue was purified on a silica gel column (80 mL) with a petroleum ether – ethyl acetate mixture (70:30) to afford the Weinreb amide **468** (2.25 g, 11.0 mmol, 69 %): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.53 (d, *J* = 1.2 Hz, 3H), 3.27 (s, 3H), 3.71 (s, 3H), 6.57 (br s, 1H), 7.34-7.40 (m, 3H), 7.46-7.49 (m, 2H).

(*E*)-4-Phenylpent-3-en-2-one (466A), $C_{11}H_{12}O$, FW = 160.23



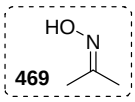
A solution of methylmagnesium bromide (3.0 M in ether, 4.80 mL, 14.3 mmol, 1.3 equiv) was added drop-wise to a solution of amide **468** (2.25 g, 11.0 mmol, 1 equiv) in anhydrous THF (20 mL) at –30 ºC and was let to warm to room temperature. Then the reaction was quenched with saturated NH_4Cl (40 mL) and extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$ and evaporated. The residue was purified on a silica gel column (30 mL) with a petroleum ether – ethyl acetate mixture (95:5) to obtain title (*E*)-alkene **466A**[179] (1.74 g, 11.0 mmol, 99 %) in overall 31 % yield over three steps: yellowish oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.45 (d, *J* = 1.2 Hz, 3H), 6.42 (q, *J* = 0.9 Hz, 1H), 7.27-7.30 (m, 3H), 7.38-7.40 (m, 2H); **^{13}C NMR** δ 18.39 (CH_3), 32.31 (CH_3), 124.54 (CH), 126.51 (2 × CH), 128.61 (2 × CH), 129.14 (CH), 142.52 (C), 153.93 (C), 198.96 (C); **IR** ν 3058, 3026, 1681, 1600, 1446, 1356, 1266, 1182 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 161 [$(M+H)^+$, 100], 89 (100); **HRMS** (CI/isobutane) 161.0965 ($C_{11}H_{13}O$ requires 161.0966).

(*E*)-3-Methyl-4-phenylbut-3-en-2-one (464), $C_{11}H_{12}O$, FW = 160.23



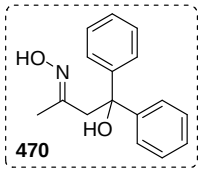
Concentrated sulphuric acid (5.33 ml, 9.81 g, 100 mmol, 1 equiv) was added slowly to a solution of butanone (17.9 mL, 14.4 g, 200 mmol, 2 equiv) and benzaldehyde (10.1 mL, 10.5 g, 100 mmol, 1 equiv) in glacial acetic acid (100 mL).[177] The solution was let to stir for 20 h at room temperature. Then the reaction was diluted with water and quenched with aqueous solution of NaOH (25 %, 50 mL). The aqueous layer was extracted with ether (3 × 100 mL), washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified on a silica gel column (120 mL) with a petroleum ether – ethyl acetate mixture (95:5) to obtain the desired alkene as yellowish oil which solidified upon standing **464**[177] (9.94 g, 62.0 mmol, 62 %): yellowish oil which solidified upon standing; mp 29-30 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.06 (d, *J* = 1.4 Hz, 3H), 2.46 (s, 3H), 7.31-7.36 (m, 1H), 7.37-7.41 (m, 4H), 7.52 (q, *J* = 1.3 Hz, 1H); **^{13}C NMR** δ 12.96 (CH_3), 25.89 (CH_3), 128.35 (2 × CH), 128.60 (CH), 129.74 (2 × CH), 135.92 (C), 139.73 (C), 142.22 (CH), 200.34 (C); **IR** ν 3057, 3026, 2963, 2924, 1665, 1625, 1445, 1365, 1244 cm^{-1}; **MS** (EI) *m/z* (%) 160 ($M^{\bullet+}$, 88), 159 (62), 145 (40), 117 (100), 115 (70), 91 (32), 86 (32), 85 (30), 84 (48), 83 (63); **HRMS** (EI) 160.0887 ($C_{11}H_{12}O$ requires 160.0888).

Propan-2-oxime (469), C_3H_7NO, FW = 73.11



Sodium hydroxide (5.6 g, 140 mmol, 1.4 equiv) was added to a solution of acetone (7.34 mL, 5.81 g, 100 mmol, 1 equiv) and hydroxylamine hydrochloride (9.03 g, 130 mmol, 1.3 equiv) in an ethanol (30 mL) – water mixture (10 mL) and the mixture was heated to 80 ºC for 1 h.[180] Then the solvent was removed *in vacuo*, re-dissolved in ethyl acetate, filtered and concentrated to afford the crude oxime **469** (3.49 g, 47.7 mmol, 48 %) which was used without further purification: white crystals; **mp** 59-59.5 ºC (EtOH, with sublimation); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.89 (s, 3H), 1.90 (s, 3H), 8.15 (br s, 1H).

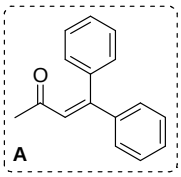
4,4-Diphenyl-4-hydroxybutan-2-oxime (470), $C_{16}H_{17}NO_2$, FW = 255.34



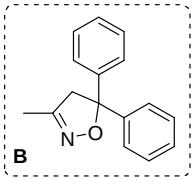
n-Butyllithium (2.0 M in pentane, 27.4 mL, 54.8 mmol, 2 equiv) was added drop-wise to a solution of oxime **469** (2.0 g, 27.4 mmol, 1 equiv) in anhydrous THF (35 mL) at 0 ºC and the mixture was let to stir for 30 min (to gain homogenous yellow solution) after which time it was cooled to –80 ºC and a solution of benzophenone (4.99 g, 27.4 mmol, 1 equiv) in THF (15 mL) was added drop-wise.[180] The solution was stirred for 10 min at this temperature, then allowed to warm to room temperature and quenched with brine (50 mL). The aqueous layer was extracted with an ether – acetone mixture (2:1, 4 × 30 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The crude oxime **470** was used without further purification: white crystals; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.22 (s, 3H), 3.35 (s, 2H), 3.64 (t, *J* = 6.6 Hz, 1H), 4.99 (br s, 2H), 7.15-7.19 (m, 2H), 7.22-7.26 (m, 4H), 7.39-7.41 (m, 4H).

Deprotection of Oxime 470:

A suspension of oxime **470** (6.90 g, 27.0 mmol) in HCl (15 % aq, 50 mL) was refluxed for 1 h after which time it was let to cool to room temperature and extracted with ether (3 × 30 mL).[181] The combined organic layers were dried over $MgSO_4$ and evaporated. The residue spontaneously crystallised from ether to afford crystalline **471B** and mother liquor which was purified on a silica gel column (40 mL) with a gradient of petroleum ether to petroleum ether – ethyl acetate mixture (90:10). The main fraction proved to be the desired alkene **471A**.

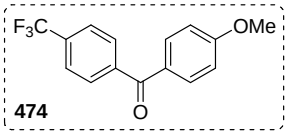


4,4-Diphenylbut-3-en-2-one (471A),[216] **$C_{16}H_{14}O$, FW = 222.30** (1.88 g, 8.46 mmol, 31 %): yellowish oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.89 (s, 3H), 6.60 (s, 1H), 7.22-7.24 (m, 2H), 7.29-7.44 (m, 8H); **^{13}C NMR** δ 30.40 (CH_3), 127.75 (CH), 128.46 (4 × CH), 128.85 (2 × CH), 129.52 (2 × CH), 129.66 (2 × CH), 139.00 (C), 140.80 (C), 154.02 (C), 200.27 (C); **IR** ν 3058, 3027, 1958, 1895, 1812, 1660, 1590, 1491, 1445, 1354, 1257, 1177 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 223 [$(M+H)^+$, 100]; **HRMS** (CI/isobutane) 223.1126 ($C_{16}H_{15}O$ requires 223.1123).



5,5-Diphenyl-3-methylisoxazoline (471B), $C_{16}H_{15}NO$, FW = 237.32 (2.32 g, 9.83 mmol, 36 %): white crystals; **mp** 111-112 ºC (ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 3.56 (d, *J* = 0.7 Hz, 2H), 7.24-7.28 (m, 2H), 7.31-7.35 (m, 4H), 7.40-7.42 (m, 4H); **^{13}C NMR** δ 13.50 (CH_3), 51.79 (CH_2), 126.06 (4 × CH), 127.54 (2 × CH), 128.41 (4 × CH), 144.39 (2 × C), 155.21 (C); **IR** ν 3059, 3023, 2985, 2921, 1957, 1881, 1807, 1596, 1490, 1445, 1387, 1329, 1217 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 238 [$(M+H)^+$, 100], 89 (35); **HRMS** (CI/isobutane) 238.1233 ($C_{16}H_{16}NO$ requires 238.1232).

4-Methoxy-4'-trifluoromethylbenzophenone (474), $C_{15}H_{11}O_2F_3$, FW = 280.2



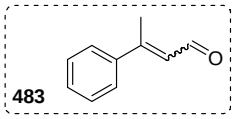
Trifluoroacetic anhydride (2.19 mL, 3.31 g, 15.8 mmol, 2 equiv) was added to a solution of *p*-trifluoromethylbenzoic acid (1.50 g, 7.89 mmol, 1 equiv) in anisole (solvent, 7.5 mL) and the mixture was heated to 80 ºC.[217] After 1h, trifluoromethanesulfonic acid (35 µL, 59 mg, 0.395 mmol, 5 mol %) was added and the mixture was stirred 2 h at 90 ºC. After this period, methanol (7 mL) was added and the product **474** crystallised overnight at 0 ºC (1.35 g, 4.82 mmol, 61 %): pinkish crystals; **mp** 100-101 ºC (MeOH/anisole); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 6.95-6.99 (m, 2H), 7.72-7.74 (m, 2H), 7.77.7-83 (m, 2H), 7.81-7.84 (m, 2H); **^{13}C NMR** δ 55.52 (CH_3), 113.81 (2 × CH), 123.76 (q, *J* = 272.6 Hz, CF_3), 125.24 (q, *J* = 3.7 Hz, 2 × CH), 129.33 (C), 129.78 (2 × CH), 132.62 (2 × CH), 138.22 (q, *J* = 32.6 Hz, C), 141.52 (C), 163.74 (C), 194.23 (C); **^{19}F NMR** δ –62.92; **IR** ν 3019, 2971, 2845, 1645, 1601, 1326, 1264, 1216, 1134 cm^{-1}; **MS** (EI) *m/z* (%) 280 ($M^{\bullet+}$, 37), 145 (15), 135 (100), 92 (13); **HRMS** (EI) 280.0707 ($C_{15}H_{11}O_2F_3$ requires 280.0711).

Vilsmeier-Haack formylation of α-methyl styrene: [218]

Phosphorus oxytrichloride (9.32 mL, 15.3 g, 100 mmol, 1 equiv) was added drop-wise with stirring and cooling to dimethylformamide (31.0 mL, 29.2 g, 0.40 mol, 4 equiv) so that the temperature was kept under 20 ºC. Neat α-methyl styrene (13.0 mL, 11.8 g, 100 mmol, 1 equiv) was added drop-wise and the solution was heated to 50 ºC when an exotermic reaction occurred and cooling was necessary to maintain this temperature. After the exotermic reaction subsided, the mixture was heated to 80 ºC for 1.5 hour. Then the mixture was cooled to 0 ºC, 200 mL of 30 % aqueous sodium acetate was added slowly (at

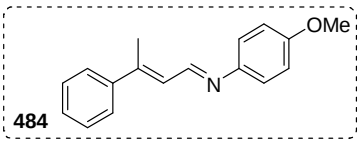
first, then rapidly) and the mixture was reheated to 80 ºC for 15 min. The aqueous layer was then extracted with ether (3 × 100 mL) and the combined organic layers were washed with water (100 mL), brine (100 mL), dried over $MgSO_4$ and evaporated. The crude material was purified on a silica gel column (200 mL) with a solvent gradient from petroleum ether to a mixture of petroleum ether – ethyl acetate (95:5) to afford **(*Z*)-** and **(*E*)-**isomers as yellow oils.

3-Phenybut-2-enal (483), $C_{10}H_{10}O$, FW = 146.20



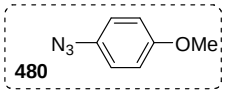
(*Z*)-483 (1.33 g, 7.79 mmol, 8 %):[219] more soluble in petroleoum ether; yellow liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.57 (d, *J* = 1.2 Hz, 3H), 6.39 (dq, *J* = 7.9, 1.2 Hz, 1H), 7.41-7.43 (m, 3H), 7.53-7.56 (m, 2H), 10.18 (d, *J* = 7.8 Hz, 1H); **(*E*)-483** (7.65 g, 52.3 mmol, 52 %):[220] yellow liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.32 (d, *J* = 1.4 Hz, 3H), 6.13 (dq, *J* = 8.3, 1.4 Hz, 1H), 7.29-7.31 (m, 2H), 7.39-7.43 (m, 3H), 9.47 (d, *J* = 8.1 Hz, 1H).

(*E*)-4-Methoxy-*N*-(3'-phenylbut-2'-en-1'-ylidene)aniline (484), $C_{17}H_{17}NO$, FW = 251.35



A solution of *p*-anisidine (3.88 g, 31.5 mmol, 1.05 euiqv) in anhydrous CH_2Cl_2 (10 mL) was added to a solution of aldehyde **(*E*)-483** (4.39 g, 30.0 mmol, 1 equiv), *p*-toluensulfonic acid (284 mg, 1.5 mmol, 5 mol %) and anhydrous $MgSO_4$ (6.0 g) in CH_2Cl_2 (20 mL) under an inert atmosphere. The mixture was let stir at room temperature for 1.5 h and then concentrated *in vacuo* to obtain the crude aldimine **484** (7.79 g, 31.0 mmol, 98 %), which was used without further purification: yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (d, *J* = 1.3 Hz, 3H), 3.83 (s, 3H), 6.83 (dq, *J* = 9.5, 1.3 Hz, 1H), 6.91-6.95 (m, 2H), 7.19-7.23 (m, 2H), 7.33-7.42 (m, 3H), 7.56-7.59 (m, 2H), 8.62 (d, *J* = 9.5 Hz, 1H).

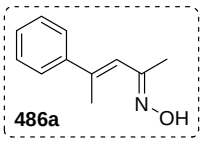
4-Azidoanisole (480), $C_7H_7N_3O$, FW = 149.17



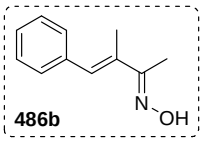
Solid sodium nitrite (8.40 g, 122 mmol, 1 equiv) was added to a cooled (0 ºC) solution of *p*-anisidine (15.0 g, 122 mmol, 1 equiv) in 12 % aqueous HCl (150 mL).[221] After stirring for 30 min at this temperature, sodium azide (9.52 g, 146 mmol, 1.2 equiv) in water (50 mL) was added and the mixture was let stir for 2 h at room temperature. The aqueous layer was extracted with ethyl acetate (3 × 70 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and evaporated. The crude azide **480**[221] (8.53 g, 57.2 mmol, 47 %) was used without further purification: grey solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.87-6.91 (m, 2H), 6.94-6.98 (m, 2H).

Procedure for Preparation of Oximes:[187]

Pyridine (753 µL, 740 mg, 9.36 mmol, 5 equiv) was added to a solution of ketone **466A** or **464** (300 mg, 1.87 mmol, 1 equiv), hydroxylamine hydrochloride (520 mg, 7.49 mmol, 4 equiv) in methanol (7.5 mL) and the mixture was refluxed for 1.5 h. Then the mixture was concentrated, dissolved in a 1:1 mixture of ethyl acetate and hexane (20 mL) and washed with diluted HCl (20 mL). The aqueous layer was extracted with the same solvent mixture (2 × 20 mL), washed with water (20 mL), brine (20 mL) and evaporated. The oximes were used without further purification (319 mg, 1.82 mmol, 97 %).



(2*E*,3*E*)-4-phenylpent-3-en-2-one oxime (486a), $C_{11}H_{13}NO$, FW = 175.25: white solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.32 (d, *J* = 1.4 Hz, 3H), 6.1 (q, *J* = 1.3 Hz, 1H), 7.29-7.37 (m, 3H), 7.43-7.45 (m, 2H).

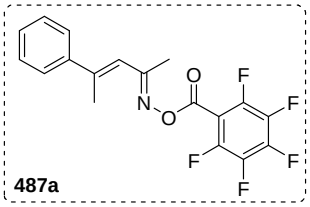


(2*E*,3*E*)-3-methyl-4-phenylbut-3-en-2-one oxime (486b), $C_{11}H_{13}NO$, FW = 175.25: yellowish solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.08 (d, *J* = 1.2 Hz, 3H), 2.17 (s, 3H), 6.92 (d, *J* = 0.4 Hz, 1H), 7.28-7.39 (m, 5H).

Preparation of Pentafluorobenzoates of Oximes:[187]

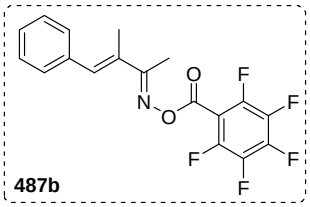
Pentafluorobenzoyl chloride (166 µL, 277 mg, 1.20 mmol, 1.2 equiv) was added drop-wise to a cooled (0 ºC) solution of oxime **486** (175 mg, 1.00 mmol, 1 equiv) and triethylamine (279 µL, 202 mg, 2.00 mmol, 2 equiv) in anhydrous CH_2Cl_2 (3 mL) and the mixture was

stirred at this temperature for 2 h. The reaction was quenched with saturated $NaHCO_3$ (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue after evaporation was purified on a silica gel column (40 mL) with a petroleum ether – ethyl acetate mixture (85:15) to obtain white crystalline solid **487a** or the evaporation residue of **487b** was used crude.



487a

(2*E*,3*E*)-4-phenylpent-3-en-2-one pentafluorobenzoyl-*O*-oxime ester (487a), $C_{18}H_{12}NO_2F_5$, FW = 369.31 (269 mg, 0.763 mmol, 76 %): white crystals; **mp** 121-122 ºC (visible softening and sublimation, hexane/AcOEt); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.46 (d, *J* = 1.3 Hz, 3H), 6.15 (d, *J* = 1.3 Hz, 1H), 7.33-7.40 (m, 3H), 7.45-7.47 (m, 2H); **^{13}C NMR** δ 19.14 (CH_3), 19.44 (CH_3), 120.80 (CH), 126.28 (2 × CH), 128.45 (2 × CH), 128.48 (CH), 142.70 (C), 147.59 (C), 156.58 (C), 164.53 (C), 136-147 (pentafluorophenyl); **^{19}F NMR** δ (–160.02)-(–159.87) (m, 2F), –147.92 (tt, *J* = 20.8, 4.5 Hz, 1F), (–137.23)-(–137.12) (m, 2F); **IR** ν 1747, 1497, 1324, 1199 999, 987 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 370 [$(M+H)^+$, 20], 350 (25), 214 (15), 160 (100), 158 (45), 113 (22); **HRMS** (CI/isobutane) 370.0867 ($C_{18}H_{13}NO_2F_5$ requires 370.0866).



487b

(2*E*,3*E*)-3-methyl-4-phenylbut-3-en-2-one pentafluorobenzoyl-*O*-oxime ester (487b), $C_{18}H_{12}NO_2F_5$, FW = 369.31 (327 mg, 0.926 mmol, 93 %): white crystals; **mp** 115-117 ºC (visible softening and sublimation, hexane/AcOEt); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.20 (d, *J* = 1.2 Hz, 3H), 2.32 (s, 3H), 7.13 (br s, 1H), 7.30-7.42 (m, 5H); **^{13}C NMR** δ 13.18 (CH_3), 14.51 (CH_3), 127.94 (CH), 128.39 (2 × CH), 129.50 (2 × CH), 133.27 (C), 135.34 (CH), 136.24 (C), 156.58 (C), 166.87, 134-150 (pentafluorophenyl); **^{19}F NMR** δ (–159.92)-(–159.77) (m, 2F), –147.72 (tt, *J* = 20.9, 4.7 Hz, 1F), (–137.14)-(–137.02) (m, 2F); **IR** ν 1751, 1652, 1525, 1487, 1415, 1376, 1322, 1189, 999, 986 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 370 [$(M+H)^+$, 25], 310 (20), 308 (22), 160 (100); **HRMS** (CI/isobutane) 370.0869 ($C_{18}H_{13}NO_2F_5$ requires 370.0866).

6.3.Imines

General Procedures for Preparation of Imines:

Method A. 5Å Molecular sieves (6.25 g) were added to a solution of the corresponding ketone (5.00 mmol, 1 equiv) and *p*-anisidine (770 mg, 6.25 mmol, 1.25 equiv) in anhydrous toluene (25 mL) and the reaction mixture was heated under reflux for 5 h. The cooled reaction mixture was filtered from the sieves, the filtrate was evaporated and the residue was purified by flash chromatography on a silica gel column (5 g unless otherwise stated, pre-treated overnight with 10% triethylamine in petroleum ether) with a petroleum ether – ethyl acetate mobile phase, followed by recrystallisation.

Method B. A solution of the corresponding ketone (5.00 mmol, 1 equiv), *p*-anisidine (647 mg, 5.25 mmol, 1.05 equiv) and *p*-toluenesulfonic acid monohydrate (47 mg, 0.250 mmol, 5 mol % equiv) in anhydrous benzene (25 mL) was heated under reflux with a Dean-Stark trap for 16 h, then cooled and evaporated to dryness. The residue was purified by flash chromatography on a silica gel column (25 g, treated overnight with 10 % triethylamine in petroleumether) with a petroleum ether – ethyl acetate mixture.

Method C. A solution of titanium(IV) chloride (1.0 M in CH_2Cl_2 or toluene, 3.0 mL, 3.00 mmol, 1 equiv) was added dropwise to a pre-cooled (0 ºC) solution of the ketone (3.00 mmol, 1 equiv) and *p*-anisidine (1.11 g, 9.00 mmol, 3 equiv) in anhydrous ether. The reaction was let to reflux overnight and after cooling to room temperature it was filtered and the solids were washed with anhydrous ether. The filtrate was then washed with a KOH solution (2.0 M, 15 mL) and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were dried over K_2CO_3 and evaporated. The crude mixture was purified on a silica gel column (15 g, treated overnight with 10 % triethylamine in petroleumether) with a petroleoum ether – triethylamine (99:1).

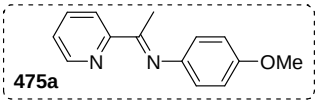
For yields and purification methods see Table 6.6, Table 6.7 and Table 6.8.

6.3.1. Imines with Heterocycles

Table 6.6. Preparation of *N*,*S*-heterocyclic Imines from the Corresponding Ketones

Method	**Ketone** ***p*-anisidine** ***p*-TsOH (mg) or $TiCl_4$ (mL)**	**SiO_2** **PE – EA**	**Imine**
A	561 µL, 606 mg, 5.00 mmol 770 mg, 6.25 mmol	25 mL 95:5	**475a** (1.03 g, 4.77 mmol, 95 %)
B	658 µL, 721 mg, 5.95 mmol 770 mg, 6.25 mmol 57 mg, 0.300 mmol	25 mL 60:40	**475b** (1.08 g, 4.82 mmol, 96 %)
B	**327** (250 mg, 1.22 mmol) 165 mg, 1.34 mmol 23 mg, 0.122 mmol	20 mL 100:0	**1475c** (~ 214 mg, 0.69 mmol, 57 %)
D	1.05 g, 4.00 mmol 542 mg, 4.40 mmol 76 mg, 0.400 mmol	Cryst. MeOH/ether (1:1)	**475z** (1.19 g, 3.23 mmol, 81 %)
A	521 µL, 636 mg, 5.00 mmol 770 mg, 6.25 mmol	25 mL 95:5	**475d** (1.10 g, 4.74 mmol, 95 %)
B	500 mg, 3.54 mmol 480 mg, 3.90 mmol 67 mg, 0.354 mmol	20 mL 97:3	**475e** (564 mg, 2.29 mmol, 65 %)
B	**334A** (1.48 g, 8.79 mmol) 1.19 g, 9.67 mmol 83 mg, 0.440 mmol	40 mL 99:1	**475f** (1.76 g, 6.46 mmol, 73 %)
B	**335** (800 mg, 4.37 mmol) 591 mg, 4.80 mmol 83 mg, 0.437 mmol	25 mL 99:1 (PE/Et_3N)	**475g** (964 mg, 3.34 mmol, 76 %)
B	**343** (349 mg, 1.75 mmol) 253 mg, 2.06 mmol 33 mg, 0.175 mmol	15 mL 99:1 → 97:3	**475h** (486 mg, 1.60 mmol, 91 %)
B	540 µL, 631 mg, 5.00 mmol 647 mg, 5.25 mmol 47 mg, 0.250 mmol	25 mL 100:0	**475i** (475 mg, 2.05 mmol, 41 %)

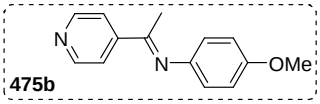
(*E*)-4-Methoxy-*N*-[1'-(pyridin-2"-yl)ethylidene]aniline (475a), $C_{14}H_{14}N_2O$, FW = 226.29



475a

475a: yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.82 (s, 3H), 6.78-6.82 (m, 2H), 6.91-6.94 (m, 2H), 7.34 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 7.77 (ddd, *J* = 8.0, 7.5, 1.8 Hz, 1H), 8.25 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H), 8.65 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H); **^{13}C NMR** δ 16.38 (CH_3), 55.50 (CH_3), 114.25 (2 × CH), 120.85 (2 × CH), 121.36 (CH), 124.66 (CH), 136.38 (CH), 144.32 (C), 148.52 (CH), 156.25 (C), 157.04 (C), 167.36 (C); **IR** ν 3001, 2952, 2834, 1636, 1504, 1241 cm^{-1}; **MS** (EI) *m/z* (%) 226 ($M^{\bullet+}$, 100), 211 (45), 185 (14), 148 (80), 123 (15), 108 (23), 92 (28); **HRMS** (EI) 226.1104 ($C_{14}H_{14}N_2O$ requires 226.1106).

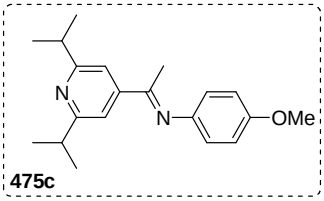
(*E*)-4-Methoxy-*N*-[1'-(pyridin-4"-yl)ethylidene]aniline (475b), $C_{14}H_{14}N_2O$, FW = 226.29



475b

475b: yellow crystals; **mp** 112-113 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.82 (s, 3H), 6.75-6.79 (m, 2H), 6.91-6.95 (m, 2H), 7.80 (dd, *J* = 4.6, 1.6 Hz, 2H), 7.77 (ddd, *J* = 8.0, 7.5, 1.8 Hz, 1H), 8.25 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H), 8.65 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H); **^{13}C NMR** δ 17.05 (CH_3), 55.51 (CH_3), 114.33 (2 × CH), 120.75 (2 × CH), 121.09 (2 × CH), 143.82 (C), 146.56 (C), 150.34 (2 × CH), 156.48 (C), 163.93 (C); **IR** ν 3019, 2965, 2837, 1634, 1597, 1504, 1216 cm^{-1}; **MS** (EI) *m/z* (%) 226 ($M^{\bullet+}$, 85), 211 (100), 148 (32), 92 (24); **HRMS** (EI) 226.1104 ($C_{14}H_{14}N_2O$ requires 226.1106).

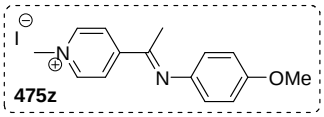
(*E*)-*N*-[1'-(2",6"-Di-*iso*-propylpyridin-4"-yl)ethylidene]-4-methoxyaniline (475c), $C_{20}H_{26}N_2O$, FW = 310.48



475c

475c: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.28 (d, *J* = 6.9 Hz, 12H), 2.58 (s, 3H), 3.08 (sept, *J* = 6.9 Hz, 2H), 6.67-6.67 (m, 2H), 6.82-6.85 (m, 2H), 7.37 (s, 2H). No further data provided as the imine was obtained only in a mixture with the corresponding ketone.

(*E*)-4-Methoxy-*N*-[1'-(1"-methylpyridinium-4"-yl)ethylidene]aniline iodide (475z), $C_{15}H_{17}N_2OI$, FW = 368.24

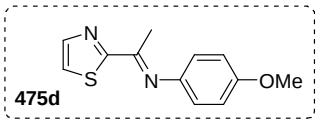


475z

475z: brown crystals; **mp** 158-160 ºC (MeOH/Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.85 (s, 3H), 4.63 (br s, 3H), 6.82-6.86 (m, 2H), 6.95-6.99 (m, 2H), 8.54 (d, *J* = 6.0 Hz, 2H), 9.25 (d, *J* = 6.0 Hz, 2H); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.39 (s, 3H), 2.78 (s, 3H), 4.39 (s, 3H), 6.91-6.95 (m, 2H), 7.00-7.04 (m, 2H), 8.54 (d, *J* = 6.4 Hz, 2H), 9.07 (d, *J* = 6.4 Hz, 2H); **^{13}C NMR** (DMSO-d_6) δ 17.18 (CH_3), 47.63 (CH_3), 55.27 (CH_3), 114.31 (2 × CH), 121.55 (2 × CH), 124.83 (2 × CH), 142.23 (C), 145.91 (2 × CH), 152.60 (C),

156.78 (C), 161.79 (C); **IR** (ATR) ν 3038, 2996, 1628, 1504, 1445, 1283 cm^{-1}; **MS** (FAB+/NOB) *m/z* (%) 241 ($M^{\bullet+}$, 100), 157 (17); **HRMS** (FAB+/NOB) 241.1340 ($C_{15}H_{17}N_2O$ requires 241.1341).

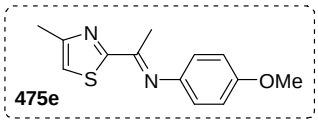
(*E*)-4-Methoxy-*N*-[1'-(thiazol-2"-yl)ethylidene]aniline (475d), $C_{12}H_{12}N_2OS$, FW = 232.32



475d

475d: yellow crystals; **mp** 44-45 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.82 (s, 3H), 6.83-6.87 (m, 2H), 6.90-6.94 (m, 2H), 7.45 (d, *J* = 3.2 Hz, 1H), 7.91 (d, *J* = 3.2 Hz, 1H); **^{13}C NMR** δ 16.81 (CH_3), 55.48 (CH_3), 114.21 (2 × CH), 121.50 (2 × CH), 122.86 (CH), 142.58 (C), 143.64 (CH), 156.77 (C), 161.30 (C), 170.92 (C); **IR** ν 3019, 2954, 2833, 1629, 1505, 1243, 1215 cm^{-1}; **MS** (EI) *m/z* (%) 232 ($M^{\bullet+}$, 100), 217 (60), 148 (53), 92 (38); **HRMS** (EI) 232.0668 ($C_{12}H_{12}N_2OS$ requires 232.0670).

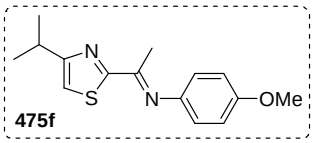
(*E*)-4-Methoxy-*N*-[1'-(4"-methythiazol-2"-yl)ethylidene]aniline (475e), $C_{13}H_{14}N_2OS$, FW = 246.35



475e

475e: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.50 (s, 3H), 3.81 (s, 3H), 6.81-6.84 (m, 2H), 6.89-6.92 (m, 2H), 6.99 (s, 1H); ^{13}C NMR δ 16.88 (CH_3), 17.37 (CH_3), 55.46 (CH_3), 114.17 (2 × CH), 117.60 (CH), 121.48 (2 × CH), 142.75 (C), 153.81 (C), 156.67 (C), 161.35 (C), 169.90 (C); **IR** ν 2954, 2923, 2834, 1626, 1504, 1455, 1365, 1244 cm^{-1}; **MS** (EI) *m/z* (%) 246 ($M^{\bullet+}$, 55), 231 (37), 148 (30); **HRMS** (EI) 246.0828 ($C_{13}H_{14}N_2OS$ requires 246.0827).

(*E*)-4-Methoxy-*N*-[1'-(4"-*iso*-propylthiazol-2"-yl)ethylidene]aniline (475f), $C_{14}H_{18}N_2OS$, FW = 274.41

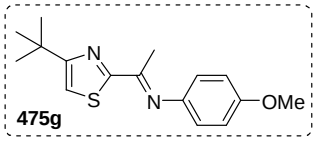


475f

475f: yellow oil; **mp** 44-45 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.9 Hz, 6H), 2.40 (s, 3H), 3.13 (sept d, *J* = 6.9, 0.8 Hz, 1H), 3.80 (s, 3H), 6.81-6.85 (m, 2H),

6.88-6.92 (m, 2H), 6.99 (d, J = 0.8 Hz, 1H); **^{13}C NMR** δ 16.76 (CH_3), 22.30 (2 × CH_3), 30.94 (CH), 55.29 (CH_3), 114.02 (2 × CH), 114.90 (CH), 121.32 (2 × CH), 142.71 (C), 156.46 (C), 161.59 (C), 164.59 (C), 169.54 (C); **IR** ν 2962, 2929, 2869, 2834, 1627, 1505, 1466, 1365, 1293, 1244 cm^{-1}; **MS** (EI) *m/z* (%) 274 ($M^{\bullet+}$, 100), 259 (52), 218 (15), 148 (50), 92 (15); **HRMS** (EI) 274.1136 ($C_{15}H_{18}N_2OS$ requires 274.1140).

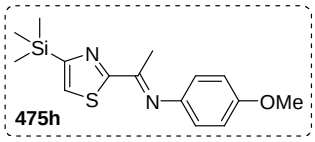
(*E*)-*N*-[1'-(4"-*tert*-Butylhiazol-2"-yl)ethylidene]-4-methoxyaniline (475g), $C_{16}H_{20}N_2OS$, FW = 288.44



475g

475g: yellow oil which solidified upon standing; **mp** 33-34 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.40 (s, 3H), 3.81 (s, 3H), 6.81-6.85 (m, 2H), 6.89-6.93 (m, 2H), 7.01 (s, 1H); ^{13}C NMR δ 16.83 (CH_3), 30.05 (3 × CH_3), 34.92 (C), 55.44 (CH_3), 114.18 (2 × CH), 114.23 (CH), 121.39 (2 × CH), 143.00 (C), 156.57 (C), 162.00 (C), 167.57 (C), 169.33 (C); **IR** ν 2959, 1628, 1505, 1364, 1295, 1243 cm^{-1}; **MS** (EI) *m/z* (%) 288 ($M^{\bullet+}$, 55), 273 (34), 148 (30); **HRMS** (EI) 288.1297 ($C_{16}H_{20}N_2OS$ requires 288.1296).

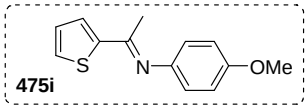
(*E*)-4-Methoxy-*N*-[1'-(4"-trimetylsilylthiazol-2"-yl)ethylidene]aniline (475h), $C_{15}H_{20}N_2OSSi$, FW = 304.52



475h

475h: colourless oil which solidified upon standing; **mp** 54-55 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.35 (s, 9H), 2.41 (s, 3H), 3.80 (s, 3H), 6.81-6.85 (m, 2H), 6.89-6.92 (m, 2H), 7.89 (s, 1H); **^{13}C NMR** δ –0.23 (3 × CH_3), 16.95 (CH_3), 55.37 (CH_3), 114.10 (2 × CH), 121.40 (2 × CH), 137.43 (C), 142.70 (C), 148.97 (CH), 156.64 (C), 161.28 (C), 174.85 (C); **IR** ν 3067, 2955, 2899, 2834, 1627, 1505, 1487, 1365, 1290, 1244 cm^{-1}; **MS** (EI) *m/z* (%) 304 ($M^{\bullet+}$, 100), 303 (80), 148 (32); **HRMS** (EI) 304.1070 ($C_{15}H_{20}N_2OSSi$ requires 304.1066).

(*E*)-4-Methoxy-*N*-[1'-(thiophen-2"-yl)ethylidene]aniline (475i), $C_{13}H_{13}NOS$, FW = 231.33

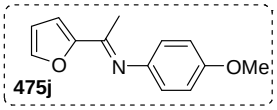


475i: yellow crystals; **mp** 77-78 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 3.81 (s, 3H), 6.76-6.80 (m, 2H), 6.88-6.91 (m, 2H), 7.09 (dd, *J* = 5.1, 3.7 Hz, 1H), 7.44 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.46 (dd, *J* = 3.7, 1.1 Hz, 1H); **^{13}C NMR** δ 17.39 (CH_3), 55.49 (CH_3), 114.14 (2 × CH), 121.42 (2 × CH), 127.44 (CH), 128.26 (CH), 129.71 (CH), 143.71 (C), 146.78 (C), 156.16 (C), 160.47 (C); **IR** ν 3009, 2961, 2837, 1617, 1502, 1428, 1239, 1241, 1206 cm^{-1}; **MS** (EI) *m/z* (%) 231 ($M^{\bullet+}$, 95), 216 (100), 201 (20), 173 (20), 92 (25); **HRMS** (EI) 231.0717 ($C_{13}H_{13}NOS$ requires 231.0718).

Table 6.7. Preparation of *O*,*N*-heterocyclic Imines from the Corresponding Ketones

Method	**Ketone** ***p*-anisidine** ***p*-TsOH (mg) or $TiCl_4$ (mL)**	**SiO_2** **PE – EA**	**Imine**
B	550 mg, 5.00 mmol 647 mg, 5.25 mmol 47 mg, 0.250 mmol	25 mL 98:2	**475j** (838 mg, 3.89 mmol, 78%)
A	349 µL, 373 mg, 3.00 mmol 462 mg, 3.75 mmol	25 mL 98:2	**475k** (507 mg, 2.211 mmol, 74 %)
A	**353b** (150 mg, 1.10 mmol) 170 mg, 1.38 mmol Heating to 50 ºC	25 mL 90:10	Amino Ketone **477** (217 mg, 0.837 mmol 76 %)
A	**344** (250 mg, 1.30 mmol) 200 mg, 1.63 mmol	25 mL 98:2	**475l** (275 mg, 0.566 mmol, 74 %)
A	**346** (182 mg, 1.00 mmol) 154 mg, 1.25 mmol	40 mL 97:3	**475m** (206 mg, 0.712 mmol, 72 %)
B	300 mg, 2.17 mmol 334 mg, 2.71 mmol 21 mg, 0.109 mmol	25 mL 99:1 (PE:Et_3N)	**475n** (~ 52 mg, 0.214 mmol, 10 %)
A	**353a** (160 mg, 1.45 mmol) 224 mg, 1.82 mmol	10 mL 85:15	**475o** (97 mg, 0.451 mmol, 31 %)
A	399 µL, 415 mg, 3.00 mmol 462 mg, 3.75 mmol	25 mL 99:1	**475p** (292 mg, 1.200 mmol, 40 %)
A	481 mg, 3.00 mmol 462 mg, 3.75 mmol	25 mL 90:10	**475q** (590 mg, 2.224 mmol, 74 %)
B	**353d** (300 mg,1.87 mmol) 254 mg, 2.06 mmol 18 mg, 0.094 mmol	30 mL 100:0 → 97:3	**475r** (282 mg, 1.06 mmol, 57 %)
B	**352** (200 mg, 1.16 mmol) 144 mg, 1.17 mmol 22 mg, 0.116 mmol	25 mL 97:3	**475s** (194 mg, 0.70 mmol, 56 %)
B	866 mg, 5.00 mmol 647 mg, 5.25 mmol 47 mg, 0.250 mmol	Cryst. DCM	**475t** (528 mg, 1.900 mmol, 38 %)

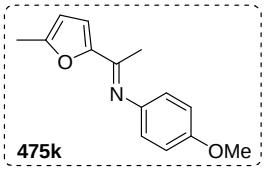
(*E*)-*N*-[1'-(Furan-2"-yl)ethylidene]-4-methoxyaniline (475j), $C_{13}H_{13}NO_2$, FW = 215.26



475j

475j: yellow crystals; **mp** 82-83 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 3.81 (s, 3H), 6.51 (dd, *J* = 3.4, 1.7 Hz, 1H), 6.78-6.81 (m, 2H), 6.87-6.90 (m, 2H), 6.92 (d, *J* = 3.4 Hz, 1H), 7.55-7.56 (m, 1H); **^{13}C NMR** δ 14.62 (CH_3), 55.56 (CH_3), 109.82 (CH), 111.01 (CH), 112.21 (2 × CH), 119.51 (2 × CH), 141.68 (C), 142.82 (CH), 151.86 (C), 154.26 (C), 154.64 (C); **IR** ν 3019, 2964, 2837, 2400, 1625, 1504, 1482, 1239, 1214 cm^{-1}; **MS** (EI) *m/z* (%) 215 ($M^{\bullet+}$, 75), 200 (100); **HRMS** (EI) 215.0948 ($C_{13}H_{13}NO_2$ requires 215.0946).

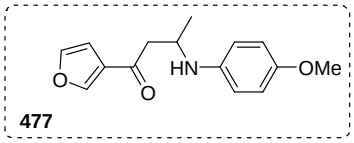
(*E*)-4-Methoxy-*N*-[1'-(5"-methylfuran-2"-yl)ethylidene]aniline (475k), $C_{14}H_{15}NO_2$, FW = 229.30



475k

475k: yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.39-2.40 (m, 3H), 3.79 (s, 3H), 6.10 (dq, *J* = 3.3, 0.9 Hz, 1H), 6.75-6.79 (m, 2H), 6.79 (br d, *J* = 3.4 Hz, 1H), 6.85-6.89 (m, 2H); **^{13}C NMR** δ 14.09 (CH_3), 16.37 (CH_3), 55.43 (CH_3), 108.15 (CH), 114.03 (2 × CH), 114.86 (CH), 121.42 (2 × CH), 143.95 (C), 152.18 (C), 155.58 (C), 155.96 (C), 156.35 (C); **IR** ν 2956, 1621, 1501, 1242, 1217 cm^{-1}; **MS** (EI) *m/z* (%) 229 ($M^{\bullet+}$, 76), 214 (100), 186 (12); **HRMS** (EI) 229.1101 ($C_{14}H_{15}NO_2$ requires 229.1103).

1-(Furan-3'-yl)-3-(4"-methoxyanilino)butan-1-one (477), $C_{15}H_{17}NO_3$, FW = 259.33

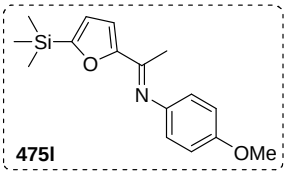


477

477 prepared according to imination Method A or B (224 mg, 0.864 mmol, 76 %): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, *J* = 6.4 Hz, 3H), 2.77 (dd, *J* = 15.6, 7.4 Hz, 1H), 3.05 (dd, *J* = 15.6, 4.5 Hz, 1H), 3.48 (br s, 1H), 3.99 (dqd, *J* = 13.7, 6.5, 4.6 Hz, 1H), 6.59-6.63 (m, 2H), 7.76-7.80 (m, 2H), 6.75 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.42 (dd, *J* = 1.8, 1.6 Hz, 1H), 7.97 (dd, *J* = 1.3, 0.9 Hz, 1H); ^{13}C NMR δ 45.39 (CH_2), 108.72 (CH), 114.84 (2 × CH), 115.47 (2 × CH), 128.38 (C), 140.96 (C), 144.35 (CH), 147.44 (CH), 152.45 (CH),

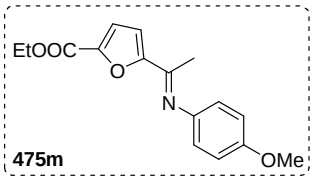
194.03 (C); IR ν 3360, 2961, 2832, 1670, 1511, 1155 cm^{-1}; MS (CI/isobutane) *m/z* (%) 260 [$(M+H)^+$, 100], 176 (21), 150 (70), 138 (26); HRMS (CI/isobutane) 260.1284 ($C_{15}H_{18}NO_3$ requires 260.1287).

(*E*)-4-Methoxy-*N*-[1'-(5"-trimetylsilylfuran-2"-yl)ethylidene]aniline (475l), $C_{16}H_{21}NO_2Si$, FW = 287.56



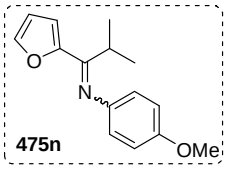
475l: yellow crystals: **mp** 65-66 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.31 (s, 9H), 2.18 (s, 3H), 3.81 (s, 3H), 6.71 (d, *J* = 3.4 Hz, 1H), 6.75-6.79 (m, 2H), 6.87-6.91 (m, 2H), 6.97 (d, *J* = 3.4 Hz, 1H); **^{13}C NMR** δ –1.62 (3 × CH_3), 16.74 (CH_3), 55.41 (CH_3), 112.09 (CH), 114.05 (2 × CH), 121.25 (2 × CH), 121.46 (CH), 155.98 (C), 155.98 (C), 157.49 (C), 158.04 (C), 163.44 (C); **IR** ν 3019, 2959, 1623, 1504, 1241, 1215 cm^{-1}; **MS** (EI) *m/z* (%) 287 ($M^{\bullet+}$, 83), 272 (100), 170 (47); **HRMS** (EI) 287.1341 ($C_{16}H_{21}NO_2Si$ requires 287.1342).

Ethyl (*E*)-5-[1'-(4"-methoxyphenylimino)ethyl]furan-2-carboxylate (475m), $C_{16}H_{17}NO_4$, FW = 287.34



475m: yellow crystals; **mp** 69-70 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.1 Hz, 3H), 2.23 (s, 3H), 3.78 (s, 3H), 4.36 (q, *J* = 7.1 Hz, 2H), 6.74-6.78 (m, 2H), 6.86-6.90 (m, 2H), 7.04 (d, *J* = 3.6 Hz, 1H), 7.22 (d, *J* = 3.6 Hz, 1H); **^{13}C NMR** δ 13.30 (CH_3), 15.49 (CH_3), 54.39 (CH_3), 60.18 (CH_2), 111.33 (CH), 113.17 (2 × CH), 118.09 (CH), 120.24 (2 × CH), 142.09 (C), 144.28 (C), 155.49 (C), 155.85 (C), 155.92 (C), 157.53 (C); **IR** ν 3019, 1718, 1627, 1502, 1291, 1242, 1225 cm^{-1}; **MS** (EI) *m/z* (%) 287 ($M^{\bullet+}$, 100), 272 (87), 244 (32), 199 (17), 148 (17), 92 (23), 86 (20), 84 (32); **HRMS** (EI) 287.1161 ($C_{16}H_{17}NO_4$ requires 287.1158).

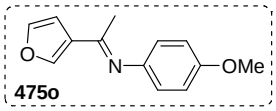
***N*-[1'-(Furan-2"-yl)-2'-methylprop-1'-ylidene]-4-methoxyaniline (475n), $C_{15}H_{17}NO_2$, FW = 243.33**



475n

475n: **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*/*Z*) isomers in ratio ca. 11:5, the minor one is marked *) δ 1.27 (d, *J* = 6.9 Hz, 8.7H), 3.16* (sept, *J* = 7.1 Hz, 0.45H), 3.40 (sept, *J* = 6.8 Hz, 1H), 3.79 (s, 4.35H), 5.67 (dd, *J* = 3.6, 0.6 Hz, 1H), 6.21 (dd, *J* = 3.6, 1.7 Hz, 1H), 6.49* (dd, *J* = 3.5, 1.8 Hz, 0.45H), 6.60-6.64 (m, 2H), 6.69-6.73* (m, 0.9H), 6.85-6.89 (m, 2H), 7.32-7.36* (m, 0.9H), 6.99* (dd, *J* = 3.5, 0.7 Hz, 0.45H), 7.31 (dd, *J* = 1.7, 0.6 Hz, 1H), 7.53* (dd, *J* = 1.8, 0.7 Hz, 0.45H). No further data provided as the imine was obtained only in a mixture with the corresponding ketone.

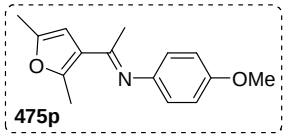
(*E*)-*N*-[1'-(Furan-3"-yl)ethylidene]-4-methoxyaniline (475o), $C_{13}H_{13}NO_2$, FW = 215.27



475o

475o: pale yellow crystals; **mp** 54-55 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 3.79 (s, 3H), 6.72-6.76 (m, 2H), 6.87-6.91 (m, 2H), 6.92 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.44 (dd, *J* = 1.7, 1.7 Hz, 1H), 7.83 (dd, *J* = 1.4, 0.8 Hz, 1H); **^{13}C NMR** δ 16.90 (CH_3), 54.46 (CH_3), 107.63 (CH), 113.17 (2 × CH), 119.97 (2 × CH), 128.11 (C), 142.73 (CH), 142.80 (CH), 143.08 (C), 154.97 (C), 158.67 (C), 160.85 (C); **IR** ν 2961, 1629, 1501, 1241, 1218 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 216 [$(M+H)^+$, 100], 85 (18); **HRMS** (CI/isobutane) 216.1026 ($C_{13}H_{14}NO_2$ requires 216.1025).

(*E*)-*N*-[1'-(2",5"-Dimethylfuran-3"-yl)ethylidene]-4-methoxyaniline (475p), $C_{15}H_{17}NO_2$, FW = 243.33

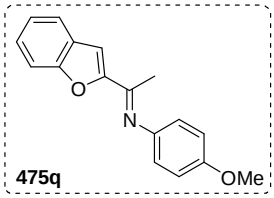


475p

475p: pale yellow crystals; **mp** 49-50 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.27 (br s, 3H), 2.56 (s, 3H), 3.79 (s, 3H), 6.24 (br s, 1H), 6.69-6.73 (m, 2H), 6.86-6.90 (m, 2H); **^{13}C NMR** δ 12.23 (CH_3), 13.42 (CH_3), 18.09 (CH_3), 54.43 (CH_3), 105.14 (CH), 113.14 (2 × CH), 119.91 (2 × CH), 121.67 (C), 143.77 (C), 148.35 (C), 150.39 (C), 154.65 (C), 160.85 (C); **IR** ν 3018, 1611, 1503, 1241, 1216 cm^{-1}; **MS** (EI) *m/z* (%) 243

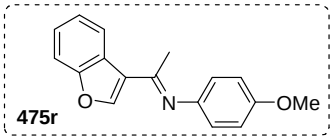
($M^{\bullet+}$, 26), 228 (25), 87 (27), 85 (100); **HRMS** (EI) 243.1256 ($C_{15}H_{17}NO_2$ requires 243.1259).

(*E*)-*N*-[1'-(Benzofuran-2"-yl)ethylidene]-4-methoxyaniline (475q), $C_{17}H_{15}NO_2$, FW = 265.33



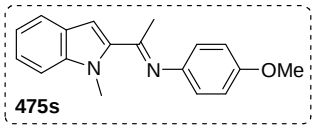
475q: yellow crystals; **mp** 119-120 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.28(s, 3H), 3.80 (s, 3H), 6.82-6.86 (m, 2H), 6.90-6.94 (m, 2H), 7.25 (d, *J* = 0.9 Hz, 1H), 7.30 (ddd, *J* = 7.8, 7.3, 1.0 Hz, 1H), 7.38 (ddd, *J* = 8.3, 7.3, 1.3 Hz, 1H), 7.60 (ddd, *J* = 8.3, 1.7, 1.0 Hz, 1H), 7.64 (ddd, *J* = 7.8, 1.3, 0.7 Hz, 1H); **^{13}C NMR** δ 16.81 (CH_3), 55.46 (CH_3), 109.49 (CH), 112.16 (CH), 114.14 (2 × CH), 121.39 (2 × CH), 122.05 (CH), 123.35 (CH), 126.49 (CH), 127.94 (C), 143.45 (C), 154.78 (C), 155.53 (C), 156.40 (C), 157.20 (C); **IR** ν 3019, 2982, 1619, 1503, 1244, 1215 cm^{-1}; **MS** (EI) *m/z* (%) 265 ($M^{\bullet+}$, 76), 250 (100), 181 (10), 115 (13), 92 (12); **HRMS** (EI) 265.1105 ($C_{17}H_{15}NO_2$ requires 265.1103).

(*E*)-*N*-[1'-(Benzofuran-3"-yl)ethylidene]-4-methoxyaniline (475r), $C_{17}H_{15}NO_2$, FW = 265.33



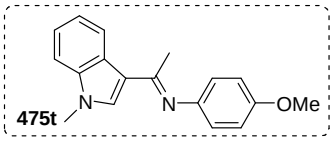
475r: yellow crystals; **mp** 101-102 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.82 (s, 3H), 6.82-6.86 (m, 2H), 6.90-6.94 (m, 2H), 7.25-7.29 (m, 2H), 7.38 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.60 (dd, *J* = 8.3, 0.7 Hz, 1H), 7.65 (br d, *J* = 7.7 Hz, 1H); **^{13}C NMR** δ 16.75 (CH_3), 55.45 (CH_3), 109.32 (CH), 112.12 (CH), 114.15 (2 × CH), 121.32 (2 × CH), 122.00 (CH), 123.31 (CH), 126.42 (CH), 127.95 (C), 143.49 (C), 154.84 (C), 155.53 (C), 156.41 (C), 157.16 (C); **IR** ν 3023, 2982, 2962, 1619, 1502, 1450, 1217 cm^{-1}; **MS** (EI) *m/z* (%) 265 ($M^{\bullet+}$, 80), 250 (100), 115 (15), 85 (53), 84 (28), 83 (82); **HRMS** (EI) 265.1101 ($C_{17}H_{15}NO_2$ requires 265.1103).

(*E*)-4-Methoxy-*N*-[1'-(1"-methyl-1*H*-indol-2"-yl)ethylidene]aniline (475s), $C_{18}H_{18}N_2O$, FW = 278.38



475s: yellowish crystals; **mp** 143-144 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.80 (s, 3H), 4.14 (s, 3H), 6.74-6.78 (m, 2H), 6.89-6.93 (m, 2H), 6.99 (d, *J* = 0.7 Hz, 1H), 7.12 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 7.30 (ddd, *J* = 8.4, 6.9, 1.1 Hz, 1H), 7.37 (ddd, *J* = 8.4, 0.7 Hz, 1H), 7.64 (dd, *J* = 7.9, 0.8 Hz, 1H); **^{13}C NMR** δ 18.62 (CH_3), 32.98 (CH_3), 55.56 (CH_3), 107.37 (CH), 110.03 (CH), 114.31 (2 × CH), 120.02 (CH), 120.85 (2 × CH), 121.57 (CH), 123.92 (CH), 126.49 (C), 137.70 (C), 140.01 (C), 144.28 (C), 156.02 (C), 160.23 (C); **IR** ν 3019, 2945, 1621, 1500, 1465, 1391, 1240, 1217 cm^{-1}; **MS** (EI) *m/z* (%) 278 ($M^{\bullet+}$, 50), 263 (12), 171 (10), 121 (54); **HRMS** (EI) 278.1417 ($C_{18}H_{18}N_2O$ requires 278.1419).

(*E*)-4-Methoxy-*N*-[1'-(1"-methyl-1*H*-indol-3"-yl)ethylidene]aniline (475t), $C_{18}H_{18}N_2O$, FW = 278.38



475t: pale yellow crystals; **mp** 222-223 ºC (CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.86 (s, 3H), 3.98 (s, 3H), 6.83-6.87 (m, 2H), 6.93-6.97 (m, 2H), 7.28 (ddd, *J* = 7.9, 6.7, 1.4 Hz, 1H), 7.34 (ddd, *J* = 8.0, 6.7, 1.3 Hz, 1H), 7.37 (ddd, *J* = 8.0, 1.4, 0.8 Hz, 1H), 7.53 (s, 1H), 8.61 (ddd, *J* = 7.8, 1.2, 0.8 Hz, 1H); **^{13}C NMR** δ 18.00 (CH_3), 33.24 (CH_3), 55.56 (CH_3), 109.21 (CH), 114.11 (2 × CH), 117.12 (C), 121.34 (2 × CH), 121.41 (CH), 122.80 (CH), 123.41 (CH), 126.17 (C), 131.86 (CH), 137.78 (C), 145.47 (C), 155.43 (C), 161.76 (C); **IR** ν 3019, 2927, 2830, 1658, 1602, 1535, 1498, 1466, 1372, 1216 cm^{-1}; **MS** (EI) *m/z* (%) 278 ($M^{\bullet+}$, 65), 263 (100), 220 (10), 85 (37), 83 (59); **HRMS** (EI) 278.1417 ($C_{18}H_{18}N_2O$ requires 278.1419).

6.3.2. Imines without Heterocycles

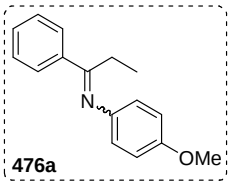
Table 6.8. Preparation of Aryl-alkyl and Dialkyl Imines

Method	**Ketone** ***p*-anisidine** ***p*-TsOH (mg) or $TiCl_4$ (mL)**	**SiO_2** **PE – EA**	**Imine**
A	671 µL, 671 mg, 5.00 mmol 770 mg, 6.25 mmol	25 mL 100:1	**476a** (571 mg, 2.39 mmol, 48 %)
B	**353f** (700 mg, 4.72 mmol) 727 mg, 5.90 mmol 89 mg, 0.472 mmol	20 mL 100:0	**476b** (345 mg, 1.36 mmol, 29 %)
C	500 mg, 3.42 mmol 1.26 g, 10.26 mmol 3.4 mL, 3.42 mmol	30 mL 100:0	**476c** (448 mg, 1.78 mmol, 52 %)
C	500 mg, 3.12 mmol 1.15 g, 9.36 mmol 3.1 mL, 3.12 mmol	30 mL 100:0	**476d** (524 mg, 1.98 mmol, 63 %)
C	395 mg, 2.10 mmol 775 mg, 6.29 mmol 2.1 mL, 2.10 mmol	30 mL 100:0	**476e** (325 mg, 1.11 mmol, 53 %)
C	517µL, 500 mg, 3.08 mmol 1.19 g, 9.65 mmol 3.1 mL, 3.08 mmol	15 mL 100:0	**476f** (560 mg, 2.09 mmol, 68 %)
C	1.04 mL, 832 mg, 8.27 mmol 3.06 g, 24.8 mmol 8.3 mL, 8.27 mmol	25 mL 100:0	**476i** (1.28 g, 6.23 mmol, 75 %)
C	**474** (500 mg, 1.78 mmol) 659 mg, 5.35 mmol 1.8 mL, 1.78 mmol	30 mL 85:15 (PE:DCM)	**476j** (476 mg, 1.24 mmol, 69 %)
A	400 µL, 439 mg, 3.00 mmol 462 mg, 3.75 mmol	40 mL 98:2	**476k** (517 mg, 2.057 mmol, 69 %)
B	750 µL, 691 mg, 5.00 mmol 677 mg, 5.50 mmol 95 mg, 0.500 mmol	30 mL 99:1 → 95:5	**476l** (809 mg, 3.32 mmol, 66 %)
B	**459** (1.00 g, 5.20 mmol) 705 mg, 5.72 mmol 49 mg, 0.260 mmol	35 mL 100:0 → 95:5	**476m** (921 mg, 3.10 mmol, 60 %)
A	630 mg, 3.62 mmol 557 mg, 5.19 mmol	25 mL 98:2	**476n** (157 mg, 0.562 mmol, 16 %)
B	390 mg, 1.905 mmol 246 mg, 2.000 mmol 18 mg, 0.095 mmol	60 mL 100:0	**476o** (237 mg, 0.761 mmol, 40 %)
A	500 mg, 2.45 mmol 377 mg, 3.06 mmol 19 mg, 0.104 mmol	40 mL 100:0	**476p** (287 mg, 0.93 mmol, 38 %)
B	500 mg, 2.68 mmol 340 mg, 2.76 mmol 25 mg, 0.134 mmol	25 mL 100:0	**476q** (573 mg, 1.940 mmol, 72 %)
C	**464** (500 mg, 3.12 mmol) 1.15 g, 9.36 mmol 3.1 mL, 3.12 mmol	25 mL 100:0 → 97:3	**476s** (185 mg, 0.697 mmol, 22 %)
B	430 mg, 1.89 mmol 255 mg, 2.07 mmol 18 mg, 0.0943 mmol	20 mL 85:15 (PE:DCM)	**476t** (~ 200 mg, 0.600 mmol, 32 %)
A	521 mg, 2.50 mmol 385 mg, 3.13 mmol	40 mL 90:10	**476u** (306 mg, 0.976 mmol, 39 %)

Table 6.8. – Cont. Preparation of Aryl-alkyl and Dialkyl Imines

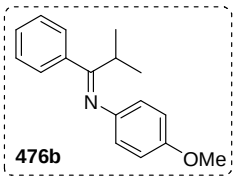
Method	**Ketone** ***p*-anisidine** ***p*-TsOH (mg) or $TiCl_4$ (mL)**	**SiO_2** **PE – EA**	**Imine**
B	1.05 g, 5.00 mmol 647 mg, 5.25 mmol 47 mg, 0.250 mmol	25 mL 100:0	**476v** (433 mg, 1.373 mmol, 27 %)
B	**463** (501 mg, 2.00 mmol) 308 mg, 2.50 mmol 19 mg, 0.104 mmol	20 mL 95:5	**476w** (644 mg, 1.75 mmol, 87 %)

(*E*)-4-Methoxy-*N*-(1'-phenylprop-1'-ylidene)aniline (476a), $C_{16}H_{17}NO$, FW = 239.33



476a:[222] yellow crystals; **mp** 104-105 ºC (hexane) [lit.[222] gives 101-102 ºC (MeOH)]; **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*/Z) isomers in ca. 10:1 ratio, the minor one is marked *) δ 1.09 (t, *J* = 7.7 Hz, 3H), 1.22* (t, *J* = 7.4 Hz, 0.3H), 2.69 (q, *J* = 7.7 Hz, 2H), 2.78* (t, *J* = 7.4 Hz, 0.2H), 3.71* (s, 0.3H), 3.82 (s, 3H), 6.55-6.59* (m, 0.2H), 6.64-6.68* (m, 0.2H), 6.73-6.77 (m, 2H), 6.89-6.93 (m, 2H), 7.04-7.07* (m, 0.2H), 7.21-7.23* (m, 0.3H), 7.44-7.46 (m, 3H), 7.90-7.93 (m, 2H); **^{13}C NMR** δ 11.01* (CH_3), 12.92 (CH_3), 23.28 (CH_2), 34.60* (CH_2), 55.29* (CH_3), 55.50 (CH_3), 113.74* (2 × CH), 114.29 (2 × CH), 120.29 (2 × CH), 122.29* (2 × CH), 127.58 (2 × CH), 127.85* (2 × CH), 128.11* (2 × CH), 128.21* (CH), 128.51 (2 × CH), 130.26 (CH), 138.08* (C), 138.29 (C), 144.10* (C), 144.86 (C), 155.58* (C), 155.77 (C), 171.37 (C), 173.06* (C); **IR** ν 3017, 2979, 2835, 1626, 1503, 1240, 1216 cm^{-1}; **MS** (EI) *m/z* (%) 239 ($M^{\bullet+}$, 44), 210 (100), 195 (12), 167 (13), 92 (18); **HRMS** (EI) 239.1307 ($C_{16}H_{17}NO$ requires 239.1310).

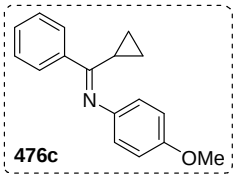
(*E*)-4-Methoxy-*N*-(2'-methyl-1'-phenylprop-1'-ylidene)aniline (476b), $C_{17}H_{19}NO$, FW = 253.37



476b: yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*/*Z*) isomers in ratio ca. 7:1, the minor one is marked *) δ 1.07* (d, *J* = 7.1 Hz, 0.9H), 1.13 (d, *J* = 6.8 Hz, 6H), 2.93 (sept, *J* = 6.8 Hz, 1H), 3.10* (sept, *J* = 7.1 Hz, 0.15H), 3.58 (s, 3H), 3.71* (s, 0.45), 6.43-6.47 (m, 2H), 6.53-6.56 (m, 2H), 6.65-6.69* (m, 0.30H), 6.79-6.83* (m, 2H), 6.91-6.93 (m,

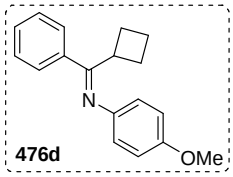
2H), 7.07-7.15 (m, 3H), 7.30-7.32 (m, 0.45H), 7.55-7.59 (m, 2H); **^{13}C NMR** δ 20.17 (2 × CH_3), 20.88* (2 × CH_3), 31.62* (CH), 38.45 (CH), 55.14 (CH_3), 55.35* (CH_3), 113.52 (2 × CH), 114.14* (2 × CH), 119.88* (2 × CH), 121.95 (2 × CH), 127.77 (3 × CH), 127.83 (4 × CH), 128.86* (3 × CH), 138.10 (C), 139.22* (C), 144.07* (C), 144.19 (C), 155.29 (C), 155.56* (C), 176.59* (C), 176.64 (C); **IR** ν 3056, 2967, 2832, 2834, 1633, 1503, 1464, 1442, 1290, 1241 cm^{-1}; **MS** (EI) *m/z* (%) 253 ($M^{\bullet+}$, 20), 210 (100), 167 (10), 106 (33), 91 (54); **HRMS** (EI) 253.1464 ($C_{17}H_{19}NO$ requires 253.1467).

(*E*)-*N*-[Cyclopropyl(phenyl)methylene]-4-methoxyaniline (476c), $C_{17}H_{17}NO$, FW = 251.35



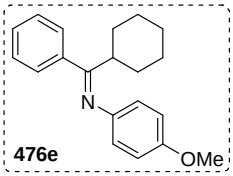
476c:[223] yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*/*Z*) isomers in ratio ca. 5:3, the minor one is marked *) δ 0.58* (ddd, *J* = 6.2, 5.8, 4.6 Hz, 1.2H), 0.82 (ddd, *J* = 8.6, 6.6, 4.6 Hz, 2H), 0.98 (ddd, *J* = 8.1, 6.5, 3.6 Hz, 2H), 1.16* (ddd, *J* = 6.3, 4.8, 3.5 Hz, 1.2H), 1.89* (tt, *J* = 8.6, 5.7 Hz, 0.6H), 1.99 (tt, *J* = 8.1, 4.8 Hz, 1H), 3.69 (s, 3H), 3.82* (s, 1.8H), 6.52-6.55 (m, 2H), 6.63-6.67 (m, 2H), 6.89-6.93* (m, 1.2H), 6.94-6.97* (m, 1.2H), 7.14-7.18 (m, 2H), 7.20-7.24 (m, 3H), 7.38-7.42* (m, 1.8H), 7.74-7.78 (m, 1.2H); **^{13}C NMR** δ 7.98 (2 × CH_2), 79.36 (2 × CH_2), 13.90* (CH), 20.19 (CH), 55.27 (CH_3), 55.44* (CH_3), 113.76 (2 × CH), 114.00* (2 × CH), 121.60* (2 × CH), 122.21* (2 × CH), 127.93* (2 × CH), 127.97 (2 × CH), 128.02* (2 × CH), 128.10 (2 × CH), 128.23 (CH), 129.25* (CH), 138.16 (C), 138.79* (C), 144.03* (C), 144.20 (C), 155.46 (C), 155.99* (C), 170.68 (C), 172.58* (C); **IR** ν 3056, 3001, 2968, 2833, 1627, 1576, 1503, 1443, 1381, 1289, 1241 cm^{-1}; **MS** (EI) *m/z* (%) 251 ($M^{\bullet+}$, 100), 250 (27), 236 (30), 212 (28), 210 (50), 174 (12), 128 (15), 92 (15); **HRMS** (EI) 251.1307 ($C_{17}H_{17}NO$ requires 251.1310).

(*E*)-*N*-[Cyclobutyl(phenyl)methylene]-4-methoxyaniline (476d), $C_{18}H_{19}NO$, FW = 265.38



476d: yellow crystals; **mp** 43-44 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*/*Z*) isomers in ratio ca. 5:3, the minor one is marked *) δ 1.48-1.56* (m, 0.6H), 1.67-1.79* (m, 0.6H), 1.81-2.06 (m, 4.4H), 2.17-2.24 (m, 2H), 2.36-2.46 (m, 2H), 3.64 (ttd, *J* = 8.2, 8.2, 1.0 Hz, 1H), 3.69 (s, 3H), 3.79 (s, 1.8H), 3.80-3.90* (m, 0.6H), 6.59-6.62 (m, 2H), 6.65-6.69 (m, 2H), 6.79-6.83* (m, 1.2H), 6.85-6.89* (m, 1.2H), 7.00-7.05 (m, 2H), 7.17-7.21 (m, 3H), 7.38-7.43* (m, 1.8H), 7.67-7.69* (m, 1.2H); **^{13}C NMR** δ 17.73 (CH_2), 18.34* (CH_2), 26.55 (2 × CH_2), 29.16* (2 × CH_2), 39.44* (CH), 44.16 (CH), 55.23 (CH_3), 55.40* (CH_3), 113.74 (2 × CH), 113.88* (2 × CH), 120.78* (2 × CH), 122.55 (2 × CH), 127.50* (2 × CH), 127.78 (2 × CH), 128.01 (2 × CH), 128.05* (2 × CH), 128.08 (CH), 129.17 (CH), 137.50 (C), 139.88* (C), 143.95* (C), 144.23 (C), 155.60 (C), 155.93* (C), 172.97* (C), 173.47 (C); **IR** ν 3056, 2944, 2866, 2833, 1630, 1502, 1442, 1289, 1241 cm^{-1}; **MS** (EI) *m/z* (%) 265 ($M^{\bullet+}$, 59), 250 (15), 236 (12), 210 (100), 134 (12), 115 (15), 92 (20); **HRMS** (EI) 265.1464 ($C_{18}H_{19}NO$ requires 265.1467).

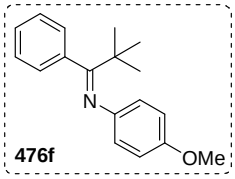
(*E*)-*N*-[Cyclohexyl(phenyl)methylene]-4-methoxyaniline (476e), $C_{20}H_{23}NO$, FW = 293.44



476e: yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*/*Z*) isomers in ratio ca. 10:1, the minor one is marked *) δ 0.98-1.10* (m, 0.3H), 1.12-1.27 (m, 3H), 1.34-1.42 (m, 2H), 1.57-1.61 (m, 1H), 1.70-1.74 (m, 2H), 1.82-1.86 (m, 2H), 1.41-1.64* (m, 0.7H), 2.57 (dddd, *J* = 11.4, 11.4, 3.3, 3.3 Hz, 1H), 2.75* (dddd, *J* = 12.2, 12.2, 3.1, 3.1 Hz, 0.1H), 3.53 (s, 3H), 3.68* (s, 0.3H), 6.41-6.45 (m, 2H), 6.49-6.53 (m, 2H), 6.63-6.66* (m, 0.2H), 6.77-6.80* (m, 0.2H), 6.69-6.91 (m, 2H), 7.04-7.10 (m, 3H), 7.26-7.28* (m, 0.3H), 7.48-7.50* (m, 0.2H); **^{13}C NMR** δ 22.66* (2 × CH_2), 25.97* (CH_2), 26.01* (2 × CH_2), 26.29 (CH_2), 26.31 (2 × CH_2), 30.65 (2 × CH_2), 30.92* (2 × CH_2), 43.15* (CH), 48.52 (CH), 55.18 (CH_3), 55.38* (CH_3), 113.63 (2 × CH), 114.20* (2 × CH), 120.05* (2 × CH), 121.95

(2 × CH), 127.75 (CH), 127.77 (4 × CH), 127.83 (4 × CH), 128.64* (CH), 138.44 (C), 140.40* (C), 144.07* (C), 144.39 (C), 155.43 (C), 155.67* (C), 176.03 (C), 176.20* (C); **IR** ν 2930, 2852, 1635, 1503, 1445, 1290, 1241 cm^{-1}; **MS** (EI) *m/z* (%) 293 ($M^{\bullet+}$, 55), 292 (25), 238 (48), 210 (100), 92 (26); **HRMS** (EI) 293.1778 ($C_{20}H_{23}NO$ requires 293.1780).

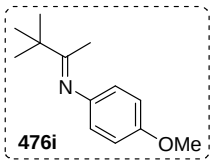
***N*-(2',2'-Dimethyl-1'-phenylprop-1'-ylidene)-4-methoxyaniline (476f), $C_{18}H_{21}NO$, FW = 267.40**



476f

476f:[189] colourless crystals; **mp** 53-54 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 3.64 (s, 3H), 6.46-6.50 (m, 2H), 6.57-6.60 (m, 2H), 6.90-6.93 (m, 1H), 7.11-7.20 (m, 3H); **^{13}C NMR** δ 28.56 (3 × CH_3), 40.45 (C), 55.20 (CH_3), 113.41 (2 × CH), 121.49 (2 × CH), 127.16 (CH), 127.39 (2 × CH), 127.98 (2 × CH), 137.40 (C), 144.54 (C), 155.09 (C), 180.15(C); **IR** ν 3046, 2955, 2930, 2905, 2867, 2833, 1640, 1503, 1461, 1390, 1361, 1291 cm^{-1}; **MS** (EI) *m/z* (%) 267 ($M^{\bullet+}$, 20), 210 (100); **HRMS** (EI) 267.1621 ($C_{18}H_{21}NO$ requires 267.1623).

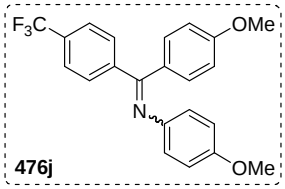
(*E*)-*N*-(3',3'-Dimethylbut-2'-ylidene)-4-methoxyaniline (476i), $C_{13}H_{19}NO$, FW =



476i

476i: colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.19 (s, 9H), 1.72 (s, 3H), 3.74 (s, 3H), 6.53-6.57 (m, 2H), 6.79-6.82 (m, 2H); **^{13}C NMR** δ 14.95 (CH_3), 27.68 (3 × CH_3), 40.05 (C), 55.19 (CH_3), 113.97 (2 × CH), 119.93 (2 × CH), 145.22 (C), 155.24 (C); **IR** ν 2966, 2907, 2867, 2834, 1650, 1504, 1466, 1364, 1288, 1240 cm^{-1}; **MS** (EI) *m/z* (%) 205 ($M^{\bullet+}$, 20), 148 (100), 92 (10); **HRMS** (EI) 205.1463 ($C_{13}H_{19}NO$ requires 205.1467).

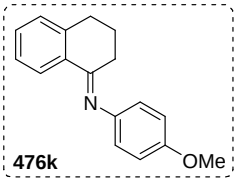
4-Methoxy-*N*-[(4'-methoxyphenyl)-(4"-trifluoromethylphenyl)methylene]aniline (476j), $C_{21}H_{18}O_2NF_3$, FW = 385.41



476j

476j: yellow oil which solidified upon standing; **mp** 60-62 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of isomers in ratio ca. 3:2, the minor one is marked *) δ 3.71 (s, 3H), 3.74* (s, 2H), 3.80* (s, 2H), 3.84 (s, 3H), 6.61-6.64* (m, 1.34H), 6.63-6.68 (m, 2H), 6.67-6.70* (m, 1.34H), 6.71-6.73 (m, 2H), 6.79-6.83* (m, 1.34H), 6.89-6.93 (m, 2H), 7.03-7.06* (m, 1.34H), 7.24-7.25 (dd, *J* = 7.9, 0.7 Hz, 2H), 7.54 (dd, *J* = 8.0, 0.6 Hz, 2H), 7.63-7.65* (m, 1.34H), 7.64-7.67 (m, 2H), 7.82-7.85* (m, 1.34H); **^{13}C NMR** δ 55.21* (CH_3), 55.29 (CH_3), 55.32* (CH_3), 55.41* (CH_3), 113.67* (2 × CH), 113.68 (2 × CH), 113.91 (2 × CH), 113.95* (2 × CH), 122.48 (2 × CH), 122.59* (2 × CH), 123.89 (q, *J* = 272.5 Hz, CF_3), 124.09* (q, *J* = 272.2 Hz, CF_3), 125.06 (q, *J* = 3.6 Hz, 2 × CH), 125.06* (q, *J* = 3.6 Hz, 2 × CH), 127.96 (C), 129.80* (C), 129.60* (2 × CH), 129.89 (2 × CH), 130.74 (2 × CH), 131.31* (2 × CH), 130.31 (q, *J* = 32.6 Hz, C), 131.93* (q, *J* = 32.4 Hz, C), 131.95 (C), 132.64* (C), 144.00 (C), 144.21* (C), 155.95 (C), 156.19* (C), 159.94* (C), 161.92 (C), 165.60 (C), 166.03* (C); ^{19}F NMR δ –62.67; **IR** ν 3006, 2957, 2837, 1605, 1502, 1325, 1245, 1168 cm^{-1}; **MS** (EI) *m/z* (%) 385 ($M^{\bullet+}$, 100), 370 (44), 240 (35), 171 (15), 92 (15); **HRMS** (EI) 385.1289 ($C_{22}H_{18}NO_2F_3$ requires 385.1290).

(*E*)-*N*-(3',4'-Dihydronaphthalen-1'(2*H*)-ylidene)-4-methoxyaniline (476k), $C_{17}H_{17}NO$, FW = 251.35

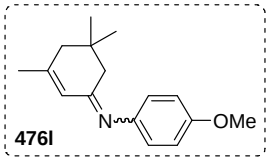


476k

476k:[224] yellow crystals; **mp** 116-117 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.88-1.95 (m, 2H), 2.56 (dd, *J* = 6.6, 6.2 Hz, 2H), 2.90 (t, *J* = 6.1 Hz, 2H), 3.82 (s, 3H), 6.74-6.78 (m, 2H), 6.89-6.92 (m, 2H), 7.20 (br d, *J* = 7.5 Hz, 1H), 7.29 (ddd, *J* = 7.9, 7.3, 0.6 Hz, 1H), 7.64 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.31 (dd, *J* = 7.9, 1.1 Hz, 1H); **^{13}C NMR** δ 23.08 (CH_2), 29.88 (CH_2), 30.00 (CH_2), 55.52 (CH_3), 114.24 (2 × CH), 120.92 (2 × CH), 126.29 (CH), 126.46 (CH), 128.77 (CH), 130.58 (CH), 134.09 (C), 141.24 (C), 144.68 (C),

155.82 (C), 166.00 (C); **IR** ν 3019, 2946, 1625, 1503, 1241, 1216 cm^{-1}; **MS** (EI) *m/z* (%) 251 ($M^{\bullet+}$, 100), 236 (80), 223 (20), 208 (24), 180 (14), 129 (20), 128 (18), 84 (22); **HRMS** (EI) 251.1313 ($C_{17}H_{17}NO$ requires 251.1310).

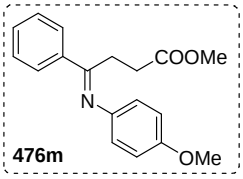
4-Methoxy-*N*-(3',5',5'-trimethylcyclohex-2'-enylidene)aniline (476l), $C_{16}H_{21}NO$, FW = 243.38



476l

476l: yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of isomers in ratio ca. 55:45, the minor one is marked *) δ 1.77* (d, *J* = 1.2 Hz, 2.4H), 1.90 (d, *J* = 1.1 Hz, 3H), 2.04 (br s, 2H), 2.07* (d, *J* = 0.5 Hz, 1.6H), 2.09 (s, 2H), 2.34* (s, 1.6H), 3.796 (s, 3H), 3.799* (s, 2.4H), 5.90* (q, *J* = 1.4 Hz, 0.8H), 6.12 (d, *J* = 1.4 Hz, 1H), 6.65-6.70 (m, 2H), 6.70-6.73* (m, 1.6H), 6.83-6.87 (m, 3.6H); **^{13}C NMR** δ 24.21 (CH_3), 24.36* (CH_3), 28.19* (CH_3), 28.25 (CH_3), 32.09 (C), 32.41* (C), 41.02 (CH_2), 45.16 (CH_2), 45.72* (CH_2), 47.99* (CH_2), 55.41 (2 × CH_3), 113.97 (2 × CH), 114.04 (2 × CH), 117.18* (CH), 121.10 (2 × CH), 121.75* (2 × CH), 126.02 (CH), 144.22* (C), 144.39 (C), 148.96* (C), 150.95 (C), 155.66 (C), 155.73* (C), 166.40* (C), 167.80 (C); **IR** ν 2955, 2896, 2833, 1637, 1608, 1502, 1466, 1287, 1241 cm^{-1}; **MS** (EI) *m/z* (%) 243 ($M^{\bullet+}$, 100), 228 (52), 187 (32), 91 (30); **MS** (CI/isobutane) *m/z* (%) 244 [$(M+H)^+$, 100].

Methyl (*E*)-4-[*N*-(4'-methoxyphenyl)imino]-4-phenylbutanoate (476m), $C_{18}H_{19}NO_3$, FW = 297.38

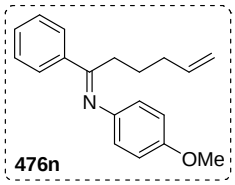


476m

476m: yellow crystals; **mp** 62-63 °C (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*/*Z*) isomers in ratio ca. 2.3:1, the minor one is marked *) δ 2.42-2.47 (m, 2H), 2.81* (dd, *J* = 7.0, 6.9 Hz, 0.86H), 3.00-3.07 (m, 2.86H), 3.60 (s, 3H), 3.698* (s, 1.29H), 3.701* (s, 1.29H), 3.82 (s, 3H), 6.51-6.55* (m, 0.86H), 6.63-6.67* (m, 0.86H), 6.71-6.75 (M, 2H), 6.89-6.92 (M, 2H), 7.98-7.12* (m, 0.86H), 7.20-7.24* (m, 1.29H), 7.42-7.47 (m, 3H), 7.85-7.90 (m, 2H); **^{13}C NMR** δ 25.18 (CH_2), 30.30* (CH_2), 31.99 (CH_2), 35.50* (CH_2), 51.67* (CH_3), 51.86 (CH_3), 55.28* (CH_3), 55.47 (CH_3), 113.77* (2 × CH), 114.45 (2 ×

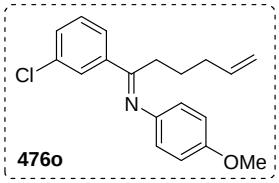
CH), 120.08 (2 × CH), 122.12* (2 × CH), 127.49 (2 × CH), 127.78* (2 × CH), 128.20* (2 × CH), 128.47* (CH), 128.66 (2 × CH), 137.91 (C), 137.99* (C), 143.74* (C), 144.31 (C), 155.69* (C), 156.00 (C), 168.29 (C), 169.20* (C), 172.40 (C), 173.80* (C); **IR** ν 3020, 2951, 2834, 11735, 1630, 1503, 1439, 1287, 1241 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 298 [$(M+H)^+$, 100]; **HRMS** (CI/isobutane) 298.1441 ($C_{18}H_{20}NO_3$ requires 298.1443).

(*E*)-4-Methoxy-*N*-(1"-phenylhex-5'-en-1'-ylidene)aniline, (476n), $C_{19}H_{21}NO$, FW = 279.41



476n: yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*/*Z*) isomers in ratio ca 10:1, only the major one is given) δ 1.44-1.52 (m, 2H), 1.86-1.92 (m, 2H), 2.56-2.60 (m, 2H), 3.73 (s, 3H), 4.81-4.65 (m, 2H), 5.57 (ddt, *J* = 17.7, 9.6, 6.6 Hz, 1H), 6.63-6.67 (m, 2H), 6.80-6.84 (m, 2H), 7.33-7.37 (m, 3H), 7.79-7.81 (m, 2H); **^{13}C NMR** δ 26.73 (CH_2), 29.54 (CH_2), 33.65 (CH_2), 55.50 (CH_3), 114.28 (2 × CH), 115.36 (CH_2), 120.33 (2 × CH), 127.52 (2 × CH), 128.61 (2 × CH), 130.25 (CH), 137.64 (CH), 138.66 (C), 144.76 (C), 155.79 (C), 158.47 (C), 170.27 (C); **IR** ν 3018, 2936, 1627, 1503, 1242, 1216 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 280 [$(M+H)^+$, 20], 228 (100), 212 (31), 206 (30), 175 (70), 124 (31).

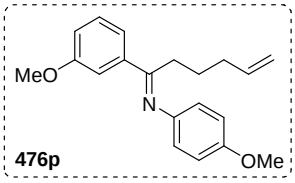
(*E*)-*N*-[1'-(3"-Chlorophenyl)hex-5'-en-1'-ylidene]-4-methoxyaniline (476o), $C_{19}H_{20}NOCl$, FW = 313.85



476o: yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*/*Z*) isomers in ratio ca. 10:1, only the major one is given) δ 1.42-1.50 (m, 2H), 1.86-1.91 (m, 2H), 2.54-2.58 (m, 2H), 3.73 (s, 3H), 4.81-4.87 (m, 2H), 5.57 (ddt, *J* = 17.7, 9.6, 6.6 Hz, 1H), 6.61-6.65 (m, 2H), 6.80-6.84 (m, 2H), 7.27 (t, *J* = 7.7 Hz, 1H), 7.33 (ddd, *J* = 7.9, 2.0, 1.3 Hz, 1H), 7.64 (ddd, *J* = 7.6, 1.5, 1.3 Hz, 1H), 7.82 (dd, *J* = 1.8, 1.7 Hz, 1H); **^{13}C NMR** δ 25.56 (CH_2), 27.11 (CH_2), 33.54 (CH_2), 55.50 (CH_3), 114.32 (2 × CH), 115.56 (CH_2), 120.23 (2 × CH), 125.63 (CH), 127.72 (CH), 129.72 (CH), 130.20 (CH), 134.25 (C), 137.43 (CH), 140.49 (C), 144.26 (C), 156.00 (C), 168.95 (C); **IR** ν 3072, 2933, 1628, 1567, 1503, 1292, 1242, 1208

cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 316 [$(M+H)^+$, 38], 314 [$(M+H)^{\bullet+}$, 100], 259 (12); **HRMS** (CI/isobutane) 316.1287 ($C_{19}H_{21}NO^{37}Cl$ requires 316.1289), 314.1315 ($C_{19}H_{21}NO^{35}Cl$ requires 314.1312).

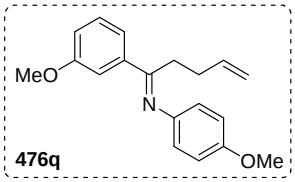
(*E*)-4-Methoxy-*N*-[1'-(3"-methoxyphenyl)hex-5'-en-1'-ylidene]aniline (476p), $C_{20}H_{23}NO_2$, FW = 309.44



476p

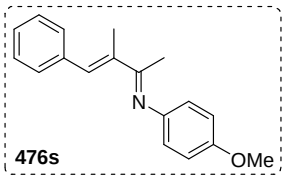
476p: yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*/*Z*) isomers in ratio ca. 7:1, the minor one is marked *) δ 1.54-1.62 (m, 2H), 1.72-1.82* (m, 0.30H), 1.95-2.01 (m, 2H), 1.15-1.21* (m, 0.30H), 2.66 (tq, *J* = 8.1, 5.3 Hz, 2H), 2.75-2.79* (m, 0.30H), 3.64* (s, 0.45H), 3.70* (s, 0.45H), 3.82 (s. 3H), 3.86 (s, 3H), 4.90-4.96 (m, 2H), 4.98* (ddt, *J* = 10.2, 2.2, 1.1 Hz, 0.15H), 5.04* (ddt, *J* = 17.1, 3.6, 1.6 Hz, 0.15H), 5.67 (ddt, *J* = 17.8, 11.3, 6.7 Hz, 1H), 5.83* (ddt, *J* = 17.1, 10.2, 6.8 Hz, 0.15H), 6.57-6.61* (m, 0.45H), 6.65-6.69* (m, 0.45H), 6.72-6.77 (m, 2.15H), 6.89-6.93 (m, 2H), 7.01 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 7.14* (dd, *J* = 8.0, 7.9 Hz, 1H), 7.34 (dd, *J* = 8.1, 7.8 Hz, 1H), 7.43 (ddd, *J* = 7.7, 1.6, 1.1 Hz, 1H), 7.50 (dd, *J* = 2.6, 1.6 Hz, 1H); **^{13}C NMR** δ 25.72* (CH_2), 27.32 (CH_2), 29.65 (CH_2), 33.41* (CH_2), 33.65 (CH_2), 40.78* (CH_2), 55.14* (CH_3), 55.29* (CH_3), 55.39 (CH_3), 55.48 (CH_3), 112.38 (CH), 113.48* (CH), 113.80* (2 × CH), 113.89* (CH), 114.29 (2 × CH), 115.03* (CH_2), 115.36 (CH_2), 116.43 (CH), 120.02 (CH), 120.23* (CH), 120.28 (2 × CH), 122.08* (2 × CH), 129.25* (CH), 129.40 (CH), 137.62 (CH), 138.37* (CH), 139.32* (C), 140.13 (C), 144.06* (C), 144.71 (C), 155.66* (C), 155.81 (C), 159.16* (C), 159.81 (C), 170.04 (C), 171.69* (C); **IR** ν 3074, 2936, 2834, 1627, 1579, 1503, 1463, 1285, 1241, 1208 cm^{-1}; **MS** (EI) *m/z* (%) 309 ($M^{\bullet+}$, 77), 268 (27), 256 (43), 255 (100), 254 (92), 240 (90), 197 (38), 134 (80), 122 (92), 92 (52); **HRMS** (EI) 309.1728 ($C_{20}H_{23}NO_2$ requires 309.1729).

(*E*)-4-Methoxy-*N*-[1'-(3"-methoxyphenyl)pent-4'-en-1'-ylidene]aniline (476q), $C_{19}H_{21}NO_2$, FW = 295.41



476q: yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*/*Z*) isomers in ratio ca. 6:1, the minor one is marked *) δ 2.11-2.17 (m, 2H), 2.31-2.37* (m, 0.28 H), 2.64-2.68 (m, 2H), 2.75-2.78* (m, 0.28H), 3.56* (s, 0.42H), 3.62* (s, 0.42H), 3.73 (s, 3H), 3.73 (s, 3H), 4.82 (ddd, *J* = 7.3, 3.0, 1.5, 1H), 4.86 (dd, *J* = 1.3, 1.2, 1H), 4.91-4.98* (m, 0.28H), 5.55 (ddt, *J* = 17.5, 10.9, 6.6, 1H), 5.84* (ddt, *J* = 17.1, 10.3, 6.6, 0.14H), 6.48-6.52* (m, 0.42H), 5.56-6.60* (m, 0.42H), 6.63-6.67 (m, 2H), 6.80-6.84 (m, 2H), 6.92 (ddd, *J* = 8.1, 2.6, 1.0, 1H), 7.06* (t, *J* = 7.9, 0.14H), 7.27 (t, *J* = 7.9, 1H), 7.34 (ddd, *J* = 7.7, 1.4, 1.1, 1H), 7.40 (dd, *J* = 2.4, 1.6, 1H); **^{13}C NMR** δ 29.507 (CH_2), 30.59* (CH_2), 32.02 (CH_2), 40.50* (CH_2), 55.17* (CH_3), 55.33* (CH_3), 55.43 (CH_3), 55.49 (CH_3), 112.38 (CH), 113.46* (CH), 113.80* (2 × CH), 113.97* (CH), 114.29 (2 × CH), 115.18* (CH_2), 115.39 (CH_2), 116.48 (CH), 120.01 (CH), 120.29 (2 × CH), 122.08* (2 × CH), 129.27* (CH), 129.44 (CH), 136.85 (CH), 137.67* (CH), 139.21* (C), 1140.03 (C), 143.97* (C), 144.57 (C), 155.68* (C), 155.84 (C), 159.15* (C), 159.83 (C), 169.47 (C), 171.00* (C); **IR** ν 3000, 2954, 2834, 1628, 1579, 1502, 1464, 1285, 1240, 1208 cm^{-1}; **MS** (EI) *m/z* (%) 295 ($M^{\bullet+}$, 61), 294 (57), 280 (38), 240 (100), 197 (16), 174 (15), 135 (28), 123 (41), 92 (30); **HRMS** (EI) 295.1570 ($C_{19}H_{21}NO_2$ requires 295.1572).

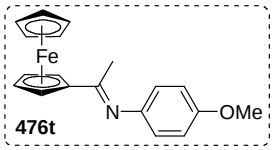
(*E*)-4-Methoxy-*N*-[(*E*)-3'-methyl-4'-phenylbut-3'-en-2'-ylidene]aniline (476s), $C_{18}H_{19}NO$, FW = 265.38



476s: yellow crystals; **mp** 72-73 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.22 (d, *J* = 1.2 Hz, 3H), 3.81 (s, 3H), 6.67-6.71 (m, 2H), 6.87-6.91 (m, 2H), 7.21 (q, *J* = 1.1 Hz, 1H), 7.28-7.33 (m, 1H), 7.40-7.42 (m, 4H); **^{13}C NMR** δ 14.66 (CH_3), 16.40 (CH_3), 55.49 (CH_3), 114.19 (2 × CH), 120.56 (2 × CH), 127.36 (CH), 128.25 (2 × CH), 129.46 (2 × CH), 133.75 (CH), 137.42 (C), 139.43 (C), 145.22 (CH), 155.80 (C), 167.91 (C); **IR** ν 3015,

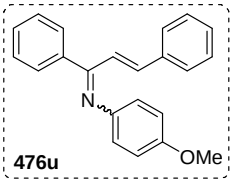
2959, 2836, 1664, 1606, 1503, 1442, 1243, 1218 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 266 [$(M+H)^+$, 45], 89 (100); **HRMS** (CI/isobutane) 266.1542 ($C_{18}H_{20}NO$ requires 266.1545).

(*E*)-*N*-[1'-(Ferrocen-1"-yl)ethylidene]-4-methoxyaniline (476t), $C_{19}H_{19}NOFe$, FW = 333.24



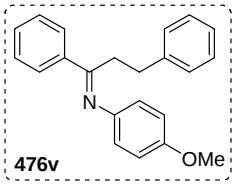
476t: orange oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 3.81 (s, 3H), 4.21 (s, 5H), 4.41 (t, *J* = 1.9 Hz, 2H), 4.79 (t, *J* = 1.9 Hz, 2H), 6.69-6.73 (m, 2H), 6.86-6.90 (m, 2H). No further data provided as the imine was obtained only in a mixture with the corresponding ketone.

(*E*,*E*)-*N*-(1',3'-Diphenylallylidene)-4-methoxyaniline (476u), $C_{22}H_{19}NO$, FW = 313.42



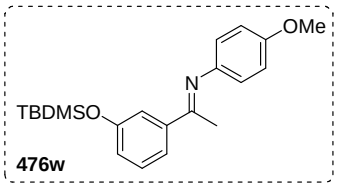
476u: yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*/Z) isomers in ca. 3:1 ratio, the minor one is marked *) δ 3.63* (s, 3H), 3.76 (s, 3H), 6.56-6.60* (m, 1.4H), 6.72* (d, *J* = 16.4 Hz, 0.4H), 6.81-6.88 (m, 6.2H), 7.05-7.07* (m, 0.8H), 7.18* (d, *J* = 5.2 Hz, 0.4H), 7.20-7.28 (both isomers, m, 7.5H), 7.36-7.43 (both isomers, m, 3.9H), 7.63-7.66 (m, 2H); **^{13}C NMR** δ 55.29* (CH_3), 55.51 (CH_3), 113.65* (2 × CH), 114.08 (2 × CH), 122.32 (CH), 122.55 (2 × CH), 122.90* (2 × CH), 127.49 (2 × CH), 127.51* (2 × CH), 128.26* (2 × CH), 128.37 (2 × CH), 128.41* (CH), 128.82* (2 × CH), 128.85 (2 × CH), 129.05 (CH), 129.18* (CH), 129.36* (2 × CH), 129.44 (2 × CH), 129.84 (CH), 132.05* (CH), 135.84 (C), 135.87* (C), 135.94* (C), 139.71 (C), 140.79* (CH), 141.14 (CH), 143.64* (C), 144.19 (C), 156.04* (C), 156.57 (C), 167.09 (C), 168.38* (C); **IR** ν 3019, 2962, 2836, 2399, 1603, 1502, 1288 cm^{-1}; **MS** (EI) *m/z* (%) 313 ($M^{\bullet+}$, 100), 312 (95), 298 (13), 236 (12), 210 (12), 191 (44); **HRMS** (EI) 313.1464 ($C_{22}H_{19}NO$ requires 313.1467).

(*E*)-*N*-(1',3'-Diphenylprop-1'-ylidene)-4-methoxyaniline (476v), $C_{22}H_{21}NO$, FW = 315.44



476v: yellow crystals; **mp** 60-61 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*/*Z*) isomers in ratio ca. 10:1, only the major one is given) δ 2.68-2.72 (m, 2H), 2.87-2.91 (m, 2H), 3.73 (s, 3H), 6.45-4.48 (m, 2H), 6.75-6.79 (m, 2H), 6.88-6.90 (m, 1H), 7.10-7.17 (m, 4H), 7.37-7.41, (m, 3H), 7.84-7.87 (m, 2H); **^{13}C NMR** δ 32.07 (CH_2), 33.98 (CH_2), 55.53 (CH_3), 114.23 (2 × CH), 120.13 (2 × CH), 126.32 (CH), 127.61 (2 × CH), 128.29 (2 × CH), 128.52 (2 × CH), 128.60 (2 × CH), 128.65 (2 × CH), 130.38 (CH), 138.52 (C), 140.65 (C), 144.61 (C), 155.79 (C), 169.37 (C); **IR** ν 3027, 2946, 1629, 1502, 1454, 1241, 1208 cm^{-1}; **MS** (EI) *m/z* (%) 315 ($M^{\bullet+}$, 100), 314 (37), 238 (24), 219 (84), 180 (16), 167 (14), 121 (25), 91 (47); **HRMS** (EI) 315.1624 ($C_{22}H_{21}NO$ requires 315.1623).

(*E*)-*N*-{1'-[3"-(*tert*-Butyldimethylsilyloxy)phenyl]ethylidene}-4-methoxyaniline (476w), $C_{21}H_{29}NO_5Si$, FW = 355.60



476w: yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.23 (s 6H), 1.00 (s, 9H), 2.22 (s, 3H), 3.82 (s, 3H), 6.73-6.77 (m, 2H), 6.89-6.93 (m, 2H), 6.93 (ddd, *J* = 8.1, 2.5, 0.9 Hz, 1H), 7.29 (dd, *J* = 8.0, 7.9 Hz, 1H), 7.44 (dd, *J* = 2.0, 1.9 Hz, 1H), 7.55 (ddd, *J* = 7.8, 1.6, 1.0 Hz, 1H); **^{13}C NMR** δ –4.34 (2 × CH_3), 17.43 (CH_3), 18.23 (C), 25.73 (3 × CH_3), 55.49 (CH_3), 114.22 (2 × CH), 118.83 (CH), 120.24 (CH), 120.74 (2 × CH), 121.94 (CH), 129.23 (CH), 141.35 (C), 144.84 (C), 155.74 (C), 155.91 (C), 165.44 (C); **IR** ν 2955, 2930, 2858, 1631, 1580, 1503, 1434, 1352, 1285, 1241 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 356 [$(M+H)^+$, 100], 298 (5), 186 (8); **HRMS** (CI/isobutane) 356.2043 ($C_{21}H_{30}NO_2Si$ requires 356.2046).

6.4. Amines

General Procedure for Racemic Reduction of Imines:

Method A: Sodium borohydride (46 mg, 1.20 mmol, 4 equiv) was added to a cooled solution (0 ºC) of the imine (0.300 mmol, 1 equiv, see Table 6.9) in anhydrous methanol (3 mL) under an argon atmosphere. The reaction mixture was let to warm to room temperature and to stir for 16 h. Then the mixture was concentrated *in vacuo*, the residue was dissolved in ethyl acetate (5 mL) and washed with water (10 mL). The aqueous layer was extracted with ethyl acetate (2 × 5 mL); the combined organic layers were washed with brine (5 mL) dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash chromatography on a silica gel column (25 mL) with a petroleum ether – ethyl acetate mixture (Table 6.9).

Method B (marked *): Trichlorosilane (60 µL, 0.600 mmol, 2 equiv) was added dropwise to a cooled solution (0 ºC) of the imine (0.300 mmol, 1 equiv, see Table 6.9), dimethylformamide (21.9 mg, 23 µL, 0.300 mmol, 1 equiv) in anhydrous toluene (3 mL) under an argon atmosphere. The reaction mixture was let to stir at room temperature for 24 h. Then the reaction mixture was diluted with ethyl acetate (5 mL), quenched with a saturated $NaHCO_3$ solution (20 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 5 mL) and washed with water (2 × 15 mL), brine (5 mL), dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by flash chromatography on a silica gel column (25 mL) with a petroleum ether – ethyl acetate mixture (Table 6.9, marked *, racemates only in Table 6.10).

Table 6.9. Racemic reduction of Imines

Imine	PE – EA	Amine
475a (67 mg)	80:20	**488a** (50 mg, 0.219 mmol, 73 %)
475b (67 mg)	60:40	**488b** (47 mg, 0.206 mmol, 69 %)
475c (88 mg)	95:5	**488c** (50 mg, 0.160 mmol, 53 %)
475z (110 mg)*	Cryst., 50:50 (EA:MeOH)	**488z** (60 mg, 0.178 mmol, 59 %)
475d (70 mg)	90:10	**488d** (38 mg, 0.162 mmol, 54 %)
475e (734 mg)	95:5	**488e** (47 mg, 0.189 mmol, 63 %)
475f (82 mg)	95:5	**488f** (78 mg, 0.283 mmol, 94 %)
475g (87 mg)	97:3	**488g** (44 mg, 0.152 mmol, 50 %)
475h (91 mg)	95:5 → 90:10	**488h** (42 mg, 0.137 mmol, 46 %)
475i (69 mg)	95:5	**488i** (56 mg, 0.240 mmol, 80 %)

Table 6.9. – Cont. Racemic reduction of Imines

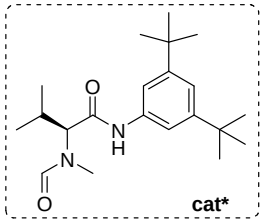
Imine	PE – EA	Amine
475j (65 mg)	95:5	**488j** (42 mg, 0.193 mmol, 64 %)
475k (69 mg)	93:7	**488k** (65 mg, 0.281 mmol, 94 %)
475l (86 mg)	95:5	**488l** (61 mg, 0.211 mmol, 70 %)
475m (90 mg)	90:10	**488m** (63 mg, 0.218 mmol, 73 %)
475n (73 mg)	95:5	**488n** (53 mg, 0.216 mmol, 72 %)
475o (63 mg)	95:5	**488o** (45 mg, 0.214 mmol, 71 %)
475p (78 mg)	97:3	**488p** (56 mg, 0.228 mmol, 76 %)
475q (80 mg)	93:7	**488q** (74 mg, 0.277 mmol, 92 %)
475r (80 mg)	96:4	**488r** (65 mg, 0.243 mmol, 81 %)
475s (84 mg)	95:5	**488s** (83 mg, 0.296 mmol, 99 %)
475t (84 mg)	80:20	**488t** (75 mg, 0.271 mmol, 90 %)
476a (72 mg)	98:2	**492a** (64 mg, 0.265 mmol, 88 %)
476b (76 mg)	98:2	**492b** (74 mg, 0.290 mmol, 96 %)
476c (75 mg)	95:5	**492c** (74 mg, 0.292 mmol, 97 %)
476d (80 mg)	95:5	**492d** (67 mg, 0.251 mmol, 84 %)
476e (88 mg)	98:2	**492e** (87 mg, 0.295 mmol, 98 %)
476f (80 mg)	98:2	**492f** (58 mg, 0.215 mmol, 72 %)
476i (62 mg)	98:2	**492i** (60 mg, 0.289 mmol, 96 %)
476j (116 mg)	96:4	**492j** (79 mg, 0.204 mmol, 68 %)
476k (75 mg)	95:5	**492k** (53 mg, 0.209 mmol, 70 %)
476l (73 mg)	97:3	**492l** (68 mg, 0.277 mmol, 92 %)
476m (594 mg) *	93:7	**492m** (201 mg, 0.872 mmol, 44 %)
262 (67 mg)	85:15	**264** (49 mg, 0.218 mmol, 73 %)
257 (86 mg) *	90:10	**260** (76 mg, 0.262 mmol, 87 %)
476n (94 mg)	97:3	**492n** (23 mg, 0.080 mmol, 27 %)
476o (94 mg)	98:2	**492o** (34 mg, 0.108 mmol, 36 %)
476p (93 mg)	95:5	**492p** (69 mg, 0.222 mmol, 74 %)
476q (89 mg)	95:5	**492q** (88 mg, 0.299 mmol, 99 %)
476s (80 mg)	97:3	**492s** (40 mg, 0.150 mmol, 50 %)
476t (100 mg)	95:5	**492t** (71 mg, 0.209 mmol, 70 %)
476u (94 mg)	-	no reaction
476v (93 mg)	95:5	**492v** (82 mg, 0.258 mmol, 86 %)
476w (107 mg)	100:0	**492w** (90 mg, 0.244 mmol, 81 %)

Table 6.10. Attempts of Enantioselective Reduction of Imines

Imine / Additives	Amine
475t (56 mg) 1. AcOH (12 µL) 2. 40 °C	no reaction
476l (49 mg)	no reaction
476t (67 mg)	no reaction
476u (63 mg) 1. AcOH (12 µL) 2. 50 ºC	no reaction

General Procedure for Enantioselective Reduction of Imines:

Trichlorosilane (40 µL, 0.400 mmol, 2 equiv) was added dropwise to a cooled solution (0 ºC) of the imine (0.200 mmol, 1 equiv, see Table 6.11) catalyst **cat*** (3.46 mg, 0.010 mmol, 5 mol %) and a possible additive (0.2 mmol, 1 equiv, see Table 6.11) in anhydrous toluene (2 mL) under an argon atmosphere. The reaction mixture was let to stir at



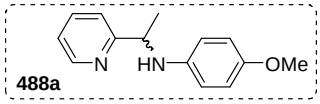
room temperature (unless otherwise stated) for 24 h. Then the reaction mixture was diluted with ethyl acetate (5 mL), quenched with a saturated $NaHCO_3$ solution (20 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 5 mL) and washed with water (2 × 15 mL), brine (5 mL), dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by flash chromatography on a silica gel column (20 mL) with a petroleum ether – ethyl acetate mixture (Table 6.11).

Table 6.11. Enantioselective reduction of Imines

Imine / Additives	**PE – EA**	**Amine**
475a (45 mg) / AcOH (12 µL)	85:15	**488a** (32 mg, 0.140 mmol, 70 %)
475b (45 mg) / AcOH (12 µL)	70:30	**488b** (33 mg, 0.145 mmol, 72 %)
475c (59 mg)	95:5	**488c** (43 mg, 0.136 mmol, 68 %)
475z (74 mg)	50:50 (EA:MeOH)	**488z** (36 mg, 0.097 mmol, 49 %) not pure, decomposition
475d (47 mg)	90:10	**488d** (39 mg, 0.166 mmol, 83 %)
475e (49 mg)	95:5	**488e** (15 mg, 0.060 mmol, 30 %)
465f (55 mg)	95:5	**488f** (39 mg, 0.142 mmol, 71 %)
475g (58 mg)	97:3	**488g** (34 mg, 0.117 mmol, 58 %)
475h (61 mg)	95:5 → 90:10	**488h** (56 mg, 0.183 mmol, 91 %)
475i (46 mg)	95:5	**488i** (36 mg, 0.154 mmol, 77 %)
475j (43 mg) / -	95:5	**488j** (27 mg, 0.124 mmol, 62 %)
475j (43 mg) / –20 ºC		**488j** (25 mg, 0.115 mmol, 57 %)
475k (46 mg)	93:7	**488k** (40 mg, 0.173 mmol, 86 %)
475l (57 mg) / AcOH (12 µL)	95:5	**488l** (36 mg, 0.124 mmol, 62 %)
475m (61 mg)	93:7	**488m** (36 mg, 0.124 mmol, 62 %)
475n (47 mg)	95:5	**488n** (37 mg, 0.150 mmol, 75 %)
475o (43 mg)	94:6	**488o** (26 mg, 0.120 mmol, 60 %)
475p (52 mg)	95:5	**488p** (44 mg, 0.180 mmol, 90 %)
475q (53 mg)	95:5	**488q** (42 mg, 0.157 mmol, 79 %)
475r (53 mg)	97:3	**488r** (45 mg, 0.168 mmol, 84 %)
475t (56 mg)	95:5	**488t** (43 mg, 0.153 mmol, 77 %)
476a (48 mg)	98:2	**492a** (39 mg, 0.162 mmol, 81 %)
476b (51 mg)	98:2	**492b** (50 mg, 0.196 mmol, 98 %)
476c (50 mg)	93:7	**492c** (44 mg, 0.174 mmol, 87 %)
476d (53 mg)	93:7	**492d** (40 mg, 0.150 mmol, 75 %)
476e (59 mg)	98:2	**492e** (49 mg, 0.166 mmol, 83 %)
476f (54 mg) / -	99.5:0.5	**492f** (25 mg, 0.0366 mmol, 10 %)
476f (54 mg) / AcOH (12 µL)		**492f** (25 mg, 0.0930 mmol, 46 %)
476i (41 mg) / -	99.5:0.5	**492i** (10 mg, 0.125 mmol, 63 %)
476i (41 mg) / AcOH (12 µL)		**492i** (38 mg, 0.183 mmol, 92 %)
476j (77 mg)	97:3	**492j** (61 mg, 0.157 mmol, 79 %)
476k (50 mg)	95:5	**492k** (45 mg, 0.178 mmol, 89 %)
476m (60 mg)	93:7	**492m** (23 mg, 0.077 mmol, 38 %)
262 (45 mg)	85:15	**264** (41 mg, 0.182 mmol, 91 %)
257 (58 mg)	90:10	**260** (40 mg, 0.138 mmol, 69 %)
476n (56 mg)	95:5	**492n** (36 mg, 0.128 mmol, 64 %)
476o (63 mg)	98:2	**492o** (39 mg, 0.124 mmol, 62 %)
476p (62 mg)	95:5	**492p** (61 mg, 0.196 mmol, 98 %)
476q (59 mg)	95:5	**492q** (59 mg, 0.198 mmol, 99 %)
476s (53 mg)	97:3	**492s** (33 mg, 0.123 mmol, 62 %)
476v (63 mg)	95:5	**492v** (60 mg, 0.189 mmol, 95 %)
476w (71 mg)	100:0	**492w** (53 mg, 0.143 mmol, 72 %)

6.4.1. Amines with Heterocycles

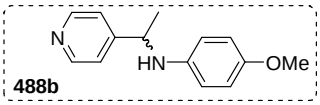
_N_-(4-Methoxyphenyl)-_N_-[1'-(pyridin-2"-yl)ethyl]amine (488a), $C_{14}H_{16}N_2O$, FW = 228.31



488a

488a:[225] yellowish oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.44 (d, *J* = 6.7 Hz, 3H), 3.56 (br s, 1H), 3.60 (s, 3H), 4.46 (q, *J* = 6.7 Hz, 1H), 6.42-6.46 (m, 2H), 6.64-6.68 (m, 2H), 7.04 (ddd, *J* = 7.4, 4.9, 1.1 Hz, 1H), 7.24 (br d, *J* = 7.9 Hz, 1H), 7.50 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 8.48 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 1H); **^{13}C NMR** δ 23.33 (CH_3), 55.72 (CH), 55.76 (CH_3), 114.76 (2 × CH), 114.81 (2 × CH), 120.40 (CH), 121.97 (CH), 136.85 (CH), 141.34 (C), 149.32 (CH), 152.02 (C), 164.21 (C); **HPLC** analysis (Chiralcel OJ-H, hexane – propan-2-ol (80:20), 0.75 mL/min, t_1 = 56.477 min, t_2 = 63.686 min) showed 7 % ee.

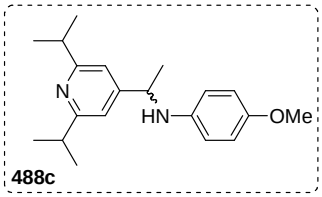
_N_-(4-Methoxyphenyl)-_N_-[1'-(pyridin-4"-yl)ethyl]amine (488b), $C_{14}H_{16}N_2O$, FW = 228.31



488b

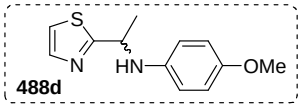
488b: yellowish oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.49 (d, *J* = 6.8 Hz, 3H), 3.69 (s, 3H), 3.93 (br s, 1H), 4.38 (q, *J* = 6.8 Hz, 1H), 6.39-6.43 (m, 2H), 6.67-6.71 (m, 2H), 7.29 (dd, *J* = 4.6, 1.5 Hz, 1H), 8.53 (dd, *J* = 4.5, 1.6 Hz, 1H); **^{13}C NMR** δ 23.57 (CH_3), 52.44 (CH), 55.66 (CH_3), 113.42 (2 × CH), 113.74 (2 × CH), 120.18 (2 × CH), 139.79 (C), 149.07 (2 × CH), 151.15 (C), 153.68 (C); **IR** ν 3424, 3015, 2969, 2834, 1600, 1512, 1237, 1216 cm^{-1}; **MS** (EI) *m/z* (%) 228 ($M^{\bullet+}$, 90), 213 (100), 150 (24), 122 (76), 106 (27); **HRMS** (EI) 228.1265 ($C_{14}H_{16}N_2O$ requires 228.1263); **HPLC** analysis (Chiralcel OJ-H, hexane – propan-2-ol (80:20), 0.75 mL/min, t_{major} = 27.009 min, t_{minor} = 39.127 min) showed 21 % ee.

(–)-*N*-[1'-(2",6"-Di-*iso*-propylpyridin-4'-yl)ethyl]-*N*-(4-methoxyphenyl)amine (488c), $C_{20}H_{28}N_2O$, FW = 312.50



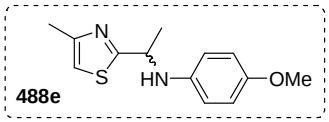
488c: colourless oil; **[α]$_D$** –12.7 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.26 (d, *J* = 7.0 Hz, 3H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.49 (d, *J* = 6.9 Hz, 3H), 3.01 (sept, *J* = 6.9 Hz, 2H), 3.71 (s, 3H), 4.34 (q, *J* = 6.7 Hz, 1H, 6.44-6.48 (m, 2H), 6.69-6.73 (m, 2H), 6.96 (s, 2H); **^{13}C NMR** δ 22.67 (2 × CH_3), 22.71 (2 × CH_3), 24.42 (CH_3), 36.30 (CH), 54.04 (CH), 55.66 (CH_3), 114.60 (2 × CH), 114.68 (2 × CH), 114.73 (2 × CH), 141.31 (C), 152.05 (C), 154.90 (C), 166.72 (2 × C); **IR** ν 3396, 2962, 2869, 1602, 1567, 1513, 1467, 1235 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 313 [$(M+H)^+$, 100], 312 (20), 192 (10), 93 (40); **HRMS** (CI/isobutane) 313.2282 ($C_{20}H_{29}N_2O$ requires 313.2280); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 12.73 min, t_{major} = 17.31 min) showed 78 % ee.

***N*-(4-Methoxyphenyl)-*N*-[1'-(thiazol-2"-yl)ethyl]amine (488d), $C_{12}H_{14}N_2OS$, FW = 234.34**



488d: yellowish oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.65 (d, *J* = 6.7 Hz, 3H), 3.71 (s, 3H), 3.97 (br s, 1H), 4.80 (q, *J* = 6.7 Hz, 1H), 6.55-6.59 (m, 2H), 6.72-6.76 (m, 2H), 7.20 (d, *J* = 3.3 Hz, 1H), 7.72 (d, *J* = 3.3 Hz, 1H); **^{13}C NMR** δ 23.57 (CH_3), 53.31 (CH), 55.68 (CH_3), 114.82 (CH), 114.96 (CH), 118.71 (CH), 140.62 (C), 142.64 (CH), 152.73 (C), 177.68 (C); **IR** ν 3419, 3018, 2834, 1512, 1237, 1216 cm^{-1}; **MS** (EI) *m/z* (%) 234 ($M^{\bullet+}$, 100), 219 (78), 150 (58), 134 (34), 122 (80), 112 (77), 108 (42), 86 (62); **HRMS** (EI) 234.0824 ($C_{12}H_{14}N_2OS$ requires 234.0827); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (93:7), 0.75 mL/min, t_1 = 16.48 min, t_2 = 19.17 min) showed 13% ee.

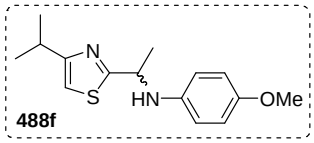
(+)-*N*-(4-Methoxyphenyl)-*N*-[1'-(4"-methylthiazol-2"-yl)ethyl]amine (488e), $C_{13}H_{16}N_2OS$, FW = 248.37



488e

488e: colourless oil; **[α]$_D$** +24 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.63 (d, *J* = 6.7 Hz, 3H), 2.44 (s, 3H), 2.50 (s, 3H), 3.71 (s, 3H), 4.74 (q, *J* = 6.7 Hz, 1H), 6.56-6.60 (m, 2H), 6.72-6.75 (m, 2H), 6.76 (s, 1H); **^{13}C NMR** δ 17.18 (CH_3), 23.93 (CH_3), 53.41 (CH), 55.68 (CH_3), 113.08 (CH), 114.79 (2 × CH), 115.08 (2 × CH), 140.43 (C), 152.63 (C), 152.79 (C), 176.78 (C); **IR** (ATR) ν 3391, 2923, 2831, 1506, 1441, 1312, 1291, 1233 cm^{-1}; **MS** (EI) *m/z* (%) 248 ($M^{\bullet+}$, 100), 233 (64), 150 (25), 126 (75), 123 (40), 122 (50), 100 (30); **HRMS** (EI) 248.0982 ($C_{13}H_{16}N_2OS$ requires 248.0983); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (97:3), 0.75 mL/min, t_{minor} = 18.63 min, t_{major} = 21.18 min) showed 31 % ee.

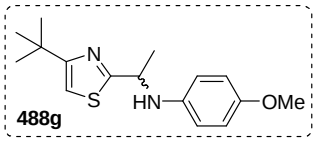
(+)-*N*-(4-Methoxyphenyl)-*N*-[1'-(4"-*iso*-propylthiazol-2"-yl)ethyl]amine (488f), $C_{13}H_{23}NO$, FW = 276.43



488f

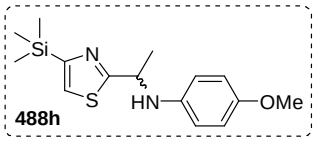
488f: yellow oil; **[α]D** +17.6 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.31 (dd, *J* = 6.9, 1.7 Hz, 6H), 1.63 (d, *J* = 6.7 Hz, 3H), 3.09 (sept d, *J* = 6.9, 0.9 Hz, 1H), 3.71 (s, 3H), 3.97 (br s, 1H), 4.74 (q, *J* = 6.7 Hz, 1H), 6.56-6.60 (m, 2H), 6.72 (d, *J* = 0.9 Hz, 1H), 6.72-6.76 (m, 2H),); **^{13}C NMR** δ 22.21 (CH_3), 22.31 (CH_3), 23.72 (CH_3), 30.91 (CH), 53.27 (CH), 55.57 (CH_3), 110.29 (CH), 114.65 (2 × CH), 114.76 (2 × CH), 140.70 (C), 152.46 (C), 163.65 (C), 176.73 (C); **IR** ν 3385, 2963, 2929, 2869, 2831, 1512, 1462, 1314, 1237 cm^{-1}; **MS** (EI) *m/z* (%) 276 ($M^{\bullet+}$, 85), 261 (60), 154 (100), 150 (30), 123 (55), 122 (37), 108 (22); **HRMS** (EI) 276.1293 ($C_{15}H_{20}N_2OS$ requires 276.1296); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 15.28 min, t_{major} = 18.92 min) showed 34 % ee.

(+)-*N*-[1'-(4"-*t*-Butylthiazol-2"-yl)ethyl]-*N*-(4-methoxyphenyl)amine (488g), $C_{16}H_{22}N_2OS$, FW = 290.46



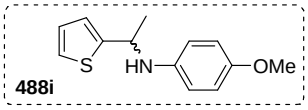
488g: white crystalline solid; **mp** 69-70 ºC; **$[\alpha]_D$** +31 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.34 (s, 9H), 1.64 (d, *J* = 6.7 Hz, 3H), 3.72 (s, 3H), 4.76 (q, *J* = 6.7 Hz, 1H), 6.59-6.63 (m, 2H), 6.72-6.75 (m, 2H), 6.76 (s, 1H); **^{13}C NMR** δ 23.58 (CH_3), 29.99 (3 × CH_3), 34.78 (C), 53.57 (CH), 55.68 (CH_3), 109.76 (CH), 114.76 (2 × CH), 115.31 (2 × CH), 140.43 (C), 152.83 (C), 166.56 (C), 175.79 (C); **IR** (ATR) ν 3285, 3104, 2959, 2899, 1507, 1313, 1238 cm^{-1}; **MS** (EI) *m/z* (%) 290 ($M^{\bullet+}$, 100), 275 (70), 168 (90), 150 (30), 123 (55), 122 (30); **HRMS** (EI) 290.1452 ($C_{16}H_{22}N_2OS$ requires 290.1453); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 12.63 min, t_{major} = 16.41 min) showed 41 % ee.

***N*-(4-Methoxyphenyl)-*N*-[1'-(4"-trimethylsilylthiazol-2"-yl)ethyl]amine (488h), $C_{15}H_{22}N_2OSSi$, FW = 306.54**



488h: yellowish crystals; **mp** 95-97 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.29 (s, 9H), 1.64 (d, *J* = 6.7 Hz, 3H), 3.72 (s, 3H), 3.99 (br s, 1H), 4.82 (q, *J* = 6.5 Hz, 1H), 6.57-6.61 (m, 2H), 6.73-6.77 (m, 2H), 7.72 (s, 1H); **^{13}C NMR** δ –0.30 (3 × CH_3), 23.44 (CH_3), 52.97 (CH), 55.40 (CH_3), 114.53 (2 × CH), 114.59 (2 × CH), 132.03 (C), 140.52 (C), 148.10 (CH), 152.33 (C), 181.61 (C); **IR** ν 3417, 3018, 2959, 2834, 1512, 1250, 1235, 1216 cm^{-1}; **MS** (EI) *m/z* (%) 306 ($M^{\bullet+}$, 100), 291 (55), 184 (95), 150 (30), 123 (33), 85 (52), 83 (80); **HRMS** (EI) 306.1221 ($C_{15}H_{22}N_2OSSi$ requires 306.1222); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (98:2), 0.75 mL/min, t_{minor} = 13.865 min, t_{major} = 16.935 min) showed 6 % ee.

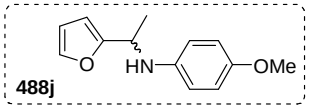
(–)-*N*-(4-Methoxyphenyl)-*N*-[1'-(thiophen-2"-yl)ethyl]amine (488i), $C_{13}H_{15}NOS$, FW = 233.35



488i

488i: yellow oil; **[α]$_D$** –9.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.61 (d, *J* = 6.6 Hz, 3H), 3.73 (s, 3H), 4.74 (q, *J* = 6.6 Hz, 1H), 6.58-6.62 (m, 2H), 6.74-6.78 (m, 2H), 6.94 (dd, *J* = 4.9, 3.5 Hz, 1H), 6.97 (ddd, *J* = 3.5, 1.2, 0.9 Hz, 1H), 7.14 (dd, *J* = 4.9, 1.4 Hz, 1H); **^{13}C NMR** δ 24.81 (CH_3), 50.54 (CH), 55.74 (CH_3), 114.79 (2 × CH), 115.09 (2 × CH), 122.95 (CH), 123.63 (CH), 126.75 (CH), 141.15 (C), 150.62 (C), 152.39 (C); **IR** ν 3417, 3017, 2835, 1510, 1239, 1216 cm^{-1}; **MS** (EI) *m/z* (%) 233 ($M^{\bullet+}$, 50), 123 (44), 111 (100); **HRMS** (EI) 233.0869 ($C_{13}H_{15}NOS$ requires 233.0874); **HPLC** analysis (Chiralcel OD-H, hexane – propan-2-ol (99:1), 0.70 mL/min, t_{minor} = 27.44 min, t_{major} = 30.94 min) showed 89% ee.

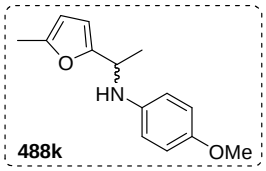
(–)-*N*-[1'-(Furan-2"-yl)ethyl]-*N*-(4-methoxyphenyl)amine (488j), $C_{13}H_{15}NO_2$, FW = 217.28



488j

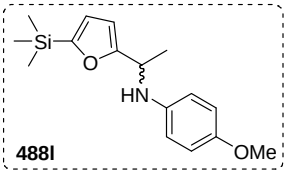
488j:[226,36b] colourless oil; **[α]$_D$** –48 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.54 (d, *J* = 6.7 Hz, 3H), 3.53 (br s, 1H), 3.74 (s, 3H), 4.56 (q, *J* = 6.7 Hz, 1H), 6.14 (br d, *J* = 3.2 Hz, 1H), 6.28 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.59-6.63 (m, 2H), 6.74-6.78 (m, 2H), 7.34 (dd, *J* = 1.8, 0.8 Hz, 1H); **^{13}C NMR** δ 20.92 (CH_3), 48.48 (CH), 55.72 (CH_3), 105.12 (CH), 110.08 (CH), 114.78 (2 × CH), 115.30 (2 × CH), 141.04 (C), 141.42 (CH), 157.44 (C); **HPLC** analysis (Chiralcel OJ-H, hexane – propan-2-ol (70:30), 0.70 mL/min, t_{major} = 42.237 min, t_{minor} = 52.590 min) or (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 14.719 min, t_{major} = 15.203 min) showed 56/62% ee (amine **9** at room temperature /- 20 ºC respectively), [lit.[36b] gives Chiralpak OJ, hexane – propan-2-ol (80:20), 1.0 mL/min, $t_{(-)\text{-minor}}$ = 12.6 min, $t_{(+)\text{-major}}$ = 16.2 min].

(–)-*N*-(4-Methoxyphenyl)-*N*-[1'-(5"-methylfuran-2"-yl)ethyl]amine (488k), $C_{14}H_{17}NO_2$, FW = 231.32



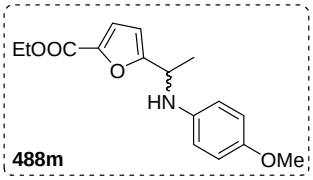
488k: colourless oil; **[α]$_D$** –44 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.51 (d, *J* = 6.7 Hz, 3H), 2.27 (d, *J* = 0.9 Hz, 3H), 3.61 (br s, 1H), 3.74 (s, 3H), 4.50 (q, *J* = 6.7 Hz, 1H), 5.86 (dq, *J* = 3.0, 1.0 Hz, 1H), 6.02 (dq, *J* = 3.0, 0.4 Hz, 1H), 6.60-6.64 (m, 2H), 6.75-6.79 (m, 2H); **^{13}C NMR** δ 13.64 (CH_3), 20.96 (CH_3), 48.38 (CH), 55.74 (CH_3), 105.83 (CH), 105.92 (CH), 114.75 (2 × CH), 115.21 (2 × CH), 141.30 (C), 151.02 (C), 152.33 (C), 155.56 (C); **IR** ν 3407, 3006, 2931, 1512, 1235 cm^{-1}; **MS** (EI) *m/z* (%) 231 ($M^{\bullet+}$, 34), 216 (8), 123 (45), 109 (100); **HRMS** (EI) 231.1259 ($C_{14}H_{17}NO_2$ requires 231.1260); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 12.27 min, t_{major} = 13.07 min) showed 45 % ee.

(–)-*N*-(4-Methoxyphenyl)-*N*-[1'-(5"-trimethylsilylfuran-2"-yl)ethyl]amine (488l), $C_{16}H_{23}NO_2Si$, FW = 289.58



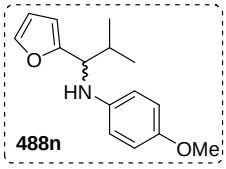
488l: colourless oil; **[α]$_D$** –39 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.24 (s, 9H), 1.54 (d, *J* = 6.7 Hz, 3H), 3.62 (br s, 1H), 3.74 (s, 3H), 4.58 (q, *J* = 6.7 Hz, 1H), 6.10 (dd, *J* = 3.1, 0.7 Hz, 1H), 6.50 (d, *J* = 3.1 Hz, 1H), 6.59-6.63 (m, 2H), 6.74-6.78 (m, 2H); **^{13}C NMR** δ –1.59 (3 × CH_3), 20.99 (CH_3), 48.60 (CH), 55.69 (CH_3), 104.88 (CH), 114.68 (2 × CH), 115.21 (2 × CH), 120.15 (CH), 141.26 (C), 152.30 (C), 159.10 (C), 161.86 (C); **IR** ν 3396, 2957, 2900, 2831, 1512, 1464, 1294, 1181 cm^{-1}; **MS** (EI) *m/z* (%) 289 ($M^{\bullet+}$, 21), 167 (70), 123 (15), 86 (50), 85 (95), 84 (80), 83 (100); **HRMS** (EI) 289.1495 ($C_{16}H_{23}NO_2Si$ requires 289.1498); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 9.06 min, t_{major} = 9.73 min) showed 63 % ee.

(–)-Ethyl 5-[1'-(4"-methoxyphenylamino)ethyl]furan-2-yl-carboxylate (488m), $C_{16}H_{19}NO_4$, FW = 289.36



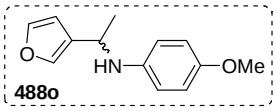
488m: colourless oil; $[\alpha]_D$ –35 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.1 Hz, 3H), 1.57 (d, *J* = 6.8 Hz, 3H), 3.71 (br s, 1H), 3.72 (s, 3H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.68 (q, *J* = 6.7 Hz, 1H), 6.23 (dd, *J* = 3.4, 0.5 Hz, 1H), 6.53-6.57 (m, 2H), 6.72-6.76 (m, 2H), 7.05 (d, *J* = 3.4 Hz, 1H); **^{13}C NMR** δ 14.42 (CH_3), 21.30 (CH_3), 48.63 (CH), 55.70 (CH_3), 60.85 (CH_2), 107.50 (CH), 114.78 (2 × CH), 115.01 (2 × CH), 118.79 (CH), 140.65 (C), 143.68 (C), 152.53 (C), 158.89 (C), 162.45 (C); **IR** ν 3384, 2981, 1714, 1512, 1299, 1235, 1137 cm^{-1}; **MS** (EI) *m/z* (%) 289 ($M^{\bullet+}$, 85), 274 (32), 216 (36), 167 (100), 139 (67), 123 (82), 122 (45), 118 (28), 93 (32), 86 (32), 84 (51); **HRMS** (EI) 289.1315 ($C_{16}H_{19}NO_4$ requires 289.1314); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{major} = 50.21 min, t_{minor} = 55.85 min) showed 70 % ee.

(–)-*N*-[1'-(Furan-2"-yl)-2'-methylprop-1'-yl]-*N*-4-methoxyphenylamine (488n), $C_{15}H_{19}NO_2$, FW = 245.35



488n: colourless oil; $[\alpha]_D$ –97 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 2.16 (oct, *J* = 6.7 Hz, 1H), 3.72 (s, 3H), 4.16 (d, *J* = 6.1 Hz, 1H), 6.12 (d, *J* = 3.2 Hz, 1H), 6.27 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.55-6.59 (m, 2H), 6.72-6.76 (m, 2H), 7.33 (dd, *J* = 1.8, 0.8 Hz, 1H); **^{13}C NMR** δ 19.07 (CH_3), 19.12 (CH_3), 32.88 (CH), 55.75 (CH_3), 58.94 (CH), 106.67 (CH), 109.99 (CH), 114.77 (2 × CH), 114.88 (2 × CH), 141.25 (CH), 141.78 (C), 152.19 (C), 155.73 (C); **IR** ν 3398, 2959, 2831, 1513, 1464, 1233 cm^{-1}; **MS** (EI) *m/z* (%) 245 ($M^{\bullet+}$, 20), 203 (20), 202 (100), 134 (10), 123 (25); **HRMS** (EI) 245.1415 ($C_{15}H_{19}NO_2$ requires 245.1416); **HPLC** analysis (Chiralcel OJ-H, hexane – propan-2-ol (90:10), 0.75 mL/min, t_{major} = 25.14 min, t_{minor} = 28.60 min) showed 85 % ee.

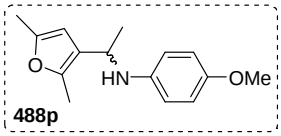
(–)-*N*-[1'-(Furan-3"-yl)ethyl]-*N*-(4-methoxyphenyl)amine (488o), $C_{13}H_{15}NO_2$, FW = 217.29



488o

488o: colourless oil; **[α]$_D$** –17 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.48 (d, *J* = 6.6 Hz, 3H), 3.48 (br s, 1H), 3.74 (s, 3H), 4.45 (q, *J* = 6.6 Hz, 1H), 6.37 (d, *J* = 0.8 Hz, 1H), 6.57-6.61 (m, 2H), 6.75-6.79 (m, 2H), 7.33 (d, *J* = 0.6 Hz, 1H), 7.33 (t, *J* = 1.6 Hz, 1H); **^{13}C NMR** δ 22.73 (CH_3), 46.42 (CH), 55.78 (CH_3), 109.08 (CH), 114.84 (2 × CH), 115.00 (2 × CH), 129.69 (C), 138.90 (CH), 141.48 (C), 143.14 (CH), 152.21 (C); **IR** ν 3397, 2967, 1511, 1299, 1235 cm^{-1}; **MS** (EI) *m/z* (%) 217 ($M^{\bullet+}$, 90), 202 (52), 123 (60), 122 (26), 108 (67), 95 (100); **HRMS** (EI) 217.1107 ($C_{13}H_{15}NO_2$ requires 217.1103); **HPLC** analysis (Chiralcel OJ-H, hexane – propan-2-ol (80:20), 0.70 mL/min, t_{major} = 37.33 min, t_{minor} = 40.73 min) showed 77 % ee.

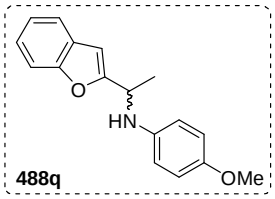
(–)-*N*-[1'-(2",5"-Dimethylfuran-3"-yl)ethyl]-*N*-(4-methoxyphenyl)amine (488p), $C_{15}H_{19}NO_2$, FW = 245.35



488p

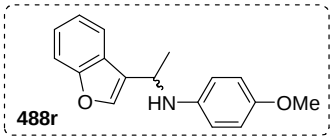
488p: yellow oil; **[α]$_D$** –4.5 (*c* 2.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.42 (d, *J* = 6.7 Hz, 3H), 2.21 (br s, 3H), 2.25 (br s, 3H), 3.36 (br s, 1H), 3.74 (s, 3H), 4.29 (q, *J* = 6.6 Hz, 1H), 5.88 (br s, 1H), 6.53-6.57 (m, 2H), 6.73-6.77 (m, 2H); **^{13}C NMR** δ 11.86 (CH_3), 13.61 (CH_3), 23.18 (CH_3), 46.37 (CH), 55.75 (CH_3), 104.64 (CH), 114.76 (2 × CH), 114.94 (2 × CH), 123.55 (C), 141.79 (C), 144.85 (C), 149.72 (C), 152.10 (C); **IR** ν 3398, 2964, 2921, 1583, 1511, 1450, 1234 cm^{-1}; **MS** (EI) *m/z* (%) 245 ($M^{\bullet+}$, 25), 123 (100), 86 (35), 84 (54); **HRMS** (EI) 245.1414 ($C_{15}H_{19}NO_2$ requires 245.1416); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 12.78 min, t_{major} = 14.55 min) showed 91 % ee.

(–)-*N*-[1'-(Benzofuran-2"-yl)ethyl]-*N*-(4-methoxyphenyl)amine (488q), $C_{17}H_{17}NO_2$, FW = 267.35



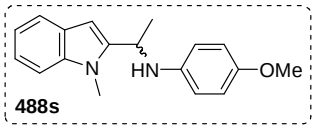
488q: colourless oil; **[α]$_D$** –121 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.51 (d, *J* = 6.7 Hz, 3H), 1.65 (d, *J* = 0.9 Hz, 3H), 3.74 (s, 3H), 4.67 (q, *J* = 6.7 Hz, 1H), 6.54 (d, *J* = 0.7 Hz, 1H), 6.63-6.67 (m, 2H), 6.75-6.79 (m, 2H), 7.17-7.27 (m, 2H), 7.45-7.50 (m, 2H); **^{13}C NMR** δ 21.17 (CH_3), 48.88 (CH), 55.73 (CH_3), 102.14 (CH), 111.07 (CH), 114.85 (2 × CH), 115.20 (2 × CH), 120.80 (CH), 122.63 (CH), 123.67 (CH), 128.47 (C), 140.89 (C), 152.59 (C), 154.77 (C), 160.39 (C); **IR** ν 3424, 3017, 2832, 1512 1235, 1216 cm^{-1}; **MS** (EI) *m/z* (%) 267 ($M^{\bullet+}$, 65), 145 (100), 123 (46), 117 (28), 115 (40), 91 (22); **HRMS** (EI) 267.1261 ($C_{17}H_{17}NO_2$ requires 267.1259); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 21.69 min, t_{major} = 24.21 min) showed 70 % ee.

(–)-*N*-[1'-(Benzofuran-3"-yl)ethyl]-*N*-(4-methoxyphenyl)amine (488r), $C_{17}H_{17}NO_2$, FW = 267.35



488r: colourless oil; **[α]$_D$** –93 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.66 (d, *J* = 6.8 Hz, 3H), 3.75 (s, 3H), 4.70 (q, *J* = 6.8 Hz, 1H), 6.56 (s, 1H), 6.65-6.69 (m, 2H), 6.78-6.82 (m, 2H), 7.22 (ddd, *J* = 7.4, 7.3, 1.0 Hz, 1H), 7.27 (ddd, *J* = 7.9, 7.3, 1.4 Hz, 1H), 7.48-7.52 (m, 2H); **^{13}C NMR** δ 21.20 (CH_3), 48.85 (CH), 55.74 (CH_3), 102.14 (CH), 111.10 (CH), 114.88 (2 × CH), 115.17 (2 × CH), 120.80 (CH), 122.67 (CH), 123.70 (CH), 128.50 (C), 140.99 (C), 152.57 (C), 154.80 (C), 160.48 (C); **IR** ν 3396, 3060, 2974, 2931, 2832, 1584, 1512, 1454, 1236 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 268 [$(M+H)^+$, 55], 267 (29), 145 (100), 124 (33); **HRMS** (CI/isobutane) 268.1339 ($C_{17}H_{18}NO_2$ requires 268.1338); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (97:3), 0.75 mL/min, t_{minor} = 14.44 min, t_{major} = 16.17 min) showed 65 % ee.

(–)-*N*-(4-Methoxyphenyl)-*N*-[1'-(1"-methyl-1*H*-indol-2"-yl)ethyl]amine (488s), $C_{18}H_{20}N_2O$, FW = 280.40

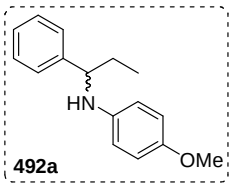


488s

488s: pale yellow crystals; **mp** 74-75 ºC (hexane/CH_2Cl_2); **[α]$_D$** –64 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.53 (d, *J* = 6.6 Hz, 3H), 3.38 (br s, 1H), 3.636 (s, 3H), 3.638 (s, 3H), 4.61 (q, *J* = 6.5 Hz, 1H), 6.37 (br s, 1H), 6.49-6.53 (m, 2H), 6.66-6.70 (m, 2H), 7.00 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 7.11 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.21 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.48 (ddd, *J* = 7.8, 1.0, 0.8 Hz, 1H); **^{13}C NMR** δ 20.27 (CH_3), 29.75 (CH_3), 46.81 (CH), 55.71 (CH_3), 99.63 (CH), 108.89 (CH), 114.64 (2 × CH), 114.93 (2 × CH), 119.36 (CH), 120.37 (CH), 121.34 (CH), 127.27 (C), 137.79 (C), 140.99 (C), 142.57 (C), 152.25 (C); **IR** ν 3395, 3009, 2975, 1933, 2834, 1511, 1467, 1306, 1233, 1216 cm^{-1}; **MS** (EI) *m/z* (%) 280 ($M^{\bullet+}$, 18), 159 (12), 158 (100), 157 (55), 156 (30), 123 (62), 108 (85); **HRMS** (EI) 280.1578 ($C_{18}H_{20}N_2O$ requires 280.1576); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (95:5), 0.75 mL/min, t_{minor} = 20.16 min, t_{major} = 29.08 min) showed 91 % ee.

6.4.2. Amines without Heterocycles

(–)-*N*-(4-Methoxyphenyl)-*N*-(1'-phenylprop-1'-yl)amine (492a), $C_{16}H_{19}NO$, FW = 241.35

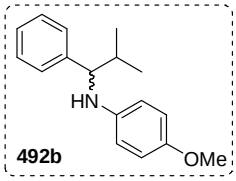


492a

492a:[225,36b] colourless oil; **[α]$_D$** –20 (*c* 2.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.4 Hz, 3H),1.62-1.78 (m, 2H), 3.59 (s, 3H), 3.72 (br s, 1H), 4.06 (t, *J* = 6.7 Hz, 1H), 6.36-6.40 (m, 2H), 6.57-6.61 (m, 2H), 7.10-7.14 (m, 1H), 7.19-7.26 (m, 4H); **^{13}C NMR** δ 10.87 (1 × CH_3), 31.74 (1 × CH_2), 55.78 (1 × CH_3), 60.61 (1 × CH), 114.52 (2 × CH), 114.81 (2 × CH), 126.59 (2 × CH), 126.87 (1 × CH), 128.51 (2 × CH), 141.86 (1 × C), 144.2 (1 × C), 151.87 (1 × C); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (80:20), 0.75 mL/min, t_{minor} = 12.80 min, t_{major} = 13.63 min) showed 92 % ee, [lit.[225] gives

Chiralcel OD, hexane – propan-2-ol (97:3), 1.0 mL/min, $t_{(+)\text{-major}}$ = 8.9 min, $t_{(-)\text{-minor}}$ = 9.8 min].

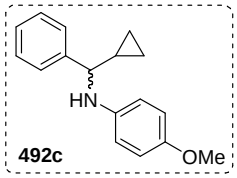
(–)-*N*-(4-Methoxyphenyl)-*N*-(2'-methyl-1'-phenylprop-1'-yl)amine (492b), $C_{17}H_{21}NO$, FW = 255.39



492b

492b:[227] colourless oil; **[α]$_D$** –22 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 1.92 (oct, *J* = 6.8 Hz, 1H), 3.58 (s, 3H), 3.78 (br s, 1H), 3.96 (d, *J* = 5.8 Hz, 1H), 6.35-6.39 (m, 2H), 6.56-6.60 (m, 2H), 7.09-7.15 (m, 1H), 7.20-7.21 (m, 4H); **^{13}C NMR** δ 18.65 (CH_3), 19.63 (CH_3), 34.85 (CH), 55.66 (CH_3), 64.55 (CH), 114.28 (2 × CH), 114.65 (2 × CH), 126.65 (CH), 127.17 (2 × CH), 128.09 (2 × CH), 141.95 (C), 142.71 (C), 151.60 (C); **IR** ν 3412, 3025, 2958, 2931, 2871, 2831, 1511, 1465, 1298, 1233 cm^{-1}; **MS** (EI) *m/z* (%) 255 ($M^{\bullet+}$, 12), 212 (100); **HRMS** (EI) 255.1622 ($C_{17}H_{21}NO$ requires 255.1623); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 10.39 min, t_{major} = 10.84 min) showed 97 % ee.

(+)-*N*-[Cyclopropyl(phenyl)methyl]-*N*-(4-methoxyphenyl)amine (492c), $C_{17}H_{19}NO$, FW = 253.37

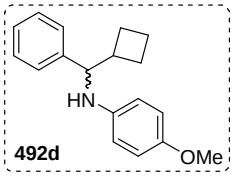


492c

492c: colourless oil; **[α]$_D$** +66 (*c* 1.0, $CHCl_3$);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.29 (ddd, *J* = 14.3, 5.2, 4.1 Hz, 1H), 0.36 (ddd, *J* = 9.5, 5.0, 4.5 Hz, 1H), 0.39-0.49 (m, 1H), 0.51 (dddd, *J* = 14.2, 8.0, 5.4, 4.0 Hz, 1H), 1.08 (dtd, *J* = 8.2, 5.0, 5.0 Hz, 1H), 3.48 (d, *J* = 8.4 Hz, 1H), 3.58 (s, 3H), 4.02 (br s, 1H), 6.32-6.36 (m, 2H), 6.55-6.59 (m, 2H), 7.14 (dddd, *J* = 8.1, 6.4, 2.2, 1.4 Hz, 1H), 7.20-7.25 (m, 2H), 7.29-7.32 (m, 2H); **^{13}C NMR** δ 3.50 (CH_2), 4.26 (CH_2), 19.86 (CH), 55.76 (CH_3), 63.87 (CH), 114.67 (2 × CH), 114.74 (2 × CH), 126.54 (2 × CH), 127.02 (CH), 128.53 (2 × CH), 141.98 (C), 143.63 (C), 151.97 (C); **IR** ν 3405, 3062, 3005, 2951, 2832, 1512, 1452, 1297, 1234 cm^{-1}; **MS** (EI) *m/z* (%) 253 ($M^{\bullet+}$, 43), 136 (20), 131 (100), 91 (38); **HRMS** (EI) 253.1473 ($C_{17}H_{19}NO$ requires 253.1467);

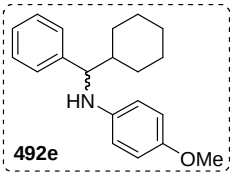
HPLC analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 12.98 min, t_{major} = 15.24 min) showed 95 % ee.

(–)-*N*-[Cyclobutyl(phenyl)methyl]-*N*-(4-methoxyphenyl)amine (492d), $C_{18}H_{21}NO$, FW = 267.40



492d: colourless oil; **[α]$_D$** –0.8 (*c* 1.0, $CHCl_3$), **[α]$_{436}$** –17.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.63-1.85 (m, 5H), 1.98-2.08 (m, 1H), 2.38-2.48 (m, 1H), 3.57 (s, 3H), 3.67 (br s, 1H), 4.01 (d, *J* = 9.1 Hz, 1H), 6.34-6.38 (m, 2H), 6.55-6.59 (m, 2H), 7.12 (dddd, *J* = 7.7, 6.2 2.4, 1.6 Hz, 1H), 7.17-7.25 (m, 3H); **^{13}C NMR** δ 17.59 (CH_2), 25.53 (CH_2), 26.20 (CH_2), 42.67 (CH), 55.77 (CH_3), 64.71 (CH), 114.62 (2 × CH), 114.77 (2 × CH), 126.66 (2 × CH), 126.90 (CH), 128.41 (2 × CH), 142.06 (C), 142.81 (C), 151.90 (C); **IR** ν 3405, 3026, 2936, 2831, 1512, 1452, 1295, 1238 cm^{-1}; **MS** (EI) *m/z* (%) 267 ($M^{\bullet+}$, 22), 212 (100), 91 (20), 85 (55), 84 (31), 83 (82); **HRMS** (EI) 267.1624 ($C_{18}H_{21}NO$ requires 267.1623); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 10.49 min, t_{major} = 10.97 min) showed 94 % ee.

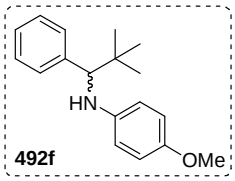
(–)-*N*-[Cyclohexyl(phenyl)methyl]-*N*-(4-methoxyphenyl)amine (492e), $C_{20}H_{25}NO$, FW = 295.46



492e:[228] colourless oil; **[α]$_D$** –11.6 (*c* 1.0, $CHCl_3$), [lit.[228] gives $[\alpha]_{435}$ –70.1 (*c* 1.59, EtOH)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.02-1.30 (m, 5H), 1.57 (br d, *J* = 12.9 Hz, 1H), 1.63-1.81 (m, 4H), 1.93 (br d, *J* = 12.6, 1H), 3.70 (s, 3H), 4.07 (d, *J* = 6.2 Hz, 1H), 6.46-6.50 (m, 2H), 6.67-6.71 (m, 2H), 7.20-7.26 (m, 1H), 7.29-7.34 (m, 4H); **^{13}C NMR** δ 26.41 (CH_2), 26.44 (CH_2), 26.48 (CH_2), 29.55 (CH_2), 30.24 (CH_2), 44.99 (CH), 55.78 (CH_3), 64.32 (CH), 114.35 (2 × CH), 114.78 (2 × CH), 126.70 (CH), 127.31 (2 × CH), 128.17 (2 × CH), 142.16 (C), 142.94 (C), 151.71 (C); **IR** ν 3421, 3023, 2928, 2853, 1512, 1451, 1236, 1217 cm^{-1}; **MS** (EI) *m/z* (%) 295 ($M^{\bullet+}$, 37), 213 (50), 212 (100), 197 (10), 168 (15), 134 (10), 91 (23); **HRMS** (EI) 295.1935 ($C_{20}H_{25}NO$ requires 295.1936); **HPLC** analysis (Chiralcel OJ-

H, hexane – propan-2-ol (85:15), 0.75 mL/min, t_{minor} = 12.85 min, t_{major} = 15.83 min) showed 76 % ee, [lit.[228] gives Chiralcel OJ, hexane – propan-2-ol (25:1), 1.0 mL/min, $t_{(-)\text{-}(S)\text{-major}}$ = 14.7 min, $t_{(+)\text{-}(R)\text{-minor}}$ = 36.0 min showing 98 % ee].

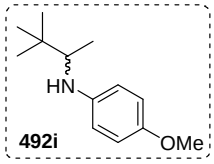
_N_-(2',2'-Dimethyl-1'-phenylprop-1'-yl)-_N_-(4-methoxyphenyl)amine (492f), $C_{18}H_{23}NO$, FW = 269.42



492f

492f:[228] colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.90 (s, 9H), 3.57 (s, 3H), 3.88 (s, 1H), 3.93 (br s, 1H), 6.33-6.37 (m, 2H), 6.54-6.58 (m, 2H), 7.10-7.14 (m, 1H), 7.16-7.24 (m, 3H); **^{13}C NMR** δ 27.05 (3 × CH_3), 34.88 (C), 55.68 (CH_3), 68.03 (CH), 114.21 (2 × CH), 114.65 (2 × CH), 126.69 (CH), 127.62 (2 × CH), 128.47 (2 × CH), 141.35 (C), 142.08 (C), 151.53 (C), 180.15 (C); **IR** ν 3430, 3026, 2954, 2604, 2869, 2831, 1511, 1396, 1366, 1237 cm^{-1}; **MS** (EI) *m/z* (%) 269 ($M^{\bullet+}$, 8), 212 (100); **HRMS** (EI) 269.1783 ($C_{18}H_{23}NO$ requires 269.1780); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.45 mL/min, t_{minor} = 12.91 min, t_{major} = 13.39 min) showed 10 % ee, [lit.[228] gives Chiralcel OJ, hexane – propan-2-ol (100:1), 0.5 mL/min, $t_{(+)\text{-}(R)\text{-minor}}$ = 33.6 min, $t_{(-)\text{-}(S)\text{-major}}$ = 39.3 min showing 90 % ee].

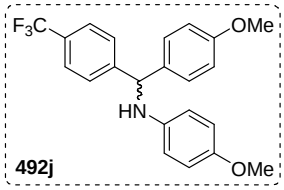
(–)-_N_-(3',3'-Dimethyl-but-2'-yl)-_N_-(4-methoxyphenyl)amine (492i), $C_{13}H_{21}NO$, FW = 207.35



492i

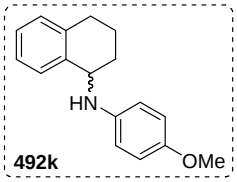
492i: colourless oil; **$[\alpha]_D$** –19 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.08 (d, *J* = 6.5 Hz, 3H), 3.09 (br s, 1H), 3.12 (q, *J* = 6.5 Hz, 1H), 3.76 (s, 3H), 6.56-6.60 (m, 2H), 6.76-6.80 (m, 2H); **^{13}C NMR** δ 15.73 (CH_3), 26.52 (3 × CH_3), 34.66 (C), 55.79 (CH_3), 58.55 (CH), 114.46 (2 × CH), 114.87 (2 × CH), 142.84 (C), 151.50 (C); **IR** ν 3399, 2960, 2869, 2831, 1511, 1465, 1371, 1233 cm^{-1}; **MS** (EI) *m/z* (%) 207 ($M^{\bullet+}$, 12), 150 (100); **HRMS** (EI) 207.1624 ($C_{13}H_{21}NO$ requires 207.1623); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{major} = 6.73 min, t_{minor} = 7.53 min) showed 39 % ee.

***N*-(4-Methoxyphenyl)-*N*-[(4'-methoxyphenyl)(4"-trifluoromethylphenyl)methyl]amine (492j) $C_{21}H_{20}O_2NF_3$, FW = 387.43**



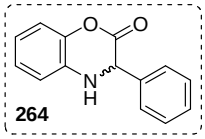
492j: colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.80 (s, 3H), 3.98 (br s, 1H), 5.44 (s, 1H), 6.48-6.52 (m, 2H), 6.72-6.76 (m, 2H), 6.86-6.90 (m, 2H), 7.22-7.26 (m, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** δ 55.28 (CH_3), 55.72 (CH_3), 62.95 (CH), 114.29 (2 × CH), 114.73 (2 × CH), 114.81 (2 × CH), 124.23 (q, *J* = 272.0 Hz, CF_3), 125.68 (q, *J* = 3.8 Hz, 2 × CH), 127.52 (2 × CH), 128.70 (2 × CH), 129.40 (q, *J* = 32.3 Hz, C), 134.79 (C), 141.29 (C), 147.45 (C), 152.43 (C), 159.14 (C); ^{19}F NMR δ –62.32; **IR** ν 3398, 3006, 2935, 2835, 1617, 1511, 1326, 1246, 1165 cm^{-1}; **MS** (EI) *m/z* (%) 387 ($M^{\bullet+}$, 20), 265 (100), 153 (10), 122 (10), 86 (16), 84 (25); **HRMS** (EI) 387.1445 ($C_{22}H_{20}NO_2F_3$ requires 387.1446); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (97:3), 0.75 mL/min, t_1 = 22.79 min, t_2 = 26.83 min) showed 6 % ee.

***N*-(4-Methoxyphenyl)-*N*-(1',2',3',4'-tetrahydronaphth-1'-yl)amine (492k), $C_{17}H_{19}NO$, FW = 253.37**



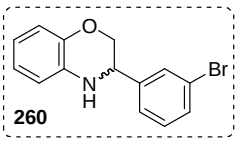
492k:[224] colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.76-2.02 (m, 4H), 2.74-2.90 (m, 2H), 3.62 (br s, 1H), 3.78 (s, 3H), 4.56 (dd, *J* = 5.0, 4.4 Hz, 1H), 6.64-6.68 (m, 2H), 6.81-6.85 (m, 2H), 7.13-7.23 (m, 3H), 7.44 (dd, *J* = 6.8, 1.7 Hz, 1H); **^{13}C NMR** δ 19.34 (CH_2), 28.66 (CH_2), 29.39 (CH_2), 52.15 (CH), 55.90 (CH_3), 114.51 (2 × CH), 115.05 (2 × CH), 126.09 (CH), 127.14 (CH), 129.06 (CH), 129.34 (CH), 137.64 (C), 138.35 (C), 141.64 (C), 152.06; **IR** ν 3398, 3018, 2933, 2860, 1513, 1452, 1239 cm^{-1}; **MS** (EI) *m/z* (%) 253 ($M^{\bullet+}$, 28), 199 (13), 131 (50), 123 (52), 108 (26), 91 (22), 86 (37), 84 (60); **HRMS** (EI) 253.1469 ($C_{17}H_{19}NO$ requires 253.1467); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_1 = 11.95 min, t_2 = 12.76 min) showed 0 % ee, [lit.[224] gives Chiralcel OD, heptanes – propan-2-ol (97:3), 0.5 mL/min, $t_{(+)\text{-major}}$ = 10.5 min, $t_{(-)\text{-minor}}$ = 13.0 min].

(–)-3-Phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (264), $C_{14}H_{11}NO_2$, FW = 225.26



264:[123] yellowish crystals; **mp** 78-79 ºC (hexane/CH_2Cl_2); **[α]$_D$** –64 (*c* 1.0, $CHCl_3$), [lit.[123] gives **[α]$_D$** –46.3 (*c* 1.0, $CHCl_3$)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.33 (br s, 1H), 5.04 (s, 1H), 6.80-6.82 (m, 1H), 6.87 (ddd, *J* = 8.1, 7.4, 1.5 Hz, 1H), 7.01-7.05 (m, 2H), 7.34-7.42 (m, 5H); **^{13}C NMR** δ 57.51 (CH), 113.20 (CH), 115.22 (CH), 118.62 (CH), 123.50 (CH), 125.77 (2 × CH), 127.27 (2 × CH), 130.70 (C), 134.63 (C), 139.15 (C), 163.61 (C); **IR** ν 3368, 3020, 2927, 1766, 1619, 1597, 1502, 1298, 1214 cm^{-1}; **MS** (EI) *m/z* (%) 225 ($M^{\bullet+}$, 58), 197 (65), 196 (70), 120 (100), 104 (12), 84 (30); **HRMS** (EI) 225.0792 ($C_{14}H_{11}NO_2$ requires 225.0790); **HPLC** analysis (Chiralcel OD-H, hexane – propan-2-ol (80:20), 0.60 mL/min, t_{major} = 16.27 min, t_{minor} = 21.85 min) showed 41 % ee, [lit.[123] gives Chiralcel OD-H, hexane – propan-2-ol (80:20), 0.60 mL/min, $t_{(–)\text{-major}}$ = 18.6 min, $t_{(+)\text{-minor}}$ = 25.5 min showing 98 % ee].

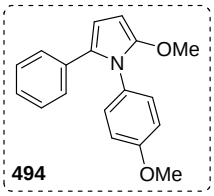
(+)-3-(3'-Bromophenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (260), $C_{14}H_{12}NOBr$, FW = 290.17



260:[123] yellowish oil; **[α]$_D$** +31 (*c* 1.0, $CHCl_3$), [lit.[123] gives **[α]$_D$** –118.2 (*c* 1.0, $CHCl_3$)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.85 (dd, *J* = 10.7, 8.4 Hz, 1H), 3.89 (br s, 1H), 4.15 (dd, *J* = 10.7, 2.9 Hz, 1H), 4.35 (dd, *J* = 8.4, 2.9 Hz, 1H), 6.58 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.62 (td, *J* = 7.6, 1.6 Hz, 1H), 6.72 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.75 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.22 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.37 (ddd, *J* = 7.8, 1.9, 1.2, 1H), 7.46 (dd, *J* = 1.9, 1.7 Hz, 1H; **^{13}C NMR** δ 53.73 (CH), 70.71 (CH_2), 115.57 (CH), 116.65 (CH), 119.25 (CH), 121.71 (CH), 122.99 (C), 125.96 (CH), 130.30 (CH), 130.45 (CH), 131.48 (CH), 133.53 (C), 141.61 (C), 143.48 (C); **IR** ν 3363, 3058, 3018, 2922, 2871, 1730, 1609, 1591, 1499, 1429, 1340, 1310, 1278, 1210 cm^{-1}; **MS** (EI) *m/z* (%) 291 ($M^{\bullet+}$, 90), 289 ($M^{\bullet+}$, 100), 184 (16), 182 (15), 180 (17), 134 (46), 120 (57), 105 (19), 103 (18), 103 (21); **HRMS** (EI) 291.0085 ($C_{14}H_{12}NO^{81}Br$ requires 3291.0083), 289.0096 ($C_{14}H_{12}NO^{79}Br$ requires

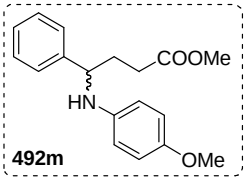
289.0102); **HPLC** analysis (Chiralcel OD-H, hexane – propan-2-ol (80:20), 0.60 mL/min, t_{minor} = 16.02 min, t_{major} = 27.17 min) showed 26 % ee, [lit.[123] gives Chiralcel OD-H, hexane – propan-2-ol (80:20), 0.60 mL/min, $t_{(–)\text{-major}}$ = 19.8 min, $t_{(+)\text{-minor}}$ = 30.6 min showing 98 % ee].

2-Methoxy-1-(4'-methoxyphenyl)-5-phenyl-1*H*-pyrrole (494), $C_{18}H_{17}NO_2$, FW = 279.36



494: white crystals; **mp** 101-102 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.81 (s, 3H), 5.45 (d, *J* = 3.7 Hz, 1H), 6.26 (d, *J* = 3.7 Hz, 1H), 6.84-6.88 (m, 2H), 7.03-7.16 (m, 7H); **^{13}C NMR** δ 54.30 (CH_3), 56.71 (CH_3), 82.86 (CH), 105.73 (CH), 112.92 (2 × CH), 124.24 (CH), 125.80 (C), 126.13 (2 × CH), 126.95 (2 × CH), 128.10 (2 × CH), 129.00 (C), 132.24 (C), 149.12 (C), 157.39 (C); **IR** ν 3019, 2956, 2931, 2832, 1599, 1564, 1515, 1454, 1420, 1294, 1250, 1216 cm^{-1}; **MS** (EI) *m/z* (%) 279 ($M^{\bullet+}$, 55), 264 (100), 193 (10), 103 (10); **HRMS** (EI) 279.1258 ($C_{18}H_{17}NO_2$ requires 279.1259).

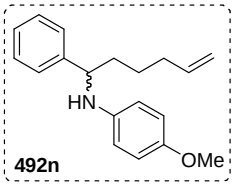
(–)-Methyl 4-[*N*-(4'-methoxyphenyl)amino]-4-phenylbutanoate (492m), $C_{18}H_{21}NO_3$, FW = 299.40



492m: yellow oil; **mp** 59-60 ºC (hexane/CH_2Cl_2); **$[\alpha]_D$** –13.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.03-2.19 (m, 2H), 2.41 (dd, *J* = 7.3, 7.2 Hz, 3H), 3.66 (s, 3H), 3.69 (s, 3H), 3.98 (br s, 1H), 4.30 (dd, *J* = 7.2, 6.5 Hz, 1H), 6.45-6.49 (m, 2H), 6.66-6.70 (m, 2H), 7.21-7.25 (m, 1H), 7.29-7.34 (m, 4H); **^{13}C NMR** δ 31.06 (CH_2), 33.32 (CH_2), 51.77 (CH_3), 55.75 (CH_3), 58.52 (CH), 114.60 (2 × CH), 114.77 (2 × CH), 126.46 (2 × CH), 127.21 (CH), 128.71 (2 × CH), 141.39 (C), 143.33 (C), 151.97 (C), 174.07 (C); **IR** ν 3394, 3025, 3005, 2951, 2833, 1733, 1513, 1452, 1237 cm^{-1}; **MS** (EI) *m/z* (%) 299 ($M^{\bullet+}$, 30), 212 (100), 117 (23); **HRMS** (EI) 299.1518 ($C_{18}H_{21}NO_3$ requires 299.1521); **HPLC**

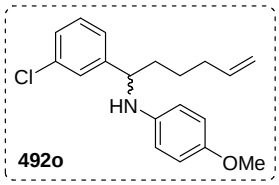
analysis (Chiralpak IB, hexane – propan-2-ol (90:10), 0.75 mL/min, t_{minor} = 16.52 min, t_{major} = 28.60 min) showed 88 % ee.

(–)-*N*-(4-Methoxyphenyl)-*N*-(1'-phenylhex-5'-en-1'-yl)amine (492n), $C_{19}H_{23}NO$, FW = 281.43



492n: colourless oil; **[α]$_D$** –6.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.28-1.49 (m, 2H), 1.61-1.78 (m, 2H), 1.96-2.02 (m, 2H), 3.60 (s, 3H), 3,73 (br s, 1H), 4.15 (t, *J* = 6.8 Hz, 1H), 4.87 (ddt, *J* = 10.2, 2.0, 1.2 Hz, 1H), 4.92 (ddd, *J* = 17.1, 3.5, 1.6 Hz, 1H), 5.68 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 6.37-6.41 (m, 2H), 6.58-6.62 (m, 2H), 7.11-7.16 (m, 1H), 7.21-7.26 (m, 4H); **^{13}C NMR** δ 23.69 (CH_2), 33.51 (CH_2), 38.32 (CH_2), 55.58 (CH_3), 58.87 (CH), 114.37 (2 × CH), 114.69 (2 × CH), 114.83 (CH_2), 126.37 (2 × CH), 126.81 (CH), 128.48 (2 × CH), 138.34 (CH), 141.64 (C), 144.34 (C), 151.74 (C); **IR** ν 3405, 3061, 3026, 2933, 2857, 2832, 1639, 1513, 1453, 1237 cm^{-1}; **MS** (EI) *m/z* (%) 281 ($M^{\bullet+}$, 65), 212 (100), 168 (20), 123 (37), 108 (23), 91 (68), 84 (22); **HRMS** (EI) 281.1778 ($C_{19}H_{23}NO$ requires 281.1780); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 13.09 min, t_{major} = 14.20 min) showed 84 % ee.

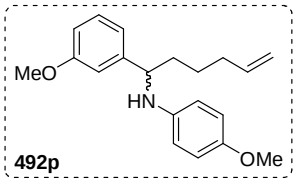
(–)-*N*-[1'-(3"-Chlorophenyl)hex-5'-en-1'-yl]-*N*-(4-methoxyphenyl)amine (492o), $C_{19}H_{22}NOCl$, FW = 315.87



492o: colourless oil; **[α]$_D$** –2.1 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.26-1.50 (m, 2H), 1.59-1.75 (m, 2H), 1.90-2.02 (m, 2H), 3.61 (s, 3H), 3.71 (br s, 1H), 4.11 (t, *J* = 6.8 Hz, 1H), 4.87-4.90 (m, 1H), 4.92 (ddd, *J* = 17.2, 3.5, 1.6 Hz, 1H), 5.68 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 6.34-6.38 (m, 2H), 6.59-6.63 (m, 2H), 7.09-7.17 (m, 3H), 7.24-7.25 (m, 1H); **^{13}C NMR** δ 25.51 (CH_2), 33.48 (CH_2), 38.30 (CH_2), 55.75 (CH_3), 58.68 (CH), 114.46 (2 × CH), 114.83 (2 × CH), 115.06 (CH_2), 124.66 (CH), 126.54 (CH), 127.12 (CH), 129.84 (CH), 134.49 (C), 138.19 (CH), 141.34 (C), 146.87 (C), 152.08 (C); **IR** ν 3406, 3072, 2934, 2832, 1639, 1595, 1510, 1574, 1470, 1433, 1237 cm^{-1}; **MS** (EI) *m/z* (%) 317 ($M^{\bullet+}$,

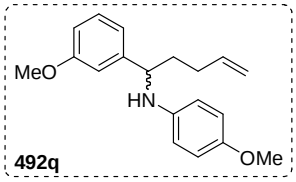
8), 315 ($M^{\bullet+}$, 20), 248 (25), 246 (70), 212 (10), 123 (13), 84 (40); **HRMS** (EI) 317.1367 ($C_{19}H_{22}NO^{37}Cl$ requires 317.1367), 315.1386 ($C_{19}H_{22}NO^{35}Cl$ requires 315.1390); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 15.44 min, t_{major} = 16.73 min) showed 82 % ee.

(–)-*N*-(4-Methoxyphenyl)-*N*-[1'-(3"-methoxyphenyl)hex-5'-en-1'-yl]amine (492p), $C_{20}H_{25}NO_2$, FW = 311.46



492p: yellowish oil; **$[\alpha]_D$** –5.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.28-1.48 (m, 2H) 1.62-1.76 (m, 2H), 1.96-2.01 (m, 2H), 3.60 (s, 3H), 3.69 (s, 3H), 4.11 (t, *J* = 6.6 Hz, 1H), 4.86-4.93 (m, 2H), 5.79 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 6.37-3.41 (m, 2H), 6.58-6.61 (m, 2H), 6.67 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.81 (d, *J* = 1.6 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 7.14 (dd, *J* = 8.0, 7.6 Hz, 1H); **^{13}C NMR** δ 25.65 (CH_2), 33.62 (CH_2), 38.33 (CH_2), 55.19 (CH_3), 55.77 (CH_3), 59.02 (CH), 111.91 (CH), 112.29 (CH), 114.48 (2 × CH), 114.77 (2 × CH), 114.93 (CH_2), 118.89 (CH), 129.55 (CH), 138.45 (CH), 141.74 (C), 146.34 (C), 151.87 (C), 159.86 (C); **IR** ν 3404, 2935, 2833, 1600, 1586, 1513, 1486, 1455, 1438, 1237 cm^{-1}; **MS** (EI) *m/z* (%) 311 ($M^{\bullet+}$, 98), 243 (94), 242 (100), 226 (46), 207 (45), 147 (48), 134 (80), 123 (84), 122 (66), 121 (90), 108 (68), 107 (40), 91 (59), 84 (35); **HRMS** (EI) 311.1886 ($C_{20}H_{25}NO_2$ requires 311.1885); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 20.32 min, t_{major} = 23.48 min) showed 90 % ee.

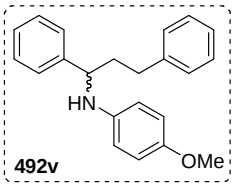
(–)-*N*-4-(Methoxyphenyl)-*N*-[1'-(3"-methoxyphenyl)pent-4'-en-1'-yl]amine (492q), $C_{22}H_{23}NO_2$, FW = 297.43



492q: colourless oil; **$[\alpha]_D$** –9.1 (*c* 2.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.71-1.85 (m, 2H), 1.97-2.10 (m, 2H), 3.59 (s, 3H), 3.69 (s, 3H), 4.14 (t, *J* = 6.7 Hz, 1H), 4.89-4.97 (m, 2H), 5.74 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 6.38-6.41 (m, 2H), 6.58-6.62 (m, 2H), 6.67 (ddd, *J* = 8.2, 2.6, 0.8 Hz, 1H), 6.81 (dd, *J* = 2.4, 1.6 Hz, 1H), 7.20 (br d, *J* = 7.6 Hz, 1H),

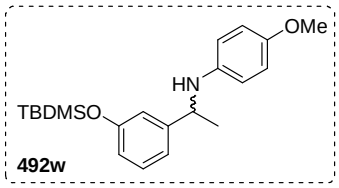
7.14 (t, *J* = 7.9 Hz, 1H); **^{13}C NMR** δ 30.54 (CH_2), 37.80 (CH_2), 55.17 (CH_3), 55.74 (CH_3), 58.65 (CH), 112.03 (CH), 112.34 (CH), 114.60 (2 × CH), 114.76 (2 × CH), 115.29 (CH_2), 118.93 (CH), 129.58 (CH), 137.95 (CH_2), 141.59 (C), 146.02 (C), 151.95 (C), 159.88 (C); **IR** ν 3403, 2936, 2833, 1600, 1513, 1454, 1238 cm^{-1}; **MS** (EI) *m/z* (%) 297 ($M^{\bullet+}$, 23), 243 (15), 242 (100), 212 (10), 154 (18), 123 (15), 121 (28), 108 (12), 91 (13), 84 (10); **HRMS** (EI) 297.1728 ($C_{19}H_{23}NO_2$ requires 297.1729); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (98:2), 0.75 mL/min, t_{minor} = 14.09 min, t_{major} = 16.16 min) showed 95 % ee.

(–)-*N*-(1',3'-Diphenylprop-1'-yl)-*N*-(4-methoxyphenyl)amine (492v), $C_{22}H_{23}NO$, FW = 317.46



492v: colourless oil; **[α]$_D$** –2.5 (*c* 2.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.94-2.09 (m, 2H), 2.52-2.66 (m, 2H), 3.58 (s, 3H), 3.75 (br s, 1H), 4.17 (t, *J* = 6.8 Hz, 1H), 6.33-6.37 (m, 2H), 6.56-6.60 (m, 2H), 7.06-7.25 (m, 10H); **^{13}C NMR** δ 32.70 (CH_2), 40.25 (CH_2), 55.76 (CH_3), 58.66 (CH), 114.68 (2 × CH), 114.79 (2 × CH), 126.04 (CH), 126.57 (2 × CH), 127.06 (CH), 128.50 (4 × CH), 128.65 (2 × CH), 141.47 (C), 141.61 (C), 144.04 (C), 151.99 (C); **IR** ν 3405, 3026, 2943, 2831, 1602, 1512, 1453, 1295, 1237 cm^{-1}; **MS** (EI) *m/z* (%) 317 ($M^{\bullet+}$, 34), 212 (100), 123 (11), 91 (40); **HRMS** (EI) 317.1782 ($C_{22}H_{23}NO$ requires 317.1780); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (98:2), 0.75 mL/min, t_{major} = 29.00 min, t_{minor} = 32.68 min) showed 95 % ee.

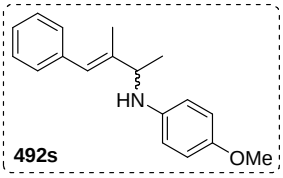
(–)-*N*-{1'-[3-(*tert*-Butyldimethylsilyloxy)phenyl]ethyl}-*N*-(4-methoxyphenyl)amine (492w), $C_{21}H_{31}NO_5Si$, FW = 357.62



492w: yellowish oil; **[α]$_D$** –2.1 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.16 (s 6H), 0.98 (s, 9H), 1.49 (d, *J* = 6.7 Hz, 3H), 3.71 (s, 3H), 4.37 (d, *J* = 6.7 Hz, 3H), 6.46-6.50 (m, 2H), 6.68-6.72 (m, 3H), 6.85 (br s, 1H), 6.96 (br d, *J* = 7.6 Hz, 1H), 7.18 (dd, *J* = 7.8, 7.7 Hz, 1H); **^{13}C NMR** δ –4.39 (2 × CH_3), 18.25 (C), 25.04 (CH_3), 25.74 (3 × CH_3), 54.08 (CH_3), 55.79 (CH_3), 114.65 (2 × CH), 114.75 (2 × CH), 117.75 (CH), 118.49 (CH), 118.93

(CH), 129.54 (CH), 141.57 (C), 147.24 (C), 151.90 (C), 155.92 (C); **IR** ν 3406, 2957, 2931, 2858, 1602, 1586, 1511, 1483, 1442, 1235 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 358 [$(M+H)^+$, 100], 235 (8), 124 (8); **HRMS** (CI/isobutane) 358.2202 ($C_{21}H_{32}NO_2Si$ requires 358.2200); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 9.21 min, t_{major} = 10.65 min) showed 93 % ee.

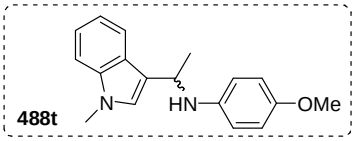
(–)-*N*-(4-Methoxyphenyl)-*N*-[(*E*)-3'-methyl-4'-phenylbut-3'-en-2'-yl]amine (492s), $C_{18}H_{21}NO$, FW = 267.40



492s: colourless oil; **$[\alpha]_D$** –63 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.41 (d, *J* = 6.7 Hz, 3H), 1.86 (d, *J* = 1.3 Hz, 3H), 3.59 (br s, 1H), 3.75 (s, 3H), 3.94 (q, *J* = 6.6 Hz, 1H), 6.58 (br s, 1H), 6.60-6.64 (m, 2H), 6.76-6.80 (m, 2H), 7.19-7.23 (m, 1H), 7.26-7.28 (m, 2H), 7.31-7.35 (m, 2H); **^{13}C NMR** δ 13.78 (CH_3), 21.57 (CH_3), 55.80 (CH_3), 57.67 (CH), 114.57 (2 × CH), 114.80 (2 × CH), 125.10 (CH), 126.17 (CH), 128.07 (2 × CH), 128.92 (2 × CH), 138.09 (C), 140.83 (C), 141.86 (CH), 151.91 (C); **IR** ν 3405, 3023, 2963, 2930, 2831, 1511, 1442, 1234 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 268 [$(M+H)^+$, 45], 145 (100), 124 (32), 85 (25); **HRMS** (CI/isobutane) 268.1701 ($C_{18}H_{22}NO$ requires 268.1701); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (98:2), 0.75 mL/min, t_{minor} = 11.09 min, t_{major} = 12.76 min) showed 84 % ee.

6.4.3. Racemic Amines

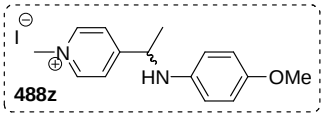
(±)-*N*-(4-Methoxyphenyl)-*N*-[1'-(1"-methyl-1*H*-indol-3"-yl)ethyl]amine (488t), $C_{18}H_{20}N_2O$, FW = 280.40



488t: pale yellow crystals; **mp** 96-97 ºC (hexane/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.63 (d, *J* = 6.6 Hz, 3H), 3.731 (s, 3H), 3.732 (s, 3H), 4.85 (q, *J* = 6.5 Hz, 1H), 6.59-6.63 (m, 2H), 6.72-6.76 (m, 2H), 6.98 (br s, 1H), 7.12 (ddd, *J* = 6.9, 6.9, 1.1 Hz, 1H), 7.24 (ddd, *J* = 7.1, 6.9, 1.1 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H); **^{13}C NMR** δ

22.88 (CH_3), 32.75 (CH_3), 47.35 (CH), 55.81 (CH_3), 109.38 (CH), 114.64 (2 × CH), 114.80 (2 × CH), 118.64 (C), 118.91 (CH), 119.38 (CH), 125.83 (CH), 126.34 (C), 137.41 (C), 142.01 (C), 151.88 (C); **IR** ν 3406, 3005, 2962, 2832, 1509, 1467, 1371, 1232 cm^{-1}; **MS** (EI) *m/z* (%) 280 ($M^{\bullet+}$, 64), 273 (20), 159 (74), 158 (100), 157 (100), 156 (88), 143 (50), 123 (100), 115 (93), 108 (100); **HRMS** (EI) 280.1577 ($C_{18}H_{20}N_2O$ requires 280.1576).

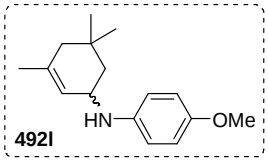
(±)-*N*-(4-Methoxyphenyl)-*N*-[1'-(1"-methylpyridinium-4"-yl)ethyl]amine iodide (488z), $C_{15}H_{19}N_2OI$, FW = 370.26



488z

488z: brown oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.56 (d, *J* = 6.8 Hz, 3H), 3.67 (s, 3H), 4.42 (br s, 3H), 4.62 (q, *J* = 6.8 Hz, 1H), 6.36-6.40 (m, 2H), 6.65-6.69 (m, 2H), 8.02 (d, *J* = 6.1 Hz, 2H), 8.88 (d, *J* = 6.1 Hz, 2H).

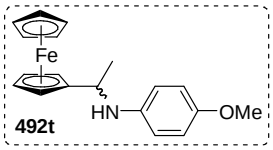
(±)-*N*-(4-Methoxyphenyl)-*N*-(3',5',5'-trimethylcyclohex-2'-enyl)amine (492l), $C_{16}H_{23}NO$, FW = 245.40



492l

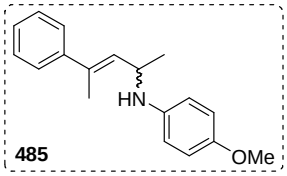
492l: colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.00 (s, 3H), 1.11 (dd, *J* = 12.4, 10.1 Hz, 1H), 1.63-1.67 (m, 1H), 1.67 (d, *J* = 1.2 Hz, 2H), 1.82 (dddd, *J* = 12.4, 5.5, 1.7, 1.2 Hz, 1H), 1.83-1.89 (m, 1H), 3.75 (s, 3H), 3.92-3.96 (m, 1H), 5.45 3.84 (q, *J* = 1.1 Hz, 1H), 6.60-6.64 (m, 2H), 6.77-6.81 (m, 2H); **^{13}C NMR** δ 23.63 (CH_3), 25.88 (CH_3), 30.74 (C), 31.54 (CH_3), 43.15 (CH_2), 44.32 (CH_2), 49.40 (CH), 55.80 (CH_3), 114.96 (2 × CH), 115.15 (2 × CH), 122.15 (CH), 135.34 (C), 141.70 (C), 152.08 (C); **IR** ν 3365, 2951, 2868, 2828, 1510, 1464, 1264, 1232, 1179 cm^{-1}; **MS** (EI) *m/z* (%) 245 ($M^{\bullet+}$, 38), 123 (100), 108 (20); **HRMS** (EI) 245.1776 ($C_{16}H_{23}NO$ requires 245.1780).

(±)-*N*-[1'-(Ferrocen-1"yl)ethyl]-4-(methoxyphenyl)amine (492t), $C_{19}H_{21}NOFe$, FW = 335.26



492t: yellow crystals; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.51 (d, *J* = 6.4 Hz, 3H), 3.62 (br s, 1H), 3.78 (s, 3H), 4.13-4.16 (m, 2H), 4.18-4.22 (m, 1H), 4.21 (s, 5H), 4.23-4.24 (m, 1H), 4.26 (q, *J* = 6.4 Hz, 1H), 6.63-6.67 (m, 2H), 6.80-6.84 (m, 2H); **^{13}C NMR** δ 21.17 (CH_3), 48.40 (CH), 55.86 (CH_3), 66.16 (CH), 67.06 (CH), 67.49 (CH), 67.71 (CH), 68.43 (5 × CH), 93.80 (C), 114.95 (2 × CH), 115.02 (2 × CH), 141.89 (C), 152.09 (C); **IR** ν 3393, 3092, 2969, 2930, 2831, 1510, 1463, 1294, 1233 cm^{-1}; **MS** (EI) *m/z* (%) 335 ($M^{\bullet+}$, 25), 213 (100), 120 (30); **HRMS** (EI) 335.0970 ($C_{19}H_{21}NO^{56}Fe$ requires 335.0973).

(±)-*N*-(4-Methoxyphenyl)-*N*-[(*E*)-4'-phenylpent-3'-en-2'-yl]amine (485), $C_{17}H_{21}NO$, FW = 267.40



A solution of methyllithium (22.5 mL, 36 mmol, 1.6 M in ether, 1.2 equiv) was added dropwise to a solution of aldimine **484** (7.54 g, 30.0 mmol, 1.0 equiv) in anhydrous THF (50 mL) at 0 ºC after which it was quenched with water (100 mL). The aqueous layer was extracted with ether (3 × 50 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and evaporated. The residue was purified on a silica gel column (200 mL) with a solvent gradient from a mixture of petroleum ether – ethyl acetate (98:2) to (95:5) to afford the amine **485** (2.03 g, 7.59 mmol, 25 %): red thick oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.5 Hz, 3H), 2.14 (d, *J* = 1.3 Hz, 3H), 3.74 (s, 3H), 4.25 (dq, *J* = 8.1, 6.6 Hz, 1H), 5.69 (dq, *J* = 8.3, 1.2 Hz, 1H), 6.58-6.62 (m, 2H), 6.74-6.78 (m, 2H), 7.20-7.25 (m, 1H), 7.28-7.32 (m, 2H), 7.36-7.38 (m, 2H).

Part C:

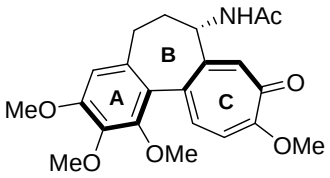
Applications of the Method

7. Applications in Synthesis of Alkaloids (I)

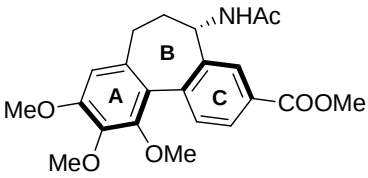
7.1. *N*-Acetylcolchinol and Other Allocholchicinoids

7.1.1. Historical Overview[229,230] *and Biological Properties*[231,232]

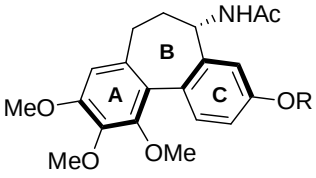
The toxic effects of plant extracts from *Colchicum autumnale* have been known for two millennia – already ancient Greeks used the *Colchicum* extracts for treatment of gout, first described by **Pedanius Dioscorides** in *De Materia Medica*, 78 AD. The active species – colchicine **495** (Figure 7.1) – was isolated only in 19th century (1820) by two French chemists **P. J. Pelletier** and **J. B. Caventou**. It took another hundred years to determine the structure of colchicine, the main contributions are indebted to **A. O. R. Windaus** (1923), **J. W. Cook** (1940) and **M. J. S. Dewar** (1945). The biological properties, the anti-tumour activity in particular, were of high interest after the observation of tumour growth inhibition (**C. Dominici**, 1932), followed by mechanistic explanations made by **F. Lits** (1934), **A. P. Dustin** (1934) and **E. C. Amoroso** (1935).



(–)-495
(–)-(a*R*,7*S*)-Colchicine



(–)-496
(–)-(a*R*,7*S*)-Allocolchicine



(–)-497: R = H
(–)-(a*R*,7*S*)-*N*-Acetylcolchinol
(–)-498: R = Me
(–)-(a*R*,7*S*)-*N*-Acetylcolchinol-methylether
(–)-499: R = $P(O)(OH)_2$
(–)-(a*R*,7*S*)-*N*-Acetylcolchinol-phosphate

Figure 7.1. Colchicine and Family of Allocolchicinoid Alkaloids

However, after years of research, the high toxicity proved it clinically unusable and the attention turned to its close biphenyl-derived analogues called allocolchicinoids as allocholchicine **496**, *N*-acetylcholchinol **497** and its methylether **498**. These compounds contain six-membered aromatic C-ring instead of the seven-membered tropolone ring.

The numbering of the allocolchicinoid structures is as follows (Figure 7.2), the oxygenated substituents on A-ring in positions 1, 2 and 3, and on ring-C in position 9; *N*-acetamide of the ring-B in position 7; the bond of axial chirality is the 11a(11b) biaryl link.

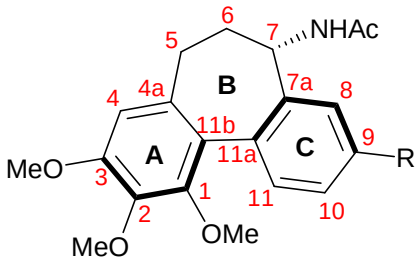
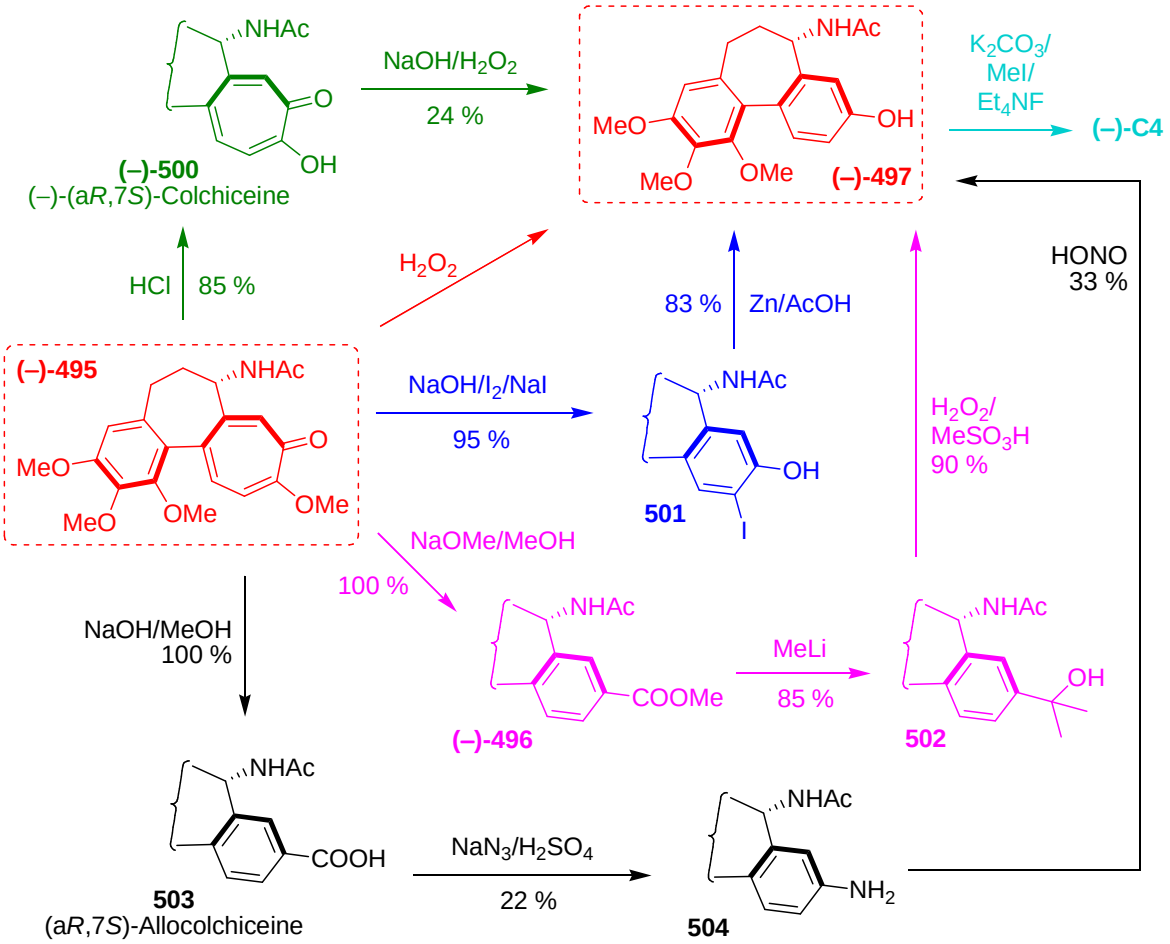


Figure 7.2. Numbering of Allocholchicinoids Structures

The main mode of action of tumour regression when low doses of colchicine (or allocolchicinoids) are administered is binding to cytoskeletal protein tubulin and disruption of the tubulin-microtubule equilibrium (in microtubulin polymerisation) in the cell, thereby suppression of the mitosis and cell division. Methylether **498** has higher tubulin affinity and better stability than colchicine **495** and it serves as *in vitro* anti-tubulin standard. It is well accepted that the primary pharmacophore of these alkaloids is the ring-A – any alteration of the trioxygenated-phenyl moiety leads to compromised tubulin-binding ability. The biological activity of the C-ring varies with its size, position and substitution. The character of B-ring influences significantly the conformational mobility of the A-C-biphenyl backbone and any change (e.g. five-, six- or eight-membered B-ring analogues) results in inability to affect the tubulin-binding. The natural (–)-(7*S*)-colchicine adopts (a*R*)-configuration and it is the only isomer active in the tubulin polymerisation process. Regarding the allocolchicinoids, in general, they are conformationally unstable, dominated by the (a*R*,7*S*)-atropoisomer. However, it is not clear whether the major (a*R*,7*S*)- or the minor (a*S*,7*S*)-isomer is the active species.

N-Acetylcholchinol (NAC) has been tested successfully *in vivo* and its phosphate pro-drug **499** (Figure 7.1) has been used in clinical trials (Astra-Zeneca). Because of this pharmaceutical potential, in recent years, much attention has been dedicated to developing effective ways of obtaining NAC. Unfortunately, adverse blood vessels congestion has been observed in clinical trials and further development has ceased.[230b]



Scheme 7.1. Degradation of Colchicine to *N*-Acetylcolchinol

In principle, the production methods are:

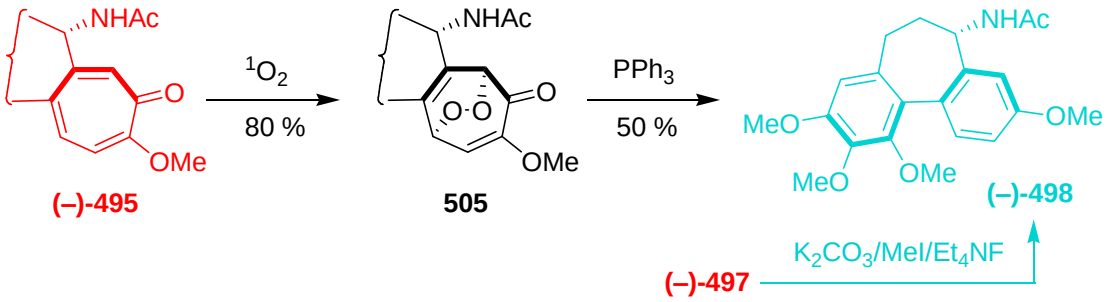
- low yielding extraction from North Indian lily *Gloriosa superba*,
- synthesis by degradation of natural (–)-colchicine[230] (Scheme 7.1),
- synthesis from commercially available starting materials (Chapter 8.1.1).

1. *One-step-degradation of colchicine to N-acetylcolchinol* (**in red**):
   - treating colchicine with aqueous hydrogen peroxide offers NAC.

2. *Two-step-degradation to N-acetylcolchinol*:
   - oxidative ring-C contraction of colchiceine (**500**, **in green**) – a product of acidic hydrolysis of colchicine – with basic hydrogen peroxide leads to NAC in overall 20 % yield,
   - reviewed original Windaus procedure (**in blue**) affords NAC in overall 79 %

yield by reaction of colchicine with sodium hypoiodite and subsequent reductive deiodination of **501**.

3. *Three-step-degradation to N-acetylcolchinol*:
   - the contraction of ring-C can also be achieved by using methanolic methoxide or hydroxide affording allocolchicine (**496**, **in pink**) or allocolchiceine (**503**, **in black**), respectively,
   - addition of methylithium to allocolchicine (**496**, **in pink**) gives tertiary alcohol **502** which is then oxidised with hydrogen peroxide and rearranged under acidic conditions to NAC in overall 76 % yield,
   - allocolchiceine (**503**, **in black**), can be converted to aniline **504** and its diazotisation with subsequent elimination leads to NAC in yield as low as 7 %.



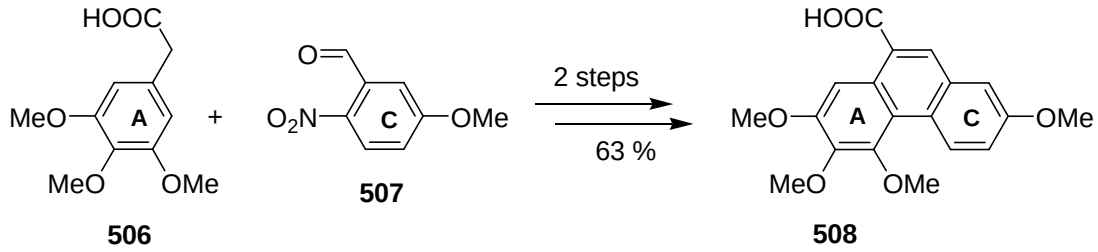
Scheme 7.2. Degradation of Colchicine to *N*-Acetylcolchinol-methylether

4. *Preparation of N-acetylcolchinol-methylether* (Scheme 7.2):
   - singlet oxygen is used to form bridged **505** from colchicine
   - triphenylphosphine-induced ring-C contraction affords *N*-acetylcolchinol-methylether **498** in overall 40 % yield,
   - methylation of NAC prepared by any of previously mentioned methods can be performed with methyliodide/potassium carbonate providing **498** in good yield.

7.1.2. Syntheses of N-Acetylcolchinol and Closely Related Allocolchicinoids

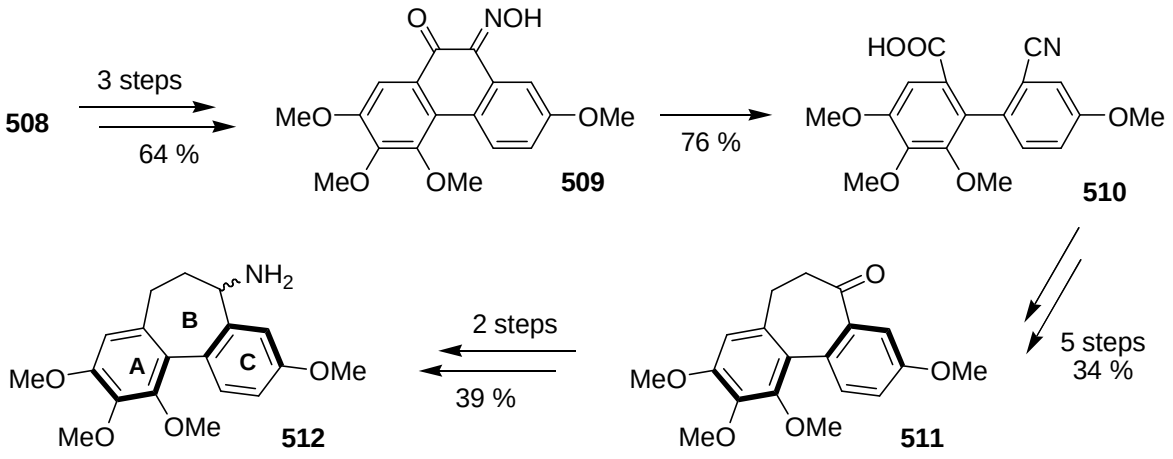
In principle, there are three synthetic approaches how to construct the dibenzocycloheptadiene tricyclic system:

- cleavage of the B-ring of phenanthrene and recyclication to seven-membered ring,
- aldol condensation of two components and subsequent oxidative coupling of substituted diphenylpropane,
- metal-mediated coupling of two components and subsequent aldol condensation.



Scheme 7.3. Synthesis of 2,3,4,7-Tetramethoxyphenanthroic Acid

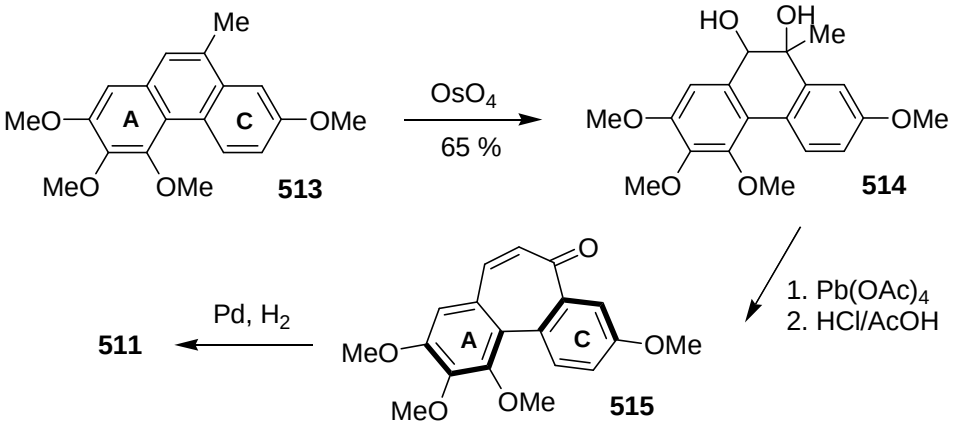
The first total synthesis was published in 1950 by Rapoport and Cisney.[233] It was based on popular phenanthrene chemistry since the 9(10)-double bond was known to be oxidatively cleaved to highly functionalised biphenyl structures. Their synthesis started from 2,3,4,7-tetramethoxyphenanthoic acid **508** which was prepared in two steps from 3,4,5-trimethoxyphenylacetic acid **506** and 2-nitro-5-methoxybenzaldehyde **507** (Scheme 7.3).



Scheme 7.4. First Total Synthesis of *N*-Acetylcolchinol-methylether

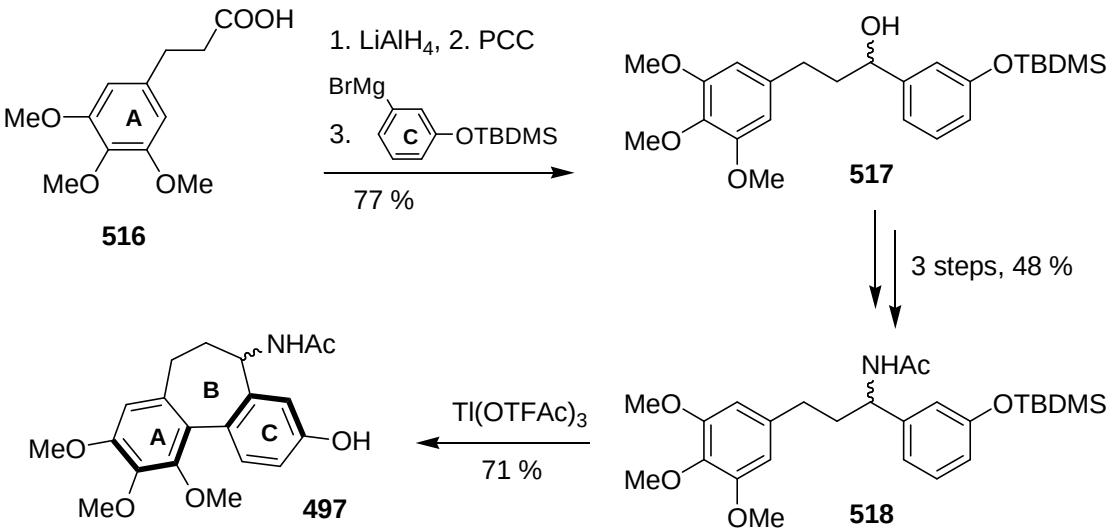
Phenanthroic acid **508** was derivatised in three steps to monoxime **509** and its Beckmann rearrangement afforded cyanoacid **510**. Recyclisation of **510** was achieved in three steps leading to dibenzocycloheptadienone **511**, an intermediate known from various degradation works. This classical synthesis provided racemic colchinol-methylether **512** in 13 steps and 4.5 % overall yield (Scheme 7.4). Resolution of **512** with *d*-tartaric acid

afforded crystalline salt from which the free amine was released and acetylated to (–)-*N*-acetylcolchinol-methylether **498**.



Scheme 7.5. Alternative Synthesis of *N*-Acetylcolchinol-methylether

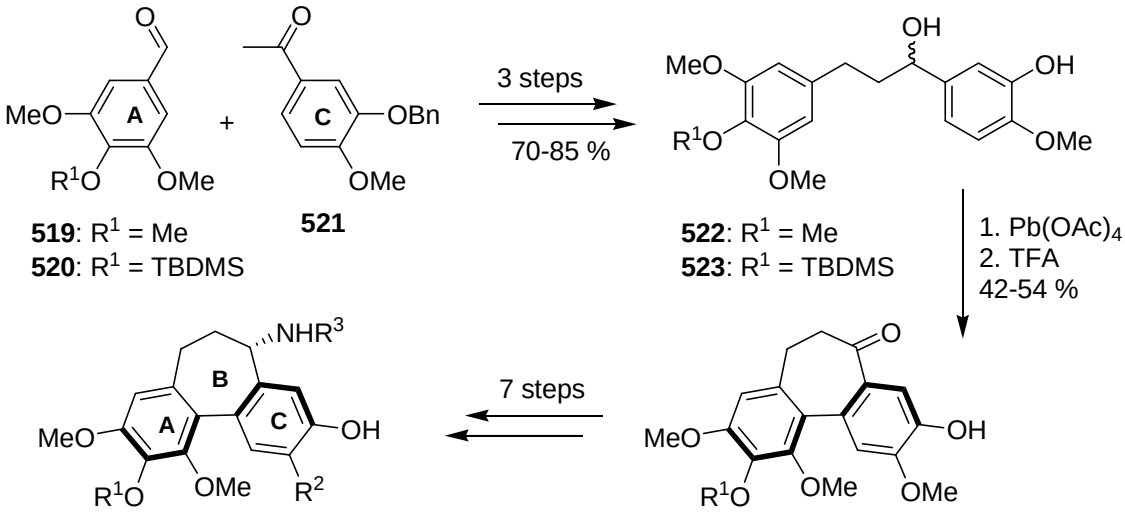
Under competitive conditions, Cook[234] published a similar synthesis, using 2,3,4,7-tetramethoxy-9-methylphenanthrene derivative **513** as the crucial precursor (Scheme 7.5). This aromatic compound was dihydroxylated on the reactive 9(10)-double bond. The resulting dialcohol **514** was cleaved with lead tetraacetate and recyclised under acidic conditions to conjugated ketone **515** which was hydrogenated over Pd-black to above-mentioned dibenzocycloheptadienone **511**.



Scheme 7.6. First Total Synthesis of N-Acetylcolchinol

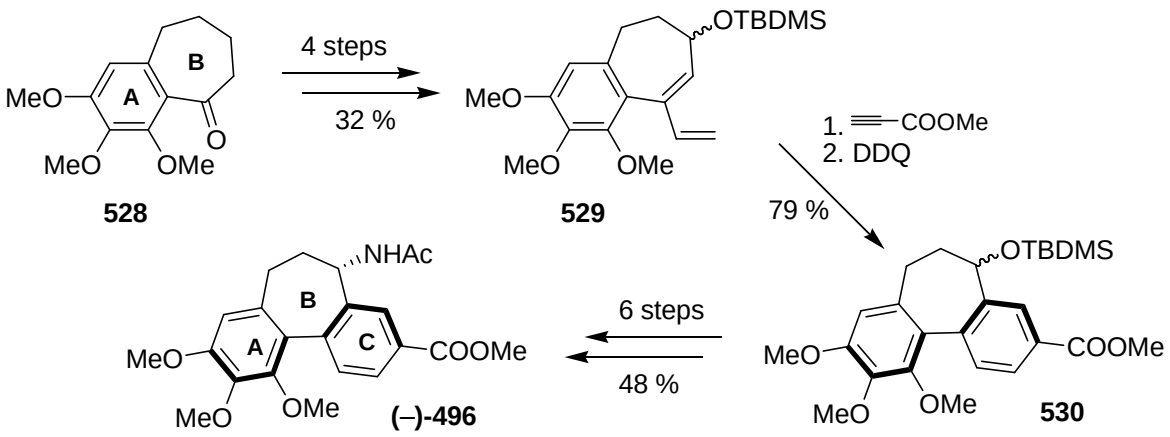
The first total synthesis of NAC[235] appeared 37(!) years later and it approached the construction of tricyclic core in very different way (Scheme 7.6). Addition of 3-(*tert*-butyldimethylsilyloxy)phenylmagensium bromide to 3,4,5-trimethoxyphenylpropanal (prepared from corresponding acid **516**) afforded racemic 1,3-diphenylpropanol **517** which was converted to acetamide **518** in three steps and 48 % yield. Non-phenolic oxidative coupling of precursor **518** gave racemic *N*-acetylcolchinol.

The Sawyer's synthesis was very effective – short (six steps) and the high yielding (26 % overall). The only drawback was the use of toxic Tl^{3+} salt for the oxidative biaryl coupling. Due to the toxicity of thallium, other coupling reagents have been tried since then. Racemic colchicine and two members from allocolchicinoid family (salimine **526**) and jerusalemine **527**, isolated from *Colchicum decaisnei*) have been synthesised[236] using lead tetraacetate for the crucial step of oxidative mono-phenolic coupling (Scheme 7.7).



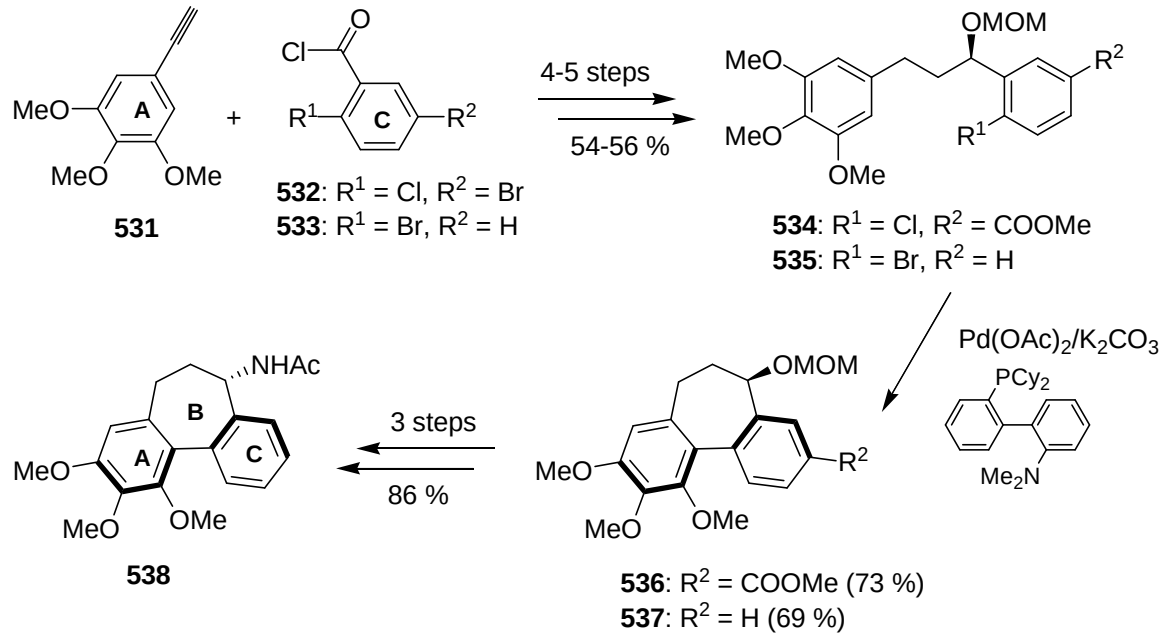
Scheme 7.7. Total Syntheses of Salimine and Jerusalemine

The coupling precursor of Banwell's synthesis were the 1,3-diphenylpropanes **522** and **523** which were subjected to Umezawa cyclisation with reagent sequence of lead tetraacetate/trifluoroacetic acid. Resulting ketones **524** or **525** were converted to the final products in additional seven steps. However, the overall yield differed significantly for salimine **526** (0.3 %) and jerusalemine **527** (34 %).



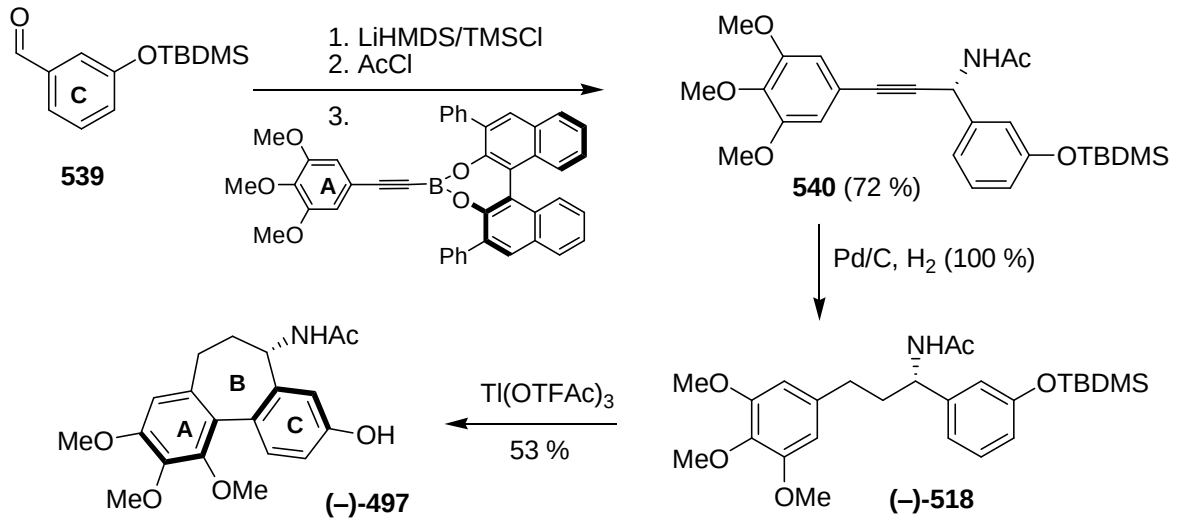
Scheme 7.8. Total Synthesis of (–)-Allocolchicine by Diels-Alder Reaction

A very original approach was adopted by Wulff et al.[232] employing Diels-Alder reaction for constructing the ring-C around the A-B-framework (Scheme 7.8). The starting material was benzosuberone **528** which was derivatised to bicyclic Diels-Alder diene **529**. The Diels-Alder reaction, using methyl propiolate as dienophile, afforded the tricyclic core in correct regiochemistry and its rearomatisation with DDQ led to **530**. A series of deprotection and oxidation-reduction steps on the *C*-7 oxygen functionality led to the desired natural (–)-allocolchicine **496**. The only stereocentre was set up by reduction of corresponding *C*-7 ketone with (+)-TarB-NO_2/$LiBH_4$ in 91 % ee.



Scheme 7.9. Syntheses of Allocolchicinoids by Direct Arylation

Another novel approach for synthesis of allocolchicinoids exploited several palladium-catalysed reactions (Scheme 7.9),[237] starting with a coupling of 3-(3',4',5'-trimethoxyphenyl)propyne **531** and acid chlorides **532** or **533**. The resulting ketone was enantioselectively reduced with (*S*)-pinene/9-BBN in 97 % ee followed by a short sequence, including Pd-catalysed carboxylation (R^2 substituent). The formed intermediates **534** or **535** were cyclised by direct arylation method to **536**/**537** in overall 39 % yield. Unnatural allo-analogue **538** was prepared in three steps and 86 % yield from **537**.

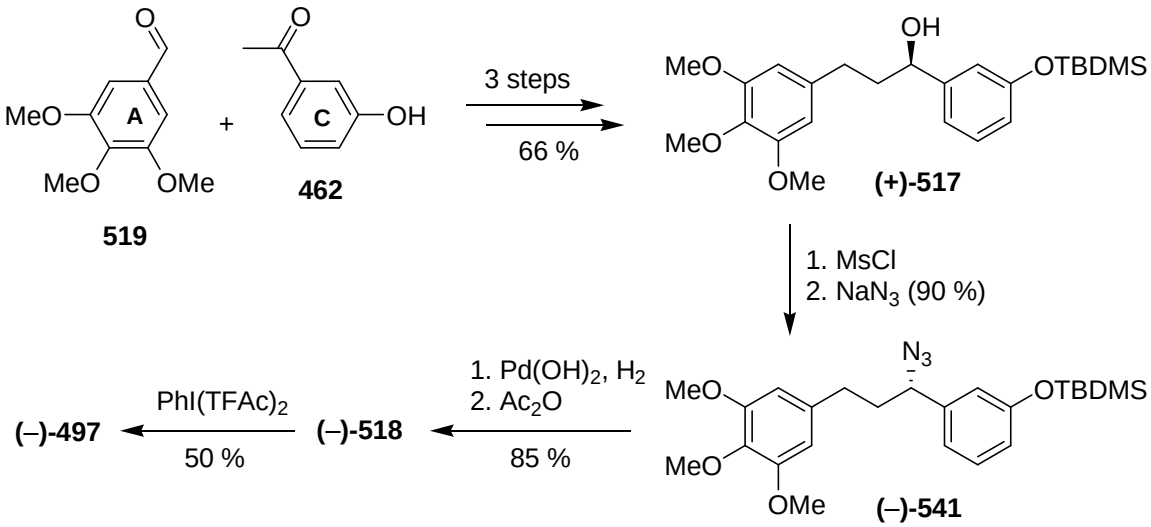


Scheme 7.10. First Enantioselective Synthesis of (–)-*N*-Acetylcolchinol

Wu and Chong[238] have used their own enantioselective protocol of alkynylation of *N*-acetylaldimines (formed in situ from aldehyde as **539**) to form the stereogenic centre in enantioenriched diphenylpropyne **540** (72 % yield, 94 % ee) which was hydrogenated to known precursor (–)-**518** (Scheme 7.10). Sawyer's Tl^{3+}-mediated oxidative coupling afforded cyclised (–)-*N*-acetylcolchinol **497** in 53 % yield. This synthesis featured only three separate synthetic steps and 38 % overall yield.

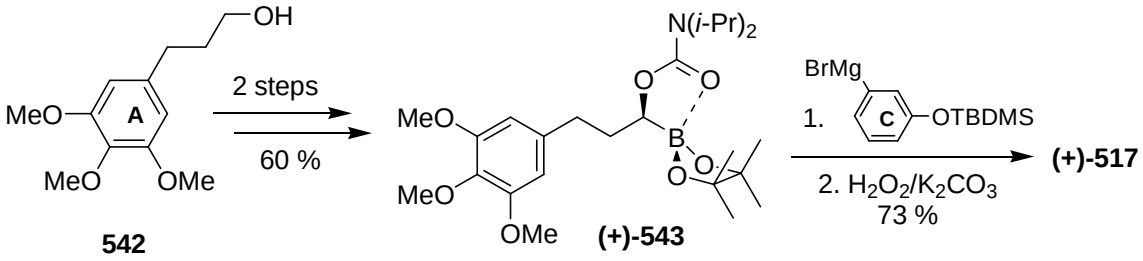
In co-operation with Astra-Zeneca, Kocienski and Boyle[230] have published several syntheses of NAC, three of them based on Sawyer's synthesis (however, employing I^{III}-based oxidant)[230a] and one based on metal-catalysed aryl coupling.[230b] The first synthesis (Scheme 7.11) starts with sequence of aldol condensation of **519** and **462** and hydrogenation of the chalcone product. The resulting saturated ketone was reduced enantioselectively in 92 % ee using Noyori's hydrogenation protocol to afford the alcohol (+)-**517** which was converted to azide (–)-**541** by Mitsunobu reaction. Hydrogenation of (–

)-**541** and acetylation of the free amine gave the enantioenriched (–)-**518** which was cyclised to (–)-NAC either with thallium tris(trifluoroacetate) in 31 % yield (in contrast to Sawyer's 71 %) or with phenyliodonium bis(trifluoroacetate) (PIFA) in 50 % yield.



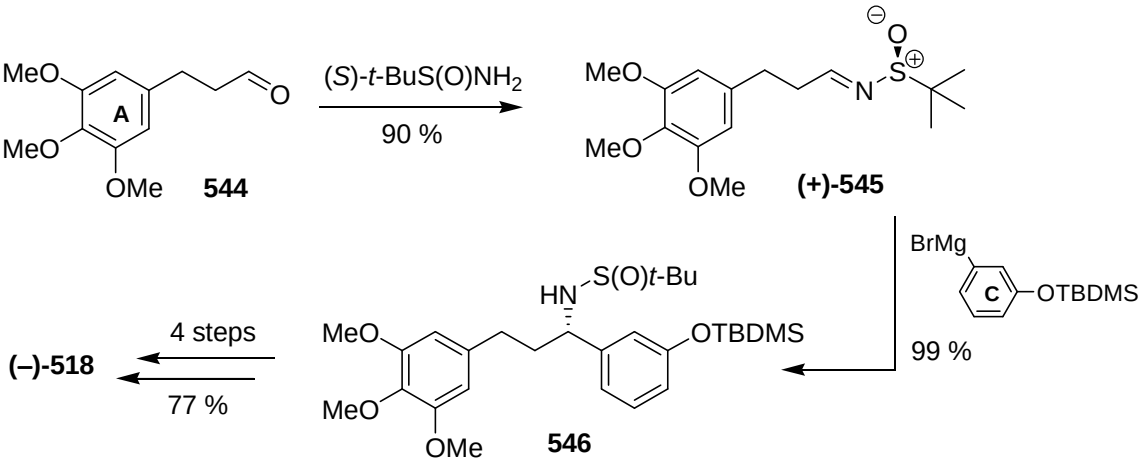
Scheme 7.11. Enantioselective Synthesis of (–)-*N*-Acetylcolchinol

An alternative way of preparing alcohol (+)-**517** (Scheme 7.12) utilised stereospecific Matteson-type [1,2]-metallate rearrangement of an α-(carbamoyloxy)alkylboronate (+)-**543**, which was synthesised from alcohol **542** in 2 steps.



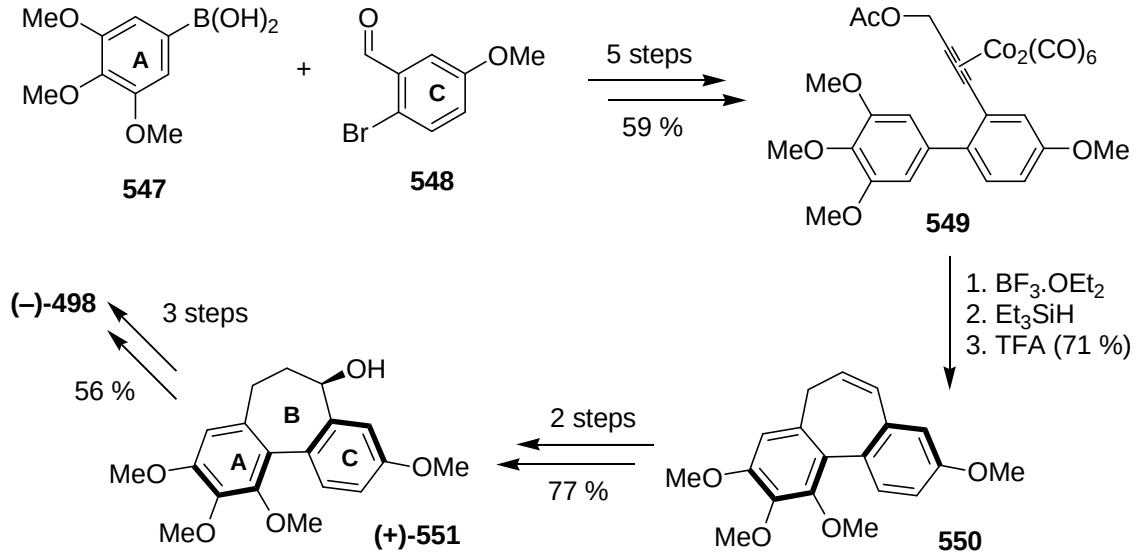
Scheme 7.12. Alternative Route for Synthesis of Alcohol **517**

Their third synthesis (Scheme 7.13) exploited addition of a Grignard reagent onto chiral *tert*-butylsulfinyl aldimine (+)-**545** (made from the corresponding aldehyde **544**). The major diastereomer of *tert*-butylsulfinyl amine **546** was obtained in 88 % de and series of protection-deprotection steps then provided the acetamide (–)-**518** which was cyclised as stated previously.



Scheme 7.13. Enantioselective Synthesis of (–)-*N*-Acetylcolchinol

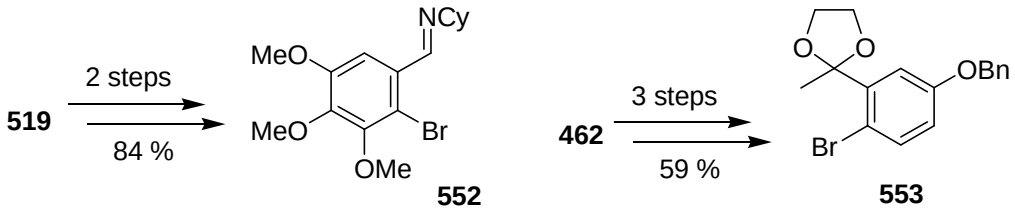
The following two syntheses have applied a complementary approach of constructing the biaryl backbone by means of metal-catalysed or metal-mediated coupling reactions and successive cyclisation providing the seven-membered ring-B.



Scheme 7.14. Enantioselective Synthesis of (–)-*N*-Acetylcolchinol-methylether

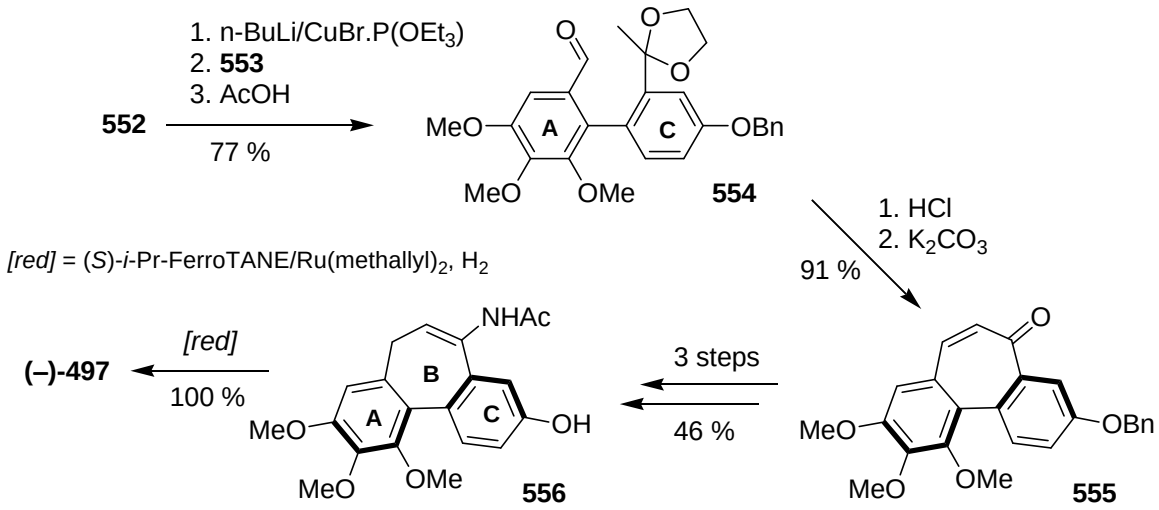
In the synthesis of Djurdjevic and Green[239] (Scheme 7.14), the Suzuki-Miyaura coupling partners **547** and **548** afforded a biaryl which was derivatised further to the cobalt-coordinated cyclisation precursor **549**. The cyclisation mediated by a Lewis acid (boron trifluoride etherate) afforded dibenzocycloheptadienyne coordinated with hexacarbonyldicoblalt which was decomplexed by hydrosilylation-acidic desilylation method to **550**. Dibenzosuberone **550** was hydroborated and oxidised to the *C*-7 ketone **511** which was enantioselectively reduced to alcohol (+)-**551** with (+)-TarB-NO_2/$LiBH_4$ in

95 % ee. Mitsunobu reaction, reduction of the azide and acetylation of the free amine provided *N*-acetylcolchinol-methylether **498**. The overall yield of this 11-step synthesis was 18 %.



Scheme 7.15. Precursors for Astra-Zeneca's Synthesis of (–)-NAC

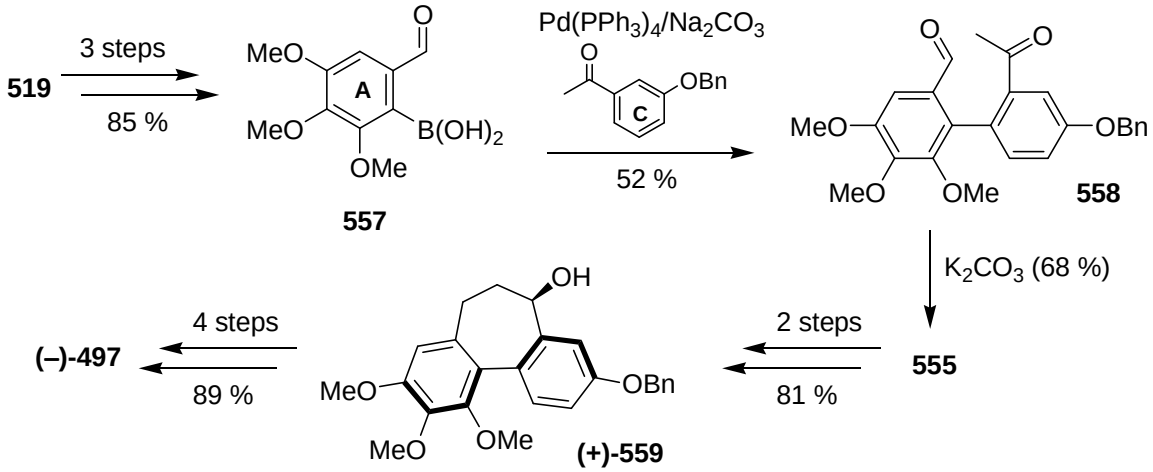
Astra-Zeneca has been involved in the development of a pro-drug (–)-**499**, a phosphate of (–)-NAC[240] (Scheme 7.16). Their approach employed Ullmann cyclisation of precursors **552** and **553** (Scheme 7.15) to biaryl **554** which on ketal-deprotection condensed to unsaturated ketone **555** (a 9-benzyloxy analogue of **515**, Scheme 7.5). Ketone **555** was converted in three steps to enamine **556**, a substrate for enantioselective hydrogenation over ruthenium/(*S*)-*iso*-propyl-ferroTANE catalyst to afford (–)-NAC. The linear sequence of seven steps provided the (–)-**497** in 32 %.



Scheme 7.16. Synthesis of (–)-NAC from Astra-Zeneca

A modification of this synthesis was published by Kocienski and Boyle[230c] (Scheme 7.17) who utilised palladium-catalysed Suzuki-Miyaura coupling instead of the copper-mediated Ullmann reaction. The resulting biaryl **558** was cyclised in basic conditions to **555** which was transformed to alcohol (+)-**559** in 98 % ee (a 9-benzyloxy

analogue of (+)-**551**, Scheme 7.14). (+)-**559** was converted to (–)-**497** in similar fashion as was (+)-**551**. The length (11 steps) of the synthesis caused drop of the overall yield to 22 % in comparison to the synthesis of Astra-Zeneca.

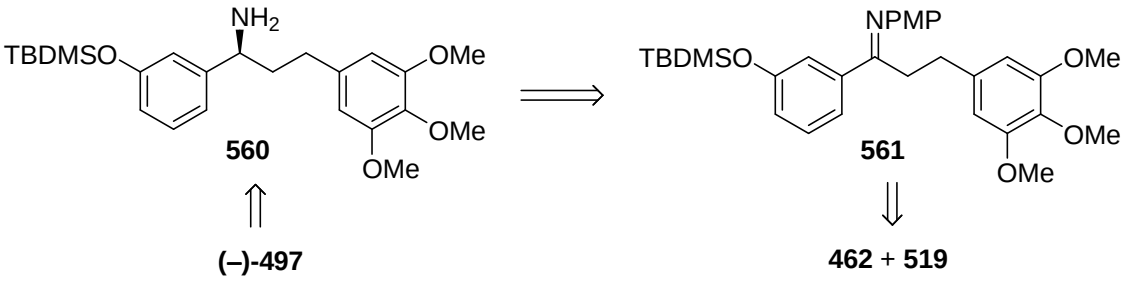


Scheme 7.17. Alternative Synthesis of (–)-NAC

7.2. Our Synthesis of *N*-Acetylcolchinol

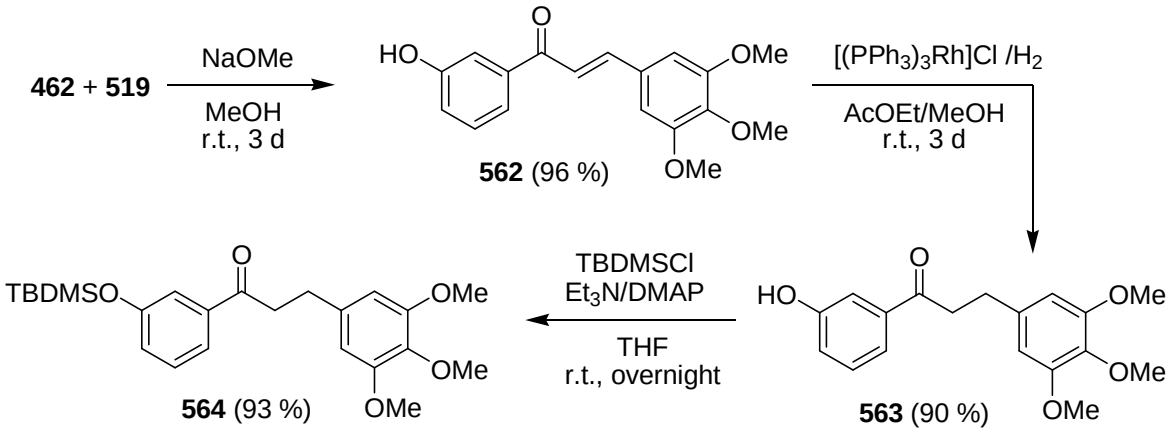
7.2.1. Synthesis of Precursors, Imine and Its Reduction to Amine

As it was previously explained, *N*-acetylcolchinol is a biologically active compound with useful anti-tumour activity. Our synthesis of this molecule is based on the synthesis of an appropriate imine (Scheme 7.18) which can be organocatalytically reduced with trichlorosilane according to our method.



Scheme 7.18. Retrosynthetic Analysis

The beginning of the synthesis (Scheme 7.19) was carried out according to known procedures. The core was constructed in the first step by sodium methoxide-catalysed aldol condensation of 3,4,5-trimethoxybenzaldehyde **519** and 3-hydroxyacetophenone **462**. This step afforded chalcone **562** which needed to be hydrogenated to saturated ketone **563**.



Scheme 7.19. Synthesis of Ketone for Imination

Literature[230] describes hydrogenation on PtO_2 affording **563** in 85 % yield. However, with attempted methods of heterogenous hydrogenation over different palladium or platinum catalysts (Table 7.1), a mixture of ketone **563** (not more than 70 % content) and over-hydrogenated saturated alcohol **565** (Figure 7.3) was produced when disappearance of starting material was detected. Homogenous hydrogenation over Wilkinson catalyst proved to be more efficient, affording **563** selectively in 90 % isolated yield.

Table 7.1. Hydrogenation of chalcone **562**

Catalyst / H_2 balloon	10 % Pd/carbon (2.4 % Pd)	PtO_2 (2.0 % Pt)	10 % Pt/active coal (2.4 % Pt)	Wilkinson (5 % Rh)
563:**565** ratio	1:1	2:1	5:3	< 95 :5

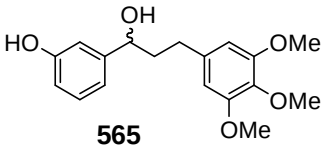
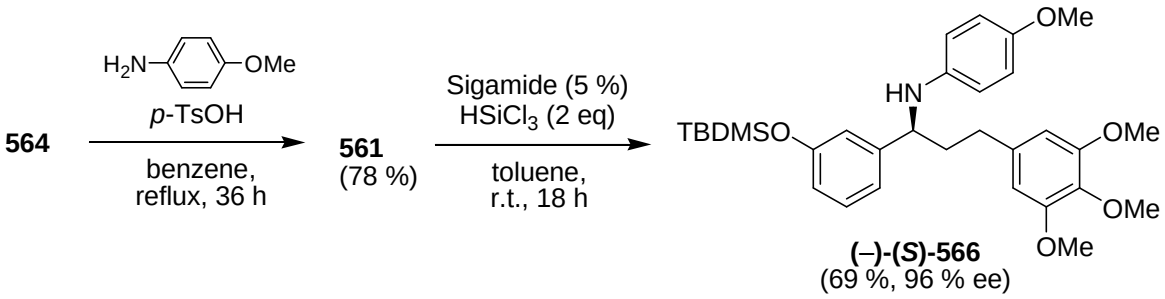


Figure 7.3. Over-hydrogenated Product

The subsequent step of silylation of the phenol moiety was performed according to literature[171] and afforded the ketone **564** in 93 % yield; 80 % over 3 steps. Imination proceeded smoothly in agreement with previous model of imine **476w**. Standard reaction time of 18 h afforded the desired imine **561** only in ~ 50 % yield; however, prolonged time to 36 h improved the yield to 78 % (Scheme 7.20).



Scheme 7.20. Synthesis of Amine Intermediate

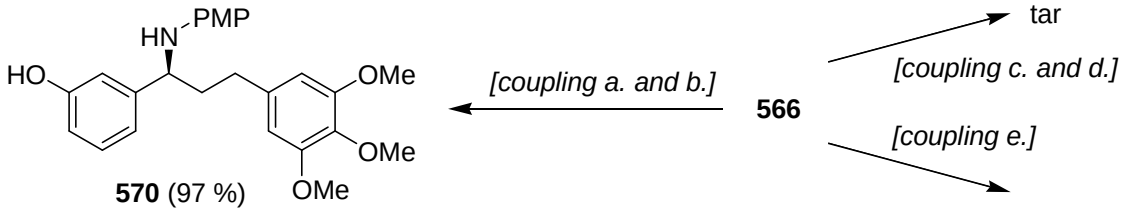
The reduction of imine **561** followed the expectations and enantioenriched amine **566** was obtained in moderate yield (69 %) and excellent enantioselectivity (96 % ee), 43 % yield after 5 steps. Attempts to crystallise this amine for X-ray analysis failed, however, according to the broad library of amines synthesised previously, the anticipated absolute configuration was (*S*).

7.2.2. Amine Deprotection and Oxidative Coupling

Obtaining the amine **566** successfully provided two possible synthetic approaches towards the advanced stages of synthesis of colchinol (Scheme 7.21). The first one was a novel route by performing phenolic or non-phenolic coupling on the amine intermediate **566**, also expecting that the oxidative conditions would deprotect the *para*-methoxyphenyl group from nitrogen. A straightforward, but somewhat lengthy sequence of deprotection of the PMP-group and carrying out the synthesis as in previously published works[230] was kept as a back-up method.

Scheme 7.21. Two Possible Synthetic Routes

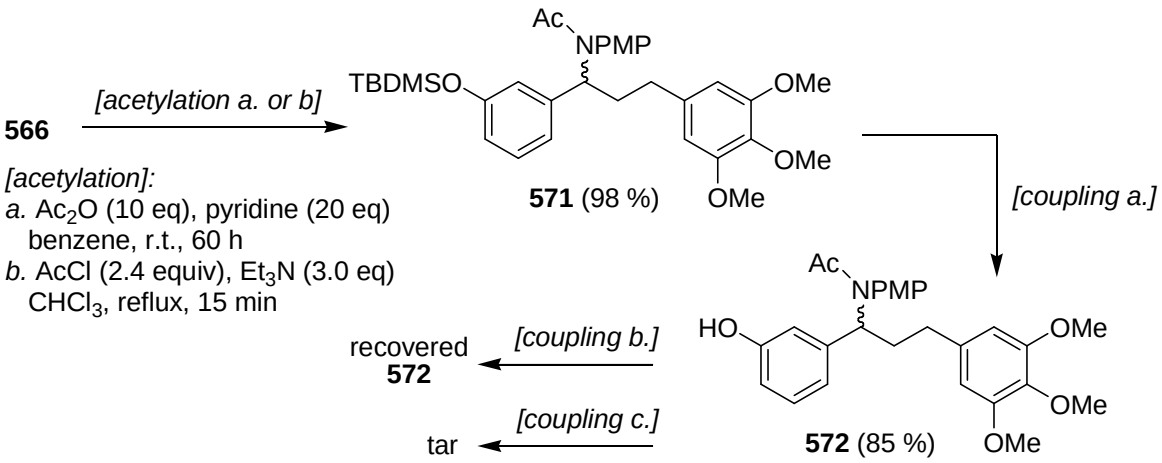
The non-phenolic oxidative coupling was trialled on amine **566** (Scheme 7.22), even if there was no literature precedent for a coupling of a substrate containing secondary amino-group. Different oxidants were used according to the literature procedures. Attempts of coupling with ruthenium(IV)[241] or molybdenum(V)[242] resulted in no coupling reaction and only provided the deprotected phenol **570**. On the other hand, vandium(V)[243] and standard BF_3-activated PIFA were too reactive and tar material was obtained. The alternative reagent, heteropolyacid-activated PIFA,[244] did mediate *a* reaction, however according to ^{1}H NMR, no coupled product was obtained.



[coupling]:
a. RuO_2 (2.0 equiv), $BF_3.OEt_2$ (2 eq), CH_2Cl_2/TFA/TFAA, r.t., 24 h
b. $MoCl_5$ (1.9 or 3.2 equiv), $TiCl_4$ (1.9 or 3.2 equiv), CH_2Cl_2, 0-20 ℃, 16 h
c. $VOCl_3$ (2.5 equiv), CH_2Cl_2 or ether, –80 ℃ to r.t., 5 h
d. PIFA (1.2 equiv), $BF_3.OEt_2$ (2 eq), CH_2Cl_2/TFA/TFAA, –5 ℃ to r.t., 5 h
e. PIFA (1.0 equiv), PMA (1.0 eq), MeCN, –10 ℃ to r.t., 1.5 h

Scheme 7.22. Attempts of Oxidative Coupling of Amine **566**

The *N*-acetamide **571** was prepared from **566** by standard acetylation procedure in virtually quantitative yield (Scheme 7.23). The same coupling procedure with ruthenium(IV) was applied on this substrate. The result was very similar to the previous case, only desilylated phenol **572** was recovered. This phenol was subjected to molybdenum(V) and vanadium(V)-mediated coupling conditions, again leading to similar results as before. This synthetic approach was left due to probable problems with removal of PMP-group, even if the coupling did afford the desired product.



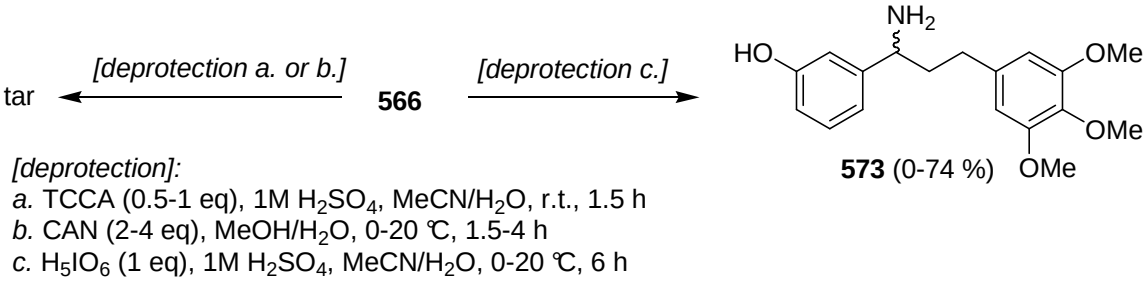
Scheme 7.23. Attempts of Oxidative Coupling of Acetamide **571**

The PMP-deprotection reaction was carried out using established methods with cerium(IV)-ammonium nitrate (CAN)[245] or trichlorocyanuric acid (TCCA)[246] (Scheme 7.24). Despite some variation of conditions, i.e. change of amount of the oxidant and/or solvent system, they failed to produce the free amine and only small quantities of tar material were isolated (Table 7.2).

Table 7.2. Deprotection of PMP-group of Amine **566**

Oxidant	Temp., Time	Additives, Solvents	Product
TCCA (0.5 equiv)	r.t., 75 min	1M H_2SO_4, MeCN / H_2O (1:1)	tar
CAN (4 equiv)	0 °C, 4 h	MeCN / H_2O (4:1)	tar
CAN (2 equiv)	r.t., 4 h	MeOH / H_2O (1:1)	tar

Partial success was achieved with less active periodic acid.[246] However, this method afforded the free amino alcohol **573** in extremely variable yields! Unfavourable outcome of biaryl couplings and other deprotection methods has led us to optimisation of the reaction conditions rather than trying more deprotection reagents (Table 7.3). The reproduction of literature procedure[246] (run 1) afforded the free amine **573** in 38 % yield. Increasing the content of acetonitrile and keeping the temperature under 16 °C seemed to improve the yield (run 2). Decreasing the amount of sulfuric acid or not adding it at all, caused faster side reactions and isolation of only traces of the desired product (runs 4 to 6). On contrary, higher content of acid appeared to be beneficial (runs 7 and 8).



Scheme 7.24. Attempts of Deprotection of the PMP-group from amine **566**

From the results of these experiments, it could be concluded that important features of this oxidative deprotection reaction were acidity of the aqueous acetonitrile, reaction temperature and work-up:

- the cleanliness of the reaction benefited from higher content of acid (H_2SO_4),
- lowered temperature to 12-16 ºC had also positive impact; however, temperature close to 0 ºC significantly slowed down the deprotection reaction, and higher temperature (~ 20 ºC) caused faster decomposition of the substrate (presumably by over-oxidation at other sites of the electron rich aryl rings or free phenol),
- pH of the work-up – extraction from aqueous phase must have been done at pH 8, as the amino alcohol **573** is well soluble in acidic or basic aqueous layer.

Table 7.3. Deprotection of PMP-amine **566** (0.033 M solution) with Periodic Acid (H_5IO_6, 1 equiv)

Run	1M H_2SO_4	Time, Temp.	Solvents	Product
1	1 mL	overnight, r.t.	MeCN / H_2O (1:1)	**573** (38 %)
2	1 mL	1h at 0 ºC then 3 h at 16 ºC	MeCN / H_2O (2:1)	**573** (74 %)
3	1 mL	2h at 0 ºC then 3 h at 18 ºC	MeCN / H_2O (2:1)	tar
4	-	SM disappearance, 200 min at 16 ºC	MeCN / H_2O (2:1)	tar
5	0.1 mL	SM disappearance, 3 h at 16 ºC	MeCN / H_2O (2:1)	tar + **566** in acid washes
6	2 mL	SM disappearance, 6.5 h at 16 ºC	MeCN / H_2O (2.5:1)	**573** (trace)
7	10 mL	SM disappearance, 2.5 h at 16 ºC	MeCN	**573** (trace) + **570** in acid washes
8	10 mL	completion, 5 h at 16 ºC	MeCN	**573** (69 % overall)

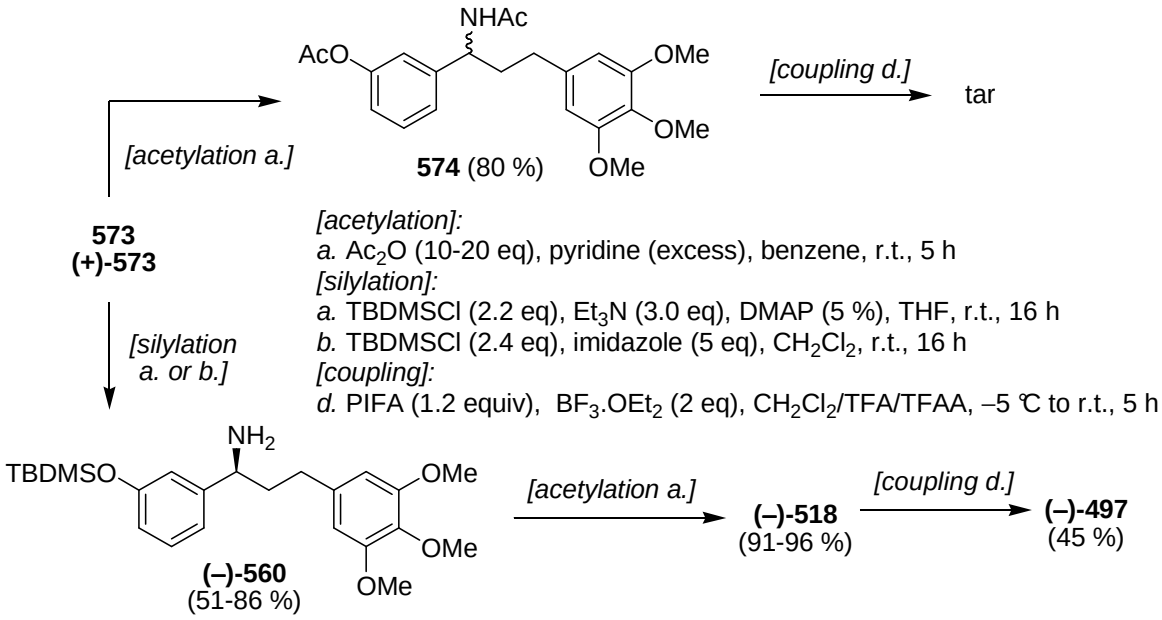
These observations helped to develop the improved procedure that is as follows: the 0.033 M concentration of the substrate **566** was kept by using two-components solvent system of acetonitrile and 1M sulfuric acid in 2:1 (V/V) ratio while the temperature was held between 12-16 ºC. These modifications increased the reliability of the deprotection;

however, the yields stayed mediocre (47 % in average) and the reaction time varied (Table 7.4).

Table 7.4. Deprotection of PMP-group of Amine **566** with Periodic Acid (1 equiv)

Amine	Time, Temp.	Product
566	6 h at 14-16 ºC	**573** (41 %)
566	5 h at 11 ºC	**573** (63 %)
566	20 h at 9-15 ºC	**573** (27 %)
(–)-566	5 h at 11 ºC	**(–)-573** (63 %)
(–)-566	9 h at 12-16 ºC	**(–)-573** (42 %)

Having obtained the free amine, *O*-resilylation and *N*-acetylation was required to reach the known intermediate **518** for the iodine(III)-mediated oxidative coupling (Scheme 7.25). In parallel, amido ester **574** was also synthesised as it was reported[230] to be a suitable substrate for the coupling and it would have saved some protection steps. Unfortunately, the coupling of this substrate yielded tar material. Therefore, amino alcohol **573** was protected as silylether **560.** Interestingly, resilylation[171] using triethylamine as a base and mopping reagent did not proceed to completion and 1:1 mixture was obtained even if 2.5 equivalents of the silicon source was used. Applying another common silylation procedure[230] with imidazole base solved this inconvenience.



Scheme 7.25. Synthesis of NAC from amine **573**

Acetylation of the silylether **560** afforded the crucial coupling substrate **518** (Scheme 7.25), also known from literature. The coupling itself was a reproduction of

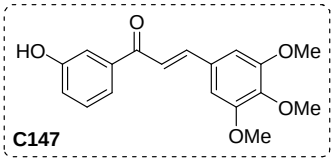
Kocienski et al.[230] method using phenyliodonium bis(trifluoroacetate) and it proceeded as described. However, the purification was more laborious as crystallisation was not feasible in our scale (30 mg), the yield was 45 % (compared to published 53 %).

7.2.3. Conclusions

The optical rotation of the coupling product was in very good agreement with literature sources,[229,230,238] therefore we can assume that the natural occurring (–)-*N*-acetylcolchinol was successfully prepared, in 9-step linear sequence and 7 % overall yield.

7.3.Experimental Part (I)

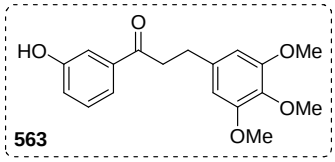
(*E*)-1-(3'-Hydroxyphenyl)-3-(3",4",5"-trimethoxyphenyl)prop-2-en-1-one (562), $C_{18}H_{18}O_5$, FW = 314.36



A solution of 3,4,5-trimethoxybenzaldehyde (9.81 g, 50.0 mmol, 1 equiv) was added drop-wise to a solution of freshly prepared MeONa in MeOH (2.0 M, 100 mL) at 0 ºC and 3-hydroxyacetophenone (6.81 g, 50.0 mmol, 1 equiv) in anhydrous MeOH (100 mL) over 1 h.[230] The resulting solution was let to stir at ambient temperature for 60 h. The solvent was then removed *in vacuo* and the residue was dissolved in water (150 mL). The basic aqueous layer (pH 12) was washed with Et_2O (3 × 40 mL) and acidified by addition of conc. HCl to pH 1. The precipitate was filtered, thoroughly washed with water and dried under reduced pressure to obtain chalcone **562**[230] (15.2 g, 48.3 mmol, 96 %) which was used without further purification: yellow crystals; **mp** 150-151 ºC (AcOEt), [lit.[230] 177-178.5 ºC (EtOH-water), lit.[247] 173-174 ºC (EtOH)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.92 (s, 6H), 6.17 (br s, 1H), 6.86 (s, 2H), 7.11 (ddd, *J* = 8.1, 2.6, 0.9 Hz, 1H), 7.39 (dd, *J* = 7.9, 7.8 Hz, 1H), 7.38 (d, *J* = 15.6 Hz, 1H), 7.57-7.60 (m, 2H), 7.73 (d, *J* = 15.6, 1H); **^{13}C NMR** δ 56.26 (2 × CH_3), 61.08 (CH_3), 105.72 (2 × CH), 115.18 (CH), 120.29

(CH), 120.98 (CH), 121.27 (CH), 129.94 (CH), 130.28 (C), 139.67 (C), 140.49 (C), 145.53 (CH), 153.49 (2 × C), 156.36 (C), 190.55 (C); **IR** ν 3020, 1650, 1576, 1459, 1504, 1418, 1287, 1215 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 315 [$(M+H)^+$, 13], 113 (34), 97 (28), 95 (42), 93 (28), 85 (78); **HRMS** (CI/isobutane) 315.1234 ($C_{18}H_{19}O_5$ requires 315.1232).

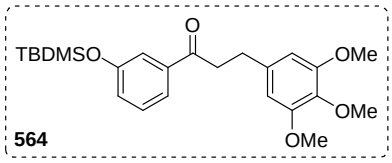
1-(3'-Hydroxyphenyl)-3-(3",4",5"-trimethoxyphenyl)propan-1-one (563), $C_{18}H_{20}O_5$, FW = 316.38



563

A solution of Wilkinson catalyst (97 mg, 0.100 mmol, 5 mol %) and chalcone **562** (629 mg, 2.00 mmol, 1 equiv) in an ethyl acetate (20 mL) – methanol (2 mL) mixture was placed under an atmosphere of H_2 (balloon). The reaction was monitored by TLC and when the starting material was consumed (ca 70 h) the mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate and the resulting suspension was filtered through a Celite pad and washed with ethyl acetate. The filtrate was evaporated to afford **563** as a crystalline residue (573 mg, 1.81 mmol, 90 %), which was used without further purification: white crystals; **mp** 119-120 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.98-3.02 (m, 2H), 3.25-3.29 (m, 2H), 3.82 (s, 3H), 3.83 (s, 6H), 6.24 (br s, 1H), 6.45 (s, 2H), 7.11 (ddd, *J* = 8.1, 2.6, 0.9 Hz, 1H), 7.39 (ddd, *J* = 8.1, 7.7, 0.7 Hz, 1H), 7.49-7.52 (m, 2H); **^{13}C NMR** δ 30.63 (CH_2), 40.70 (CH_2), 55.09 (2 × CH_3), 60.91 (CH_3), 105.34 (2 × CH), 114.59 (CH), 120.51 (CH), 120.65 (CH), 129.95 (CH), 136.15 (C), 137.08 (C), 138.20 (C), 153.18 (2 × C), 156.44 (C), 199.82 (C); **IR** ν 2942, 1684, 1592, 1508, 1450, 1421, 1216 cm^{-1}; **MS** (EI) *m/z* (%) 316 ($M^{\bullet+}$, 93), 302 (13), 195 (100), 181 (75), 121 (70), 94 (38), 84 (33); **HRMS** (EI) 316.1310 ($C_{18}H_{20}O_5$ requires 316.1311.

1-[3'-(*tert*-Butyldimethylsilyloxy)phenyl]-3-(3",4",5"-trimethoxyphenyl)propan-1-one (564), $C_{24}H_{34}O_5Si$, FW = 430.67

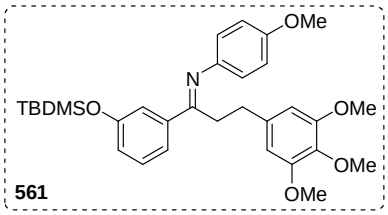


564

A solution of *tert*-butyldimethylsilyl chloride (1.64 g, 10.8 mmol, 1.3 equiv) in anhydrous THF (4 mL) was added to a mixture of ketone **563** (2.64 g, 8.34 mmol), triethylamine (2.52 mL, 1.60 g, 16.7 mmol, 2.0 equiv) and 4-(*N*,*N*-dimethylamino)pyridine (102 mg,

0.830 mmol, 5 mol%) in THF (9 mL) at 0 ºC.[171] The mixture was let to warm to room temperature and to stir overnight. The reaction was quenched with a saturated NH_4Cl solution (80 mL) and the aqueous layer was extracted with ether (2 × 80 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to afford **564** (3.35 g, 7.77 mmol, 93%) which was used in the next step without further purification: colourless oil which solidified upon standing; **mp** 66-67 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.20 (s, 6H), 0.98 (s, 9H), 2.97-3.01 (m, 2H), 3.23-3.27 (m, 2H), 3.81 (s, 3H), 3.83 (s, 6H), 6.45 (s, 2H), 7.02 (ddd, *J* = 8.1, 2.5, 1.0 Hz, 1H), 7.30 (dd, *J* = 8.0, 7.8 Hz, 1H), 7.41 (dd, *J* = 2.1, 1.8 Hz, 1H), 7.53 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.49-7.52 (m, 2H); **^{13}C NMR** δ –4.42 (2 × CH_3), 18.19 (C), 25.64 (3 × CH_3), 30.65 (CH_2), 40.69 (CH_2), 56.05 (2 × CH_3), 60.84 (CH_3), 105.30 (2 × CH), 119.28 (CH), 121.19 (CH), 124.96 (CH), 129.62 (CH), 136.24 (C), 137.13 (C), 138.32 (C), 153.19 (2 × C), 156.01 (C), 199.01 (C); **IR** ν 2955, 2932, 2858, 1686, 1590, 1508, 1461, 1434, 1284, 1252, 1129 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 431 [$(M+H)^+$, 70], 251 (13), 133 (82); **HRMS** (CI/isobutane) 431.2252 ($C_{24}H_{35}O_5Si$ requires 431.2254).

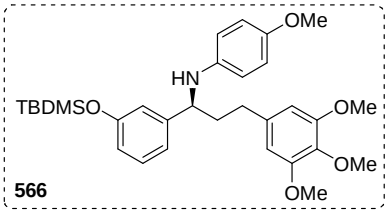
(*E*)-*N*-{1'-[3"-(*tert*-Butyldimethylsilyloxy)phenyl]-3'-(3'",4'",5'"-trimethoxyphenyl)prop-1'-ylidene}-4-methoxyaniline (561), $C_{31}H_{41}NO_5Si$, FW = 535.82



561 prepared according general procedure for imination, Method A: yellow crystals; **mp** 76-77 ºC (hexane); **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*/*Z*) isomers in ratio ca. 5:1, the minor one is marked *) δ 0.01* (s, 1.2H), 0.24 (s, 6H), 0.90* (s, 1.8H), 1.01 (s, 9H), 2.70 (dd, *J* = 8.0, 7.2 Hz, 2H), 2.91-3.00 (m, 2.4H), 3.02-3.07* (m, 0.4H), 3.70* (s, 0.6H), 3.74 (s, 6H), 3.78 (s, 3H), 3.81 (s, 3H), 3.830-3.833* (m, 1.8H), 6.08 (s, 2H), 6.44-6.48 (m, 2.4H), 6.54-6.58* (m, 0.4H), 6.62-6.74* (m, 1.0H), 6.81-6.85 (m, 2H), 6.96 (ddd, *J* = 8.0, 2.4, 0.9 Hz, 1H), 7.12* (dd, *J* = 8.0, 7.7 Hz, 0.2H), 7.33 (dd, *J* = 8.0, 7.9 Hz, 1H), 7.40 (dd, *J* = 2.0, 2.0 Hz, 1H), 7.51 (ddd, *J* = 7.8, 1.5, 1.0 Hz, 1H); **^{13}C NMR** δ –4.60* (2 × CH_3), –4.28 (2 × CH_3), 18.14* (C), 18.24 (C), 25.61* (3 × CH_3), 25.68 (3 × CH_3), 32.26 (CH_2), 33.10* (CH_2), 34.34 (CH_2), 43.04* (CH_2), 55.27* (CH_3), 55.44 (CH_3), 55.93 (2 × CH_3), 56.04* (2 × CH_3), 60.88 (2 × CH_3), 105.16 (2 × CH), 105.38* (2 × CH), 113.94* (2 × CH),

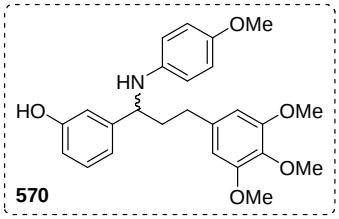
114.02 (2 × CH), 119.32 (CH), 119.81* (CH), 120.21 (2 × CH), 120.50* (CH), 120.74 (CH), 120.87* (CH), 121.96 (CH), 122.12* (2 × CH), 129.46* (CH), 129.56 (CH), 136.10* (C), 136.30 (C), 136.28 (C), 137.29* (C), 139.19* (C), 140.11 (C), 143.78* (C), 144.59 (C), 153.09 (4 × C), 155.36* (C), 155.73 (C), 155.83* (C), 155.95 (C), 169.11 (C), 170.74* (C); **IR** ν 2954, 2932, 2858, 1624, 1590, 1503, 1462, 1423, 1240, 1128 cm^{-1}; **MS** (+FAB) *m/z* (%) 536 [$(M+H)^+$, 100], 535 (75), 340 (20), 181 (70); **HRMS** (+FAB) 536.2830 ($C_{31}H_{42}O_5NSi$ requires 536.2832).

(–)-*N*-{1'-[3"-(*tert*-Butyldimethylsilyloxy)phenyl]-3'-(3'",4'",5'"-trimethoxyphenyl)prop-1'-yl}-*N*-(4-methoxyphenyl)amine (566), $C_{31}H_{43}NO_5Si$, FW = 537.84



566 prepared according to general procedure for imine reduction: colourless oil; **$[\alpha]_D$** –11.0 (*c*, 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.16 (s, 6H), 0.97 (s, 9H), 2.02-2.17 (m, 2H), 2.68 (dd, *J* = 7.7, 7.5 Hz, 2H), 3.69 (s, 3H), 3.80 (s, 6H), 3.85 (s, 3H), 4.21 (dd, *J* = 7.0, 6.5 Hz, 1H), 6.39 (s, 2H), 6.44-6.48 (m, 2.4H), 6.67-6.71 (m, 2H), 6.73 (ddd, *J* = 8.0, 2.4, 0.9 Hz, 1H), 6.83 (dd, *J* = 2.0, 1.8 Hz, 1H), 6.94 (br d, *J* = 7.7 Hz, 1H), 7.40 (dd, *J* = 7.8, 7.8 Hz, 1H); **^{13}C NMR** δ –4.56 (CH_3), –4.51 (CH_3), 18.11 (C), 25.59 (3 × CH_3), 32.97 (CH_2), 39.92 (CH_2), 55.62 (CH_3), 55.84 (2 × CH_3), 58.06 (CH), 60.73 (CH_3), 105.13 (2 × CH), 114.50 (2 × CH), 114.60 (2 × CH), 118.28 (CH), 118.55 (CH), 119.42 (CH), 129.40 (CH), 135.95 (C), 137.15 (C), 141.40 (C), 145.66 (C), 151.80 (C), 153.01 (2 × C), 155.73 (C); **IR** ν 3397, 3008, 2932, 2857, 1589, 1512, 1463, 1239 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 206 [$(M+H)^+$, 65], 537 (25), 415 (28), 308 (40), 161 (52), 143 (47), 85 (83); **HRMS** (CI/isobutane) 538.2991 ($C_{31}H_{44}NO_5Si$ requires 538.2989); **HPLC** analysis [Chiralpak IB, hexane – propan-2-ol (75:25), 0.75 mL/min, t_{minor} = 12.37 min, t_{major} = 19.67 min] showed 96 % ee.

***N*-[1'-(3"-Hydroxyphenyl)-3'-(3'",4'",5'"-trimethoxyphenyl)prop-1'-yl]-*N*-(4-methoxyphenyl)amine (570), $C_{25}H_{29}NO_5$, FW = 423.55**

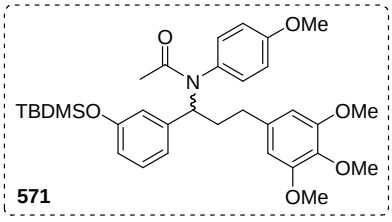


570: white crystals; **mp** 139-140 ºC (CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.04-2.09 (m, 2H), 2.67 (dd, *J* = 7.6, 7.4 Hz, 2H), 3.69 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 4.19 (dd, *J* = 7.0, 6.4 Hz, 1H), 6.36 (s, 2H), 6.41-6.45 (m, 2H), 6.66-6.70 (m, 2H), 6.81 (dd, *J* = 2.1, 1.8 Hz, 1H), 6.89 (d, *J* = 6.7 Hz, 1H), 7.19 (dd, *J* = 7.8, 7.8 Hz, 1H); **^{13}C NMR** δ 33.14 (CH_2), 40.01 (CH_2), 55.83 (CH_3), 56.01 (2 × CH_3), 58.25 (CH), 60.92 (CH_3), 105.29 (2 × CH), 113.30 (CH), 114.05 (CH), 114.63 (2 × CH), 114.83 (2 × CH), 118.78 (CH), 129.80 (CH), 135.98 (C), 137.30 (C), 141.52 (C), 146.15 (C), 151.89 (C), 153.12 (2 × C), 156.15; **IR** *v* 3300, 3019, 2635, 1835, 1589, 1511, 1460, 1216 cm^{-1}; **MS** (EI) *m/z* (%) 423 ($M^{\bullet+}$, 14), 300 (10), 228 (50), 181 (20); **HRMS** (EI) 423.2047 ($C_{25}H_{29}NO_5$ requires 423.2046).

General Procedure for Acetylation of Amines and Amino Alcohols:

Acetanhydride (10-20 equiv) was added to a solution of amine (1 equiv) and pyridine (<12 equiv) in solvent and the mixture was let stir at room temperature. Then diluted HCl (7 %, 5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with saturated $NaHCO_3$ (5 mL), brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude amide was purified on a silica gel column (7 or 15 mL) with a gradient of petroleum ether – ethyl acetate (1:1) to pure ethyl acetate and the amide was obtained as a thick oil. Reaction details in Table 7. 5.

***N*-{1'-[3"-(*tert*-Butyldimethylsilyloxy)phenyl]-3'-(3'",4'",5'"-trimethoxyphenyl)prop-1'-yl}-*N*-(4-methoxyphenyl)acetamide (571), $C_{33}H_{45}NO_6Si$, FW = 579.88**



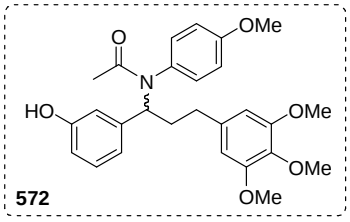
Acetyl chloride (64 μL, 71 mg, 0.900 mmol, 3 equiv) was added drop-wise to a solution of amine **566** (161 mg, 0.300 mmol, 1 equiv) and triethylamine (209 μL, 152 mg, 1.50 mmol,

5 equiv) in $CHCl_3$ (3 mL) at 0 ºC. The mixture was heated to reflux for 15 min and let to cool to room temperature. Then water (15 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 7 mL). The combined organic layer was washed with saturated $NaHCO_3$ (15 mL), brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude amide was purified on a silica gel column (10 mL) with a petroleum ether – ethyl acetate mixture (1:1) to afford the amide **571** as a thick oil (170 mg, 0.293 mmol, 98 %): colourless thick oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.11 (s. 3 H), 0.12 (s, 3H), 0.94 (s, 9H), 1.76 (s, 3H), 1.98-2.15 (m, 2H), 2.52-2.70 (m, 2H), 3.76 (s, 3H), 3.81 (s, 3H), 3.84 (s, 6H), 6.12 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.39 (s, 2H), 6.57 (dd, *J* = 1.9, 1.9 Hz, 1H), 6.73 (ddd, *J* = 8.0, 2.4, 0.8 Hz, 1H), 6.76 (br d, *J* = 7.7 Hz, 1H), 7.11 (dd, *J* = 7.8, 7.8 Hz, 1H), very broad signal in aromatic region (4H); **^{13}C NMR** δ –4.42 (CH_3), –4.39 (CH_3), 18.17 (C), 23.39 (CH_3), 25.67 (3 × CH_3), 33.06 (CH_2), 33.35 (CH_2), 55.32 (CH_3), 56.09 (2 × CH_3), 56.44 (CH), 60.83 (CH_3), 105.39 (2 × CH), 114.03 (4 × CH), 119.38 (CH), 120.38 (CH), 122.21 (CH), 129.10 (CH), 129.10 (C), 131.69 (C), 136.21 (C), 137.52 (C), 141.05 (C), 153.13 (2 × C), 155.48 (C), 159.13 (C), 170.85 (C); **IR** *v* 2955, 2932, 2858, 1653, 1589, 1510, 1463, 1250 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 580 [$(M+H)^+$, 50], 417 (30), 166 (100); **HRMS** (CI/isobutane) 580.3099 ($C_{33}H_{46}NO_6Si$ requires 580.3094).

Table 7. 5. Acetylations with Acetanhydride According to Method A

Substrate	Acetanhydride / Pyridine	Solvent	Time	Product
566 (108 mg, 0.200 mmol)	95 µL, 102 mg, 1.00 mmol / 97 µL, 95 mg, 1.20 mmol	benzene (1 mL)	64 h	**571** (55 mg, 0.0949 mmol, 95 %)
560 (40 mg, 0.0902 mmol)	85 µL, 92 mg, 0.902 mmol / 88 µL, 86 mg, 1.08 mmol	benzene (1.5 mL)	5 h	**574** (42 mg, 0.0865 mmol, 96 %)
573 (62 mg, 0.195 mmol)	369 µL, 398 mg, 3.90 mmol / 1 mL	CH_2Cl_2 (1 mL)	5 h	**518** (63 mg, 0.157 mmol, 80 %)

_N_-[1'-(3"-Hydroxyphenyl)-3'-(3'",4'",5'"-trimethoxyphenyl)prop-1'-yl]-_N_-(4-acetyl-4-methoxyphenyl)amine (572), $C_{22}H_{27}NO_6$, FW = 401.50



572

572: colourless thick oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03-2.09 (m, 2H), 2.04 (s, 3H), 2.55-2.73 (m, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 3.84 (s, 3H), 6.20 (br s, 1H), 6.21 (dd, *J* =

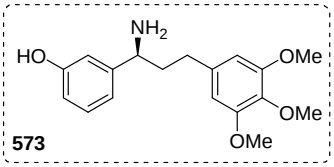
7.7, 7.5 Hz, 2H), 6.41 (s, 2H), 6.41 (br s, 1H), 6.66 (br s, 1H), 6.81 (dd, *J* = 8.0, 2.3 Hz, 1H), 6.89 (br s, 1H), 7.08 (dd, *J* = 7.9, 7.8 Hz, 1H), 7.12 (s, 1H).

Procedures for Deprotection of PMP-group with H_5IO_6:

Method A:[246] Periodic acid (34.2 mg, 0.150 mmol, 1.0 equiv) was added portion-wise to a solution of amine **566** (80.7 mg, 0.150 mmol, 1.0 equiv) in a mixture of MeCN (3 mL), water (1.5 mL) and diluted H_2SO_4 (1.0 M, 0.15 mL) at 0 ºC. The mixture was let to warm to 16 ºC and let to stir for 3 hours at this temperature. Then water was added (3 ml) and the aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The aqueous layer was basified to pH 8 (!) and the observable precipitate was extracted into AcOEt (3 × 10 mL). The combined AcOEt layers were dried over $MgSO_4$ and evaporated affording crude amino alcohol **573** as off-white solid (35 mg, 0.110 mmol, 74 %) which was used without further purification.

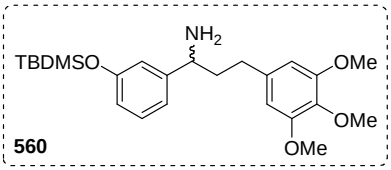
Method B: Periodic acid (98.3 mg, 0.431 mmol, 1.0 equiv) was added portion-wise to a solution of amine **566** (232 mg, 0.431 mmol, 1.0 equiv) in a mixture of MeCN (8.6 mL) and diluted H_2SO_4 (1.0 M, 4.3 mL) at 0 ºC. The mixture was let to stir for 8 hours at temperature between 10-16 ºC. Work-up as in Method A afforde **573** as off-white solid (114 mg, 0.359 mmol, 42 %) which was used without further purification.

(+)-*N*-[1-(3'-Hydroxyphenyl)-3-(3",4",5"-trimethoxyphenyl)prop-1-yl]amine (573), $C_{18}H_{23}NO_4$, FW = 317.42



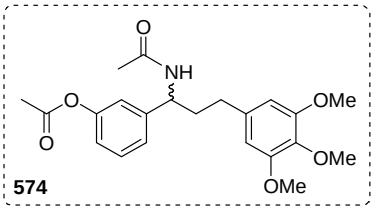
573: white solid; mp 132-133 ºC (CH_2Cl_2); **$[\alpha]_D$** +4.8 (*c* 1.0, MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.00-2.07 (m, 2H), 2.49 (dd, *J* = 7.8, 7.8 Hz, 2H), 3.80 (s, 9H), 6.33 (s, 2H), 6.73 (dd, *J* = 7.9, 2.0 Hz, 1H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.84 (s, 1H), 7.12 (dd, *J* = 7.8, 7.7 Hz, 1H); IR *v* 3426, 3019, 1937, 1591, 1462, 1214 cm^{-1}.

***N*-{1-[3'-(*tert*-Butyldimethylsilyloxy)phenyl]-3-(3",4",5"-trimethoxyphenyl)prop-1-yl} amine (560), $C_{25}H_{37}NO_4Si$, FW = 443.72**



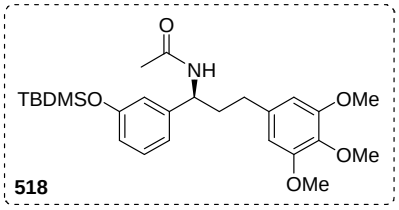
tert-Butyldimethylsilyl chloride (41.0 mg, 0.272 mmol, 2.4 equiv) was added in one portion to a solution of amino alcohol **573** (36 mg, 0.113 mmol, 1.0 equiv) and imidazole (38.5 mg, 0.567 mmol, 5.0 equiv) in anhydrous CH_2Cl_2 (5 mL) at 0 ºC.[230] The mixture was let to warm to room temperature and stir overnight. Then water was added (10 ml) and the aqueous phase (at pH 8) was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over $MgSO_4$ and evaporated. The crude silylated amino alcohol was filtered on a short silica gel column (5 mL) with a mixture of petroleum ether – ethyl acetate (1:1) and ethyl acetate – methanol (5:1) to elute the free amine **560** which was concentrated to oil (40 mg, 0.0902 mmol, 79 %): colourless thick oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.20 (s, 6H), 0.98 (s, 9H), 1.93-2.06 (m, 2H), 2.15 (br s, 2H), 2.45-2.59 (m, 2H), 3.81 (s, 3H), 3.82 (s, 6H), 4.95 (br s, 2H), 6.36 (s, 2H), 6.73 (ddd, *J* = 8.0, 2.4, 0.8 Hz, 1H), 6.81 (dd, *J* = 2.0, 1.8 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 7.19 (dd, *J* = 7.8, 7.8 Hz, 1H).

***N*-[1'-(3"-Acetoxyphenyl)-3'-(3'",4'",5'"-trimethoxyphenyl)prop-1'-yl]-*N*-(4-acetyl-4-methoxyphenyl)amine (574), $C_{22}H_{27}NO_6$, FW = 401.50**



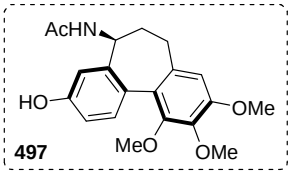
574 prepared according to acetylation Method A (*vide supra*): colourless thick oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.94 (s, 3H), 2.04-2.16 (m, 2H), 2.27 (s, 3H), 2.51-2.57 (m, 2H), 3.80 (s, 3H), 3.81 (s, 3H), 5.01 (ddd, *J* = 7.9, 7.8, 7.4 Hz, 1H), 6.02 (d, *J* = 7.9 Hz, 1H), 6.35 (s, 2H), 6.98 (ddd, *J* = 8.0, 2.2, 0.9 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.33 (dd, *J* = 7.8, 7.8 Hz, 1H); **^{13}C NMR** δ 21.15 (CH_3), 23.34 (CH_3), 32.89 (CH_2), 37.26 (CH_2), 52.74 (CH_3), 56.04 (2 × CH_3), 60.84 (CH), 105.17 (2 × CH), 119.94 (CH), 120.74 (CH), 124.27 (CH), 129.75 (CH), 136.05 (C), 136.96 (C), 143.64 (C), 150.92 (C), 153.13 (2 × C), 169.47 (C), 171.24 (C); **IR** ν 3286, 2938, 1765, 1650, 1590, 1508, 1459, 1371, 1206, 1127 cm^{-1}; **MS** (EI) *m/z* (%) 401 ($M^{\bullet+}$, 40), 195 (55), 182 (40); **HRMS** (EI) 401.1836 ($C_{22}H_{27}NO_6$ requires 401.1838).

(–)-*N*-{1'-[3"-(*tert*-Butyldimethylsilyloxy)phenyl]-3'-(3'",4'",5'"-trimethoxyphenyl)prop-1'-yl}-*N*-(4-acetyl-4-methoxyphenyl)amine (518), $C_{26}H_{39}NO_5Si$, FW = 473.75



518:[230,235,238] colourless thick oil; **[α]$_D$** –39.8 (*c* 1.0, $CHCl_3$), [lit.[230a] gives **[α]$_D$** –42 (*c* 1.0, $CHCl_3$) for 99.6 % ee, lit.[238] gives **[α]$_D^{25}$** –35 (*c* 1.1, $CHCl_3$) for 94 % ee]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.20 (s, 6H), 0.98 (s, 9H), 1.97 (s, 3H), 1.00-2.08 (m, 1H), 2.13-2.22 (m, 1H), 2.45-2.60 (m, 2H), 3.81 (s, 3H), 3.83 (s, 6H), 7.97 (ddd, *J* = 7.9, 7.5, 7.5 Hz, 1H), 5.72 (d, *J* = 8.0 Hz, 1H), 6.36 (s, 2H), 6.76 (ddd, *J* = 6.8, 2.4, 0.9 Hz, 1H), 6.77 (d, *J* = 1.3 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 7.21 (dd, *J* = 8.8, 7.5 Hz, 1H); **^{13}C NMR** δ –4.36 (2 × CH_3), 18.20 (C), 23.41 (CH_3), 25.68 (3 × CH_3), 32.94 (CH_2), 37.48 (CH_2), 53.28 (CH_3), 56.03 (2 × CH_3), 60.84 (CH), 105.23 (2 × CH), 118.58 (CH), 119.18 (CH), 119.60 (CH), 129.80 (CH), 136.17 (C), 137.09 (C), 143.22 (C), 153.15 (2 × C), 156.03 (C), 169.33 (C); **MS** (EI) *m/z* (%) 473 ($M^{\bullet+}$, 50), 416 (20), 222 (25), 185 (90), 182 (100), 181 (80), 47 (30), 116 (32), 91 (45); **HRMS** (EI) 473.2602 ($C_{26}H_{39}NO_5Si$ requires 473.2598); **HPLC** analysis [Chiralpak IB, hexane – propan-2-ol (80:20), 0.75 mL/min, t_{minor} = 13.326 min, t_{major} = 16.529 min] showed 96 % ee.

(–)-*N*-Acetylcolchinol (497), $C_{20}H_{23}NO_5$, FW = 357.44



An oven-dried flask was charged with phenyliodonium bis(trifluoroacetate) (PIFA, 105 mg, 0.244 mmol, 1.2 equiv) and dissolved in anhydrous CH_2Cl_2 (3 mL) under an argon atmosphere.[230] After trifluoroacetic acid (2.0 mL) and trifluoroacetic acid anhydride (0.4 mL) were added, the mixture was cooled to –4 ºC. A solution of the acetamide **518** (93 mg, 0.203 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (1 mL) was added and followed immediately by $BF_3.OEt_2$ (60 μL, 69 mg, 0.487 mmol, 2.4 equiv). The reaction mixture turned yellow on addition of the acetamide and then from yellow to green and dark brown on addition of

$BF_3.OEt_2$. The reaction mixture was allowed to warm to room temperature and stir for 4 hours at room temperature. The reaction was quenched by drop-wise addition of saturated $NaHCO_3$ solution and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The brown residue was purified on a silica gel column (10 mL) twice: first with a gradient of petroleum ether – ethyl acetate (1:1) to pure ethyl acetate and then with CH_2Cl_2 – methanol (98:2) to afford acetylcolchinol **497** as off-white solid (29 mg, 0.0820 mmol, 40 %):[229,230,235,238] off-white amorphous solid; $[\alpha]_D^{23}$ –30.1 (*c* 0.5, $CHCl_3$), [lit.[229b] gives $[\alpha]_D^{20}$ –51.6 (*c* 1.23, $CHCl_3$), lit.[230a] gives $[\alpha]_D^{20}$ –45.2 (*c* 0.6, $CHCl_3$) for 94 % ee, lit.[238] gives $[\alpha]_D^{27}$ –34.0 (*c* 1.0, $CHCl_3$) for 94 % ee]; **^{1}H NMR** (400 MHz, MeOH-d_4) δ 1.90-1.96 (m, 1H), 2.01 (s, 3H), 2.25-2.27 (m, 2H), 2.49-2.51 (m, 1H), 3.49 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.58-4.65 (m, 1H), 6.71 (s, 1H), 6.72 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.79 (d, *J* = 2.7 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 8.49 (d, *J* = 7.8 Hz, 1H); **^{13}C NMR** δ 22.66 (CH_3), 31.55 (CH_2), 39.92 (CH_2), 50.53 (CH), 56.62 (CH_3), 61.33 (CH_3), 61.62 (CH_3), 109.07 (CH), 110.86 (CH), 114.19 (CH), 126.55 (C), 126.77 (C), 132.14 (CH), 136.68 (C), 142.39 (C), 142.46 (C), 152.14 (C), 153.71 (C), 157.98 (C), 172.45 (C); **IR** ν 3284, 2930, 2855, 1643, 1608, 1535, 1483, 1452, 1404, 1325, 1236, 1142 cm^{-1}; **MS** (EI) *m/z* (%) 357 ($M^{\bullet+}$, 18), 298 (10); **HRMS** (EI) 357.1573 ($C_{20}H_{23}NO_5$ requires 357.1576).

8. Applications in Synthesis of Alkaloids (II)

8.1. Properties and Synthesis of Atracurium

8.1.1. What is Atracurium

Atracurium **402** is a drug designed to act as a non-depolarising neuromuscular blocker binding to acetylcholine (Ach) receptors (Figure 8.1). Its development was based on the previously widely used suxamethonium **401**, a polarising blocker.[248] The pharmaceutical outcome of these two drugs is similar, as both block the muscle activity required during surgery. However, the substantial difference between them is the mode of muscle blockage. Suxamethonium is acetylcholine *agonist*, relatively stable to degradation by Ach-esterase; thus, it depolarises the plasma membrane of the muscle and the muscle fibre becomes resistant to stimulation of acetylcholine. This results in muscle twitching during the depolarising phase and post-experience pains. Atracurium acts as a post-synaptic competitive acetylcholine-receptor *antagonist* that only blocks the receptors without further effects.

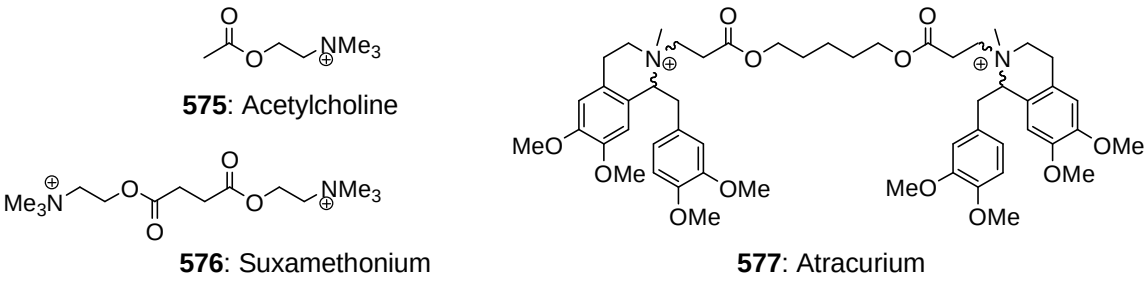
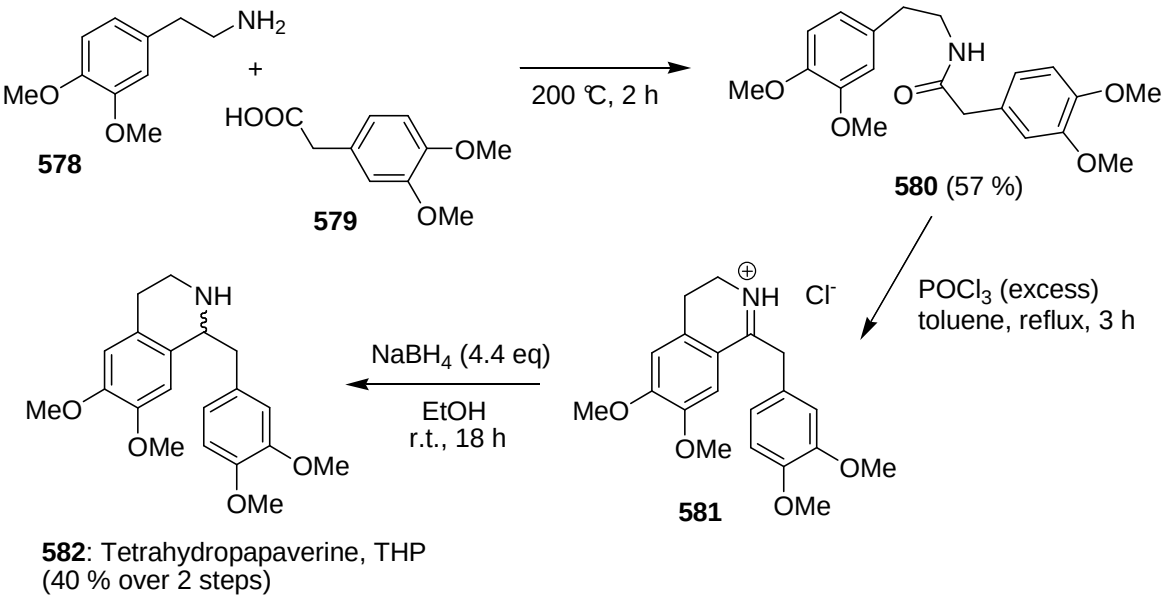


Figure 8.1. Neuromuscular Transmitter Acetylcholine and Blockers Suxamethonium and Atracurium

Stenlake and co-workers provided extensive study on the synthesis, stereochemical analysis,[249] structure-and-properties relationships[248,249] and pharmacological data which was very successful and the drug became commercial from Borroughs Wellcome, NC, USA under the name Tracrium (for atracurium) or Nimbex (for cisatracurium, *vide infra*).

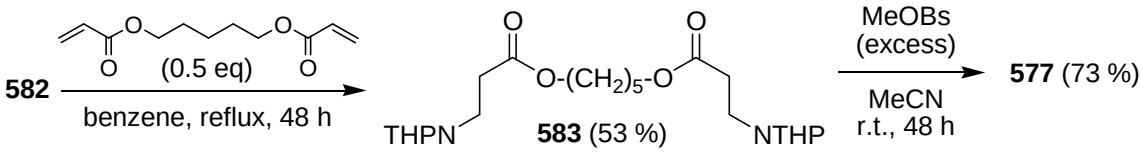
Atracurium means a mixture of ten possible isomeric molecules, each containing four stereocentres – the asymmetric carbon in the tetrahydropapaverin part and the asymmetric quaternary nitrogen. Its synthesis is very short, only five steps, starting from

homoveratrylamine **578** and 3,4-dimethoxyphenylacetic acid **579** (Scheme 8.1). The amide **580** was prepared just by heating the components to 200 ºC and collecting the crystals. Bischler-Napieralski cyclisation of **580** with phosphorus oxytrichloride afforded the protonated dihydropapaverine **581** which was reduced with sodium borohydride to tetrahydropapaverine **582** in overall 23 % yield.



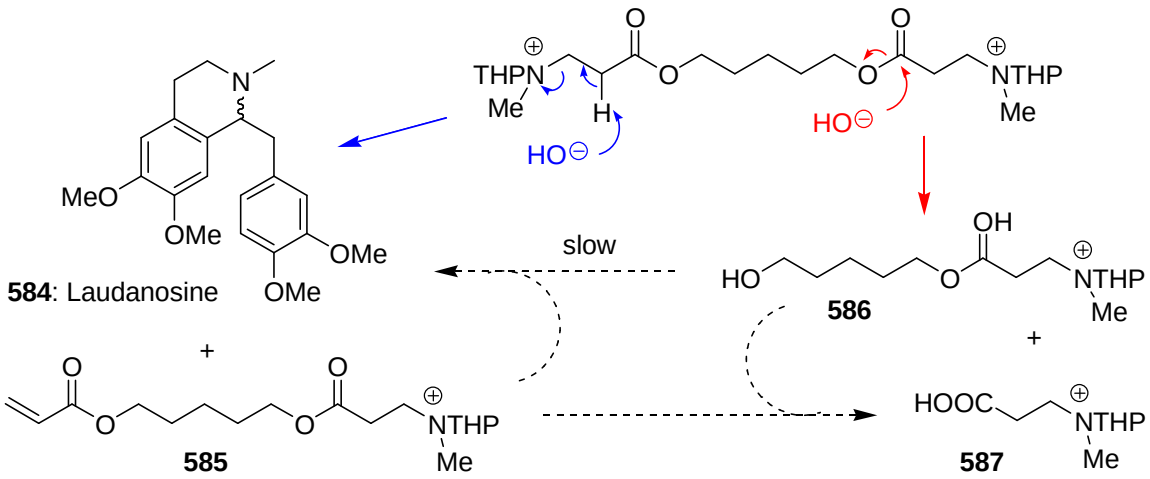
Scheme 8.1. Synthesis of Tetrahydropapaverine, Intermediate in Synthesis of Atracurium

Michael addition of **582** to pentandiol diacrylate afforded the tertiary diamine **583** which was quaternised with methyl besylate to salt of atracurium **577** in 39 % yield (Scheme 8.2).



Scheme 8.2. Synthesis Atracurium from Tetrahydropapaverine

The main pathway for biological degradation[250] is via non-enzymatic Hofmann elimination and ester hydrolysis that produce inactive metabolites (pH of blood is ~ 7.4; Scheme 8.3). Hofmann elimination of atracurium provides laudanosine **584** and monoacrylate **585**, whereas ester hydrolysis produces alcohol **586** and quaternary acid **587** and these processes can be interlinked.



Scheme 8.3. Biodegradation of Atracurium

Optimisation of the structure according to the knowledge of its pharmacology provided valuable data, but it proved difficult to combine all of the factors and build "an ideal blocker":[248,250,251]

1. Fit of the quaternary nitrogen centre with the ACh receptors to enhance:

- the uptake – the nature and size of the quaternary centre, the overall lipophilicity,
- the potency – lipid substituents at or near the quaternary centre facilitate binding.

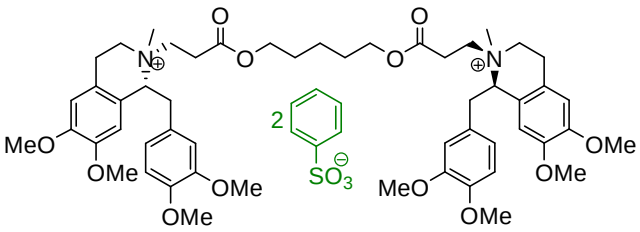
2. Increasing the rate of biodegradation:

- minimise the concurrent hydrolysis to **587** which is not susceptible to Hofmann elimination and being hydrophilic, has also reduced affinity to ACh receptor,
- substitution patterns and electron properties on the nitrogen heterocycle or polyalkylene chain – duration of action decreases with the electron-withdrawing power of the acylating group and smaller steric hindrance.

3. Pharmacology, pharmacokinetics:

- effect of counter anion on solubility – besylate of **577** is soluble in water up to 60 $mg.ml^{-1}$ at 25 °C,
- inter-quaternary spacer – 13-14 methylene or spatially equivalent groups allow adequate chain flexibility.

Atracurium was synthesised in the late 1970s and even though research continued for 15 more years, a more suitable analogue has not been identified. The only improvement was the analysis of the mixture and resolution to separate isomers or subgroups of isomers which have different potency. As mentioned earlier, the mixture consists of four racemates and two *meso*-compounds. Each isomer can be defined by absolute configuration at the carbon stereocentre and relative configuration at the quaternary nitrogen. Considering that the synthetic methods afford the *cis*-isomer 3.07 times more likely than the *trans* (attack of the methylating reagent is more probable from the less hindered site; thus, furnishing *cis*-isomer) and assuming that quaternisation at one THP-unit is not affected by the other one, the *cis-cis*, *cis-trans* and *trans-trans* isomers are in 10.5:6.2:1 ratio.[249]



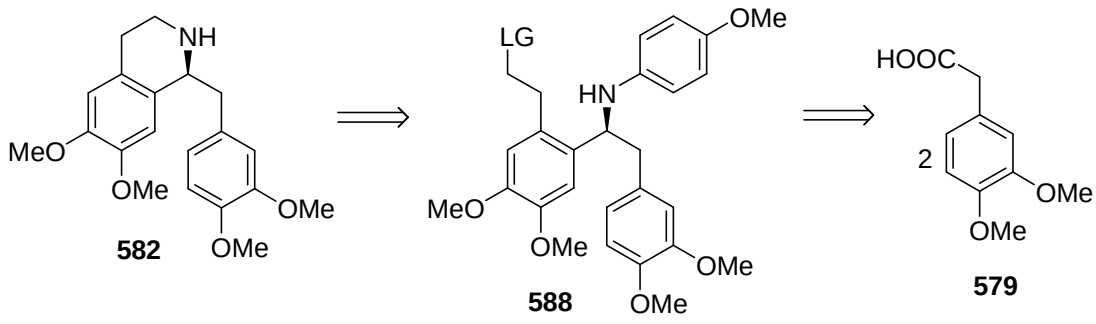
(*R-cis*,*R'-cis*)-577: Cisatracurium besylate

Figure 8.2. Cisatracurium

The potency of these isomers decreases in order (*R-cis*) > (*R-trans*) > (*S-cis*) > (*S-trans*) for each centre and it was quantified that the potency in series (*R-cis*,*R-cis*), (*R-cis*,*S-cis*) and (*S-cis*,*S-cis*) is in ratio 2.6:1.5:1.[249a] The most potent isomer (*R-cis*,*R-cis*) is called *cisatracurium* (Figure 8.2).

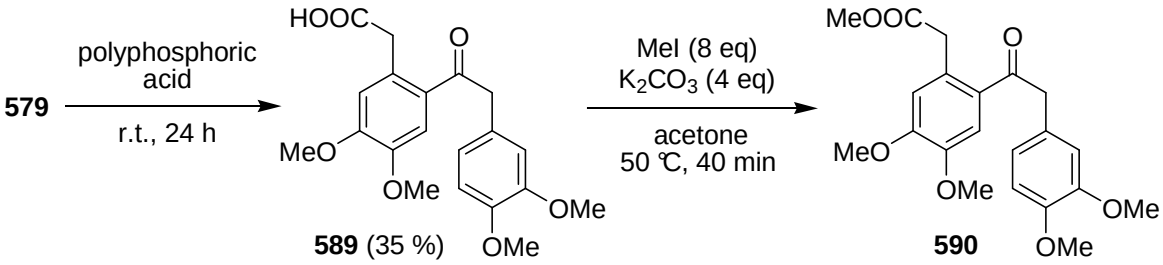
8.1.2. Our Synthesis of Atracurium

Our synthesis of atracurium was based on Stenlake's approach, using tertahydropapaverine **582** as the crucial intermediate. However, it was expected that Sigamide catalyst would afford the (*S*)-isomer of the THP-core. The retrosynthetic analysis from it to phenylacetic acid was designed through an open-chain secondary amine **588** (Scheme 8.4) as it was already known (see Chapter 5) that cyclic imines are unsuitable substrates.



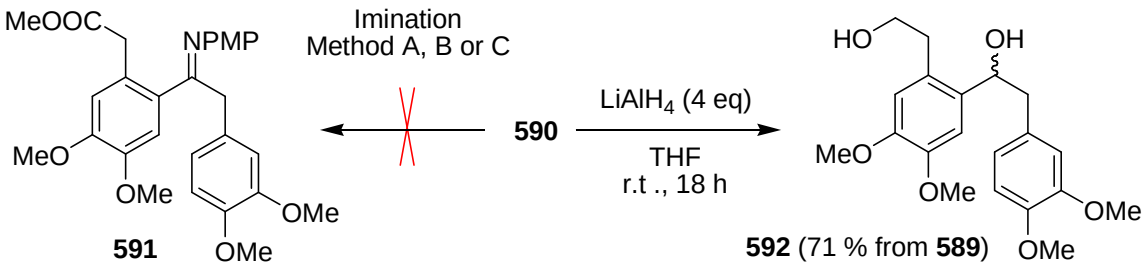
Scheme 8.4. Retrosynthetic Analysis of Tetrahydropapaverine Unit

Thus, the first synthetic step provided the 1,2-diphenylethane structure, easily prepared by Friedel-Crafts acylation of **579** by another molecule of **579** in polyphosphoric acid medium.[252] This procedure afforded essentially pure keto acid **589**, though only in 35 % yield. The acid functionality was protected as methyl ester **590**.[253]



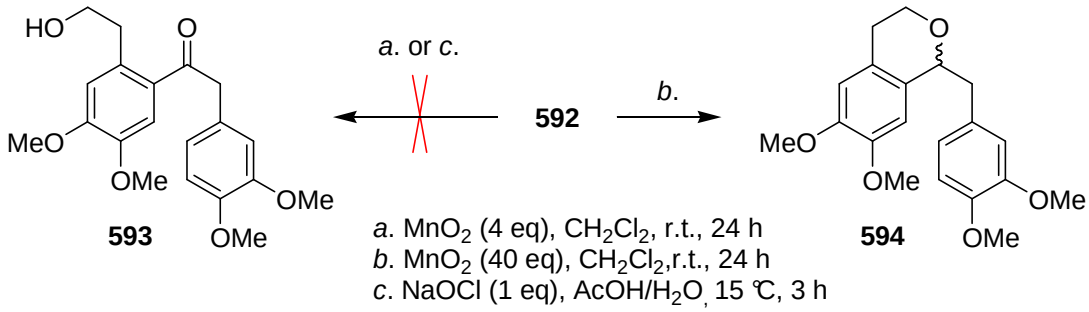
Scheme 8.5. Synthesis of Keto Ester Substrate

Keto ester **590** was used in subsequent imination step; however, all methods used so far were unsuccessful, slow reaction rate was accompanied with the formation of tar material. Assumption that the ester group is reactive enough to interact with the activated keto-group led us to an alternative route where the crude ester was reduced with lithium aluminium hydride to diol **592** (Scheme 8.6).



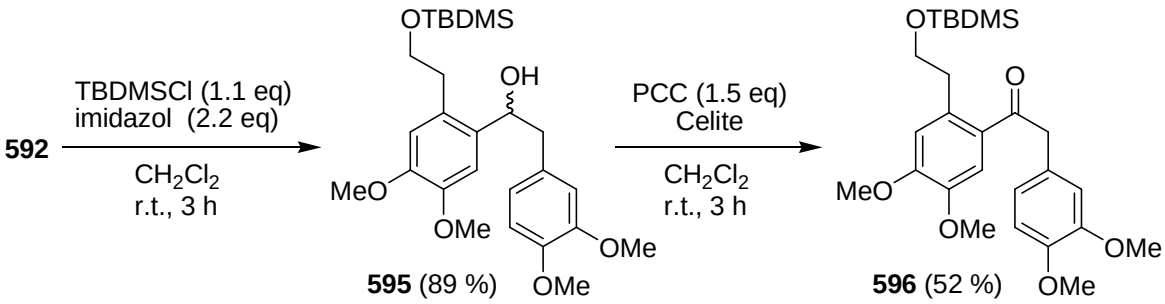
Scheme 8.6. Alternative Route from Ester **590**

It should be possible to oxidise an activated secondary alcohol selectively in the presence of a primary one. From the numerous reports in the literature describing this transformation, two representative reagents were tried – manganese dioxide and sodium hypochlorite, known for selective oxidation of benzylic alcohols, in particular (Scheme 8.7). However, NaOCl[254] afforded a mixture of compounds, from which several were identified as aldehydes. Freshly prepared manganese dioxide either did not react when 4 equivalents were used or it caused cyclisation to isochroman **594** when a large excess was used. Reaction proceeded presumably via radical mechanism.



Scheme 8.7. Attempts for Selective Oxidation of the Secondary Alcohol in **592**

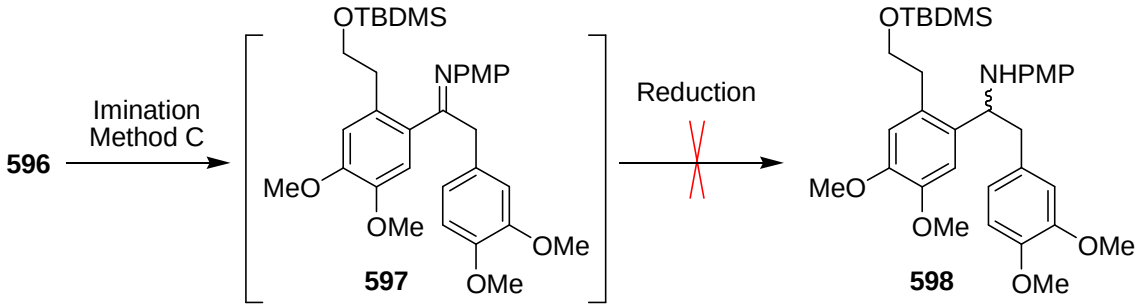
At this point, the synthesis was becoming rather lengthy, but it was interesting to find out whether it is possible to prepare the desired open-chain imine and reduce it to amine as this molecule is, obviously, very prone to close a six-membered ring. The primary alcohol group of **592** was selectively protected as silylether **595** which was then oxidised at the benzylic position to ketone **596** (Scheme 8.8).



Scheme 8.8. Alternative Route to Ketone Substrate

The mildest, Lewis-acid-mediated imination method was chosen and to our initial delight, a yellow foam was obtained. Unfortunately, the ^{1}H NMR analysis of this compound was complicated by signal overlapping in the aromatic and methoxy region of both of the *C=N* isomers. Thus, we decided not to perform full characterisation and

submitted the semi-purified sample to reduction (Scheme 8.9). However, only confusing, mixed material was isolated and amine **598** was not detected in the mixture. Racemic reduction either with $NaBH_4$ or DMF/$HSiCl_3$ did not afford the desired product.



Scheme 8.9. Attempts for Imination of Ketone **596** and Concominant Reduction

This synthetic approach proved unsuitable for a molecule, which contains benzylic carbonyl group and a side chain which can cyclise to a six-membered ring. However, our methodology does not afford *N*-cyclic amines in useful levels of enantioselectivity which means that it is not possible to apply our method onto dihydropapaverine-like substrates.

8.2. Other Applications

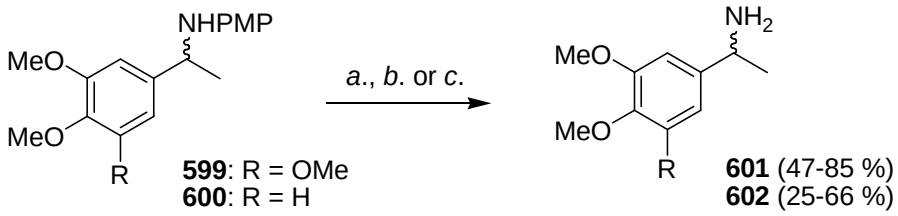
8.2.1. PMP-Deprotection Study

While the synthesis of atracurium was in process, model deprotections of the *p*-methoxyphenyl group were carried out with 3,4,5-trimethoxy- and 3,4-dimethoxy-acetophenone-derived amines (Table 8.1; Scheme 8.10) to simulate the impact of the methoxy-groups on the oxidative cleavage.

Table 8.1. PMP-deprotection of Electron-rich Amines

PMP-Amine	**Free Amine (Yield)**	**Oxidant (Method), React. Time**	**PMP-Amine**	**Free Amine (Yield)**
599	**601** (47 %)	TCCA (C), 1.5 h	**600**	**602** (58 %)
599	**601** (80 %)	H_5IO_6 (A), 1.5 h	**600**	**602** (66 %)
599	**601** (52 %)	H_5IO_6 (B), 2 h	**600**	**602** (25 %)
(+)-599	**(–)-601** (85 %)	H_5IO_6 (A), 4 h	**(–)-600**	**(–)-602** (66 %)

It was shown that the cleavage with trichlorocyanuric acid (TCCA) was fast, affording the free amines **601** and **602** in moderate yields (47-58 %). Better yields of the free amines (66-80 %) were achieved by employing the original Rutjes' procedure[246] (Method A) with peroxyiodic acid (H_5IO_6). On the other hand, the procedure optimised for the deprotection of amino alcohols (Method B, see also Chapter 7.2.2) furnished the amines **601** or **602** only in unsatisfactory yields (25-52%). Thus, the Method A was also used for preparing the enantioenriched amines, which occurred in yields comparable to the racemates.



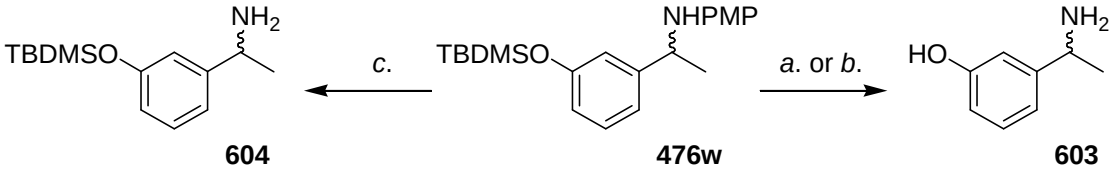
599: R = OMe
600: R = H

601 (47-85 %)
602 (25-66 %)

a. H_5IO_6 (1 eq), 1M H_2SO_4, MeCN/H_2O, 18 °C, 1.5-4 h
b. H_5IO_6 (1 eq), 1M H_2SO_4, MeCN, 18 °C, 2 h
c. TCCA (0.5 eq), MeCN/H_2O, 18 °C, 1.5 h

Scheme 8.10. Deprotection of Polymethoxy-substrates

Owing to the disappointing results of the deprotection of the *p*-methoxyphenyl group from the amine intermediate in the synthesis of colchinol (Chapter 7.2.2), some additional experiments were carried out with the model amine **476w** prepared previously. The same three methods were used – with TCCA and the two procedures with H_5IO_6 (Scheme 8.11).



604 **476w** **603**

a. H_5IO_6 (1 eq), 1M H_2SO_4, MeCN/H_2O, 18 °C, 2.5-5 h
b. H_5IO_6 (1 eq), 1M H_2SO_4, MeCN, 18 °C, 6-12 h
c. TCCA (0.5 eq), MeCN/H_2O, 18 °C, 0.5 h

Scheme 8.11. Deprotection of Amine **476w**

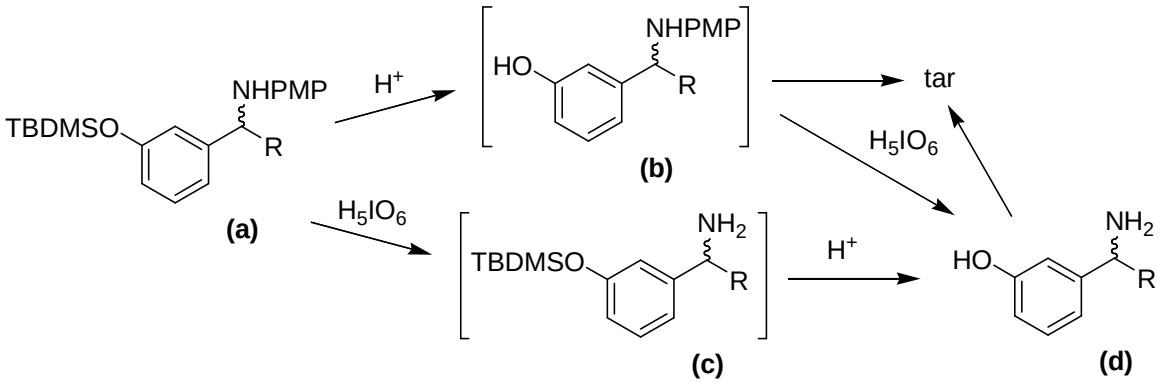
The deprotection of **476w** with TCCA was very fast; however, only small amounts of material were isolated (15 %) being the amino silylether **604**. Also in the case of colchinol, this method produced only traces of isolable material that was not examined

further. The use of H_5IO_6 in either modification afforded the free amino alcohol **603** in variable yields (Table 8.2), strongly dependent on the reaction time and temperature, 74 % at the best.

Table 8.2. PMP-deprotection of Amino Silylether **476w**

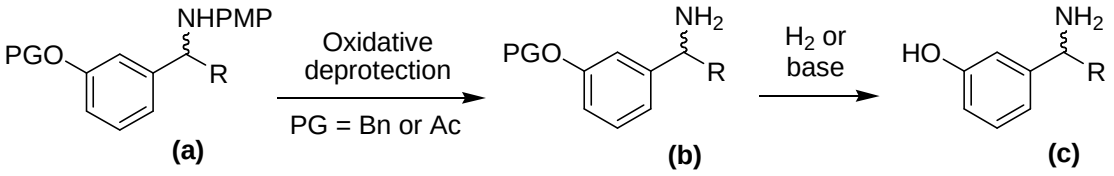
PMP-Amine	Free Amine (Yield)	Oxidant (Method), React. Time
476w	**604** (15 %)	TCCA (C), 0.5 h
476w	**603** (24 %)	H_5IO_6 (A), 5.5 h
476w	**603** (75 %)	H_5IO_6 (B), 6 h
(–)-476w	**(–)-603** (34 %)	H_5IO_6 (B), 12 h

Similar fluctuations of yields were also observed in deprotection of the model amine **476w** to **603**. Interestingly, in both cases, the enatioenriched free amine **603** was obtained in significantly lower yield and with longer reaction times (disappearance of the starting material was monitored). It is hard to explain why the reactivity should be different for the racemate and either of the enantiomers. Possibly, presence of trace of chiral impurities could catalyse over-oxidation of the major enantiomers.



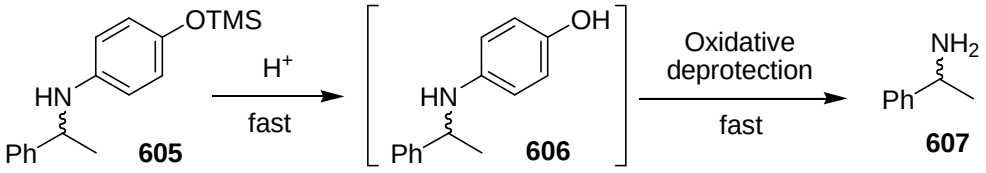
Scheme 8.12. Parallel Pathways for Deprotection of Amines **476w** or **566**

It seems plausible that the generally low yields and unreliability of the reaction were caused by the fast acid-catalysed deprotection of the silylether group of **(a)** or **(c)** to free phenols **(b)** or **(d)**. This was indicated by isolation of phenol **(b)** or mixtures of **(b)** and **(d)** when the disappearance of the starting material **(a)** was observed. Further oxidative processes can occur at the PMP-site affording the desired amino alcohol **(d)** from **(b)** or at their phenolic sites leading to uncontrolled reactivity (Scheme 8.12).



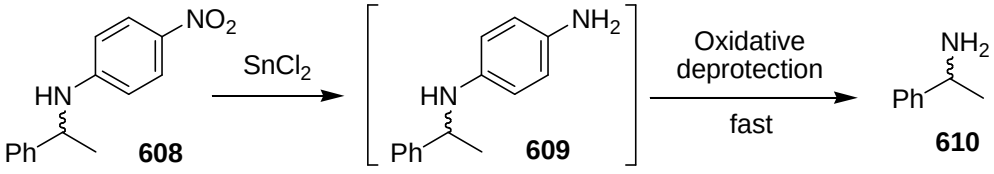
Scheme 8.13. Use of Alternative *O*-Protecting Groups

In conjunction with the results of deprotections of polymethoxy-analogues, where the reactivity problem was not observed, this knowledge could be (have been) exploited for improvement of the synthesis of colchinol (see Chapter 7.2). Benzylether or acetate protecting group instead of the TBDMS silylether would be probably tolerated better during the PMP-deprotection step (Scheme 8.13).



Scheme 8.14. Use of Alternative *N*-Protecting Groups

Another possible way of improving the yield of the free amine would be using a different protecting group on nitrogen instead of the *p*-methoxyphenyl group. Two possibilities arose, the use of *p*-trimethylsilyloxyphenyl or *p*-nitrophenyl group. The first type (Scheme 8.14) is the acid-labile silylether **605** which would easily hydrolyse to free phenol **606** and its oxidative deprotection should be very fast. However, this approach could not be trialled as the corresponding imine was not isolated.

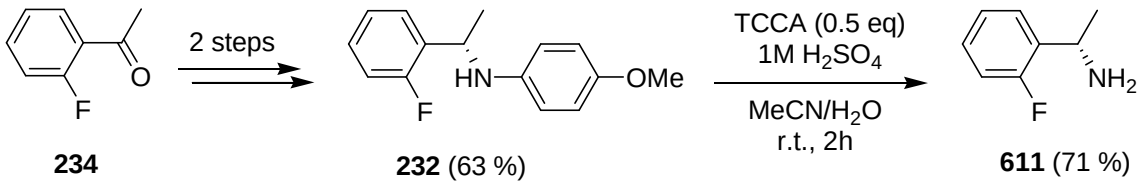


Scheme 8.15. Use of Alternative *N*-Protecting Groups

The other alternative was relatively unreactive *p*-nitroaniline derivative **608** (Scheme 8.15) which could be selectively reduced to *p*-aminoaniline derivative **609** that is known to be oxidised fast. Unfortunately, the reduction of the corresponding imine to **608** proceeded in low yields so this method could not have had a practical outcome and the deprotection was not attempted.

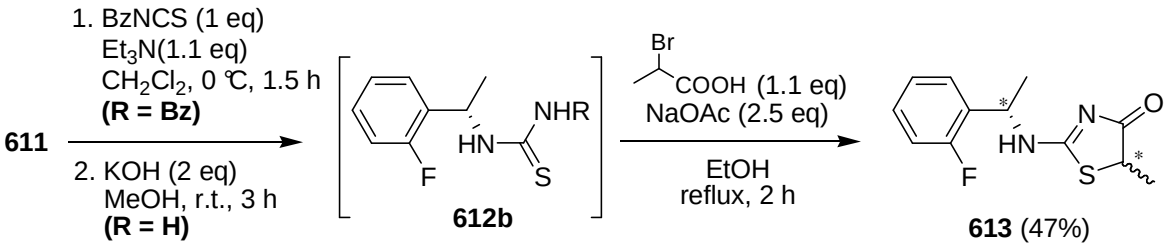
8.2.2. Synthesis of 11β-HSD Inhibitor[255]

Besides the electron-rich amines resembling alkaloid structures, the method of imine reduction was successfully applied to the synthesis of an electron-poor amine derived from *o*-fluoroacetophenone. The high-yielding imination of the ketone afforded the corresponding imine which was reduced in high yield and enantioselectivity (95 %) to amine **232**. The PMP-group was oxidatively cleaved using the Rutjes' method with TCCA,[246] which was the most efficient time- or yield-wise, and the free amine **611** was obtained in good 71 % yield (Scheme 8.16).



Scheme 8.16. Synthesis of an Electron-poor Amine

Thiazolone **613** (Scheme 8.17) is a precursor of 11β-hydroxysteroid dehydrogenase (HSD). In mammals, 11β-HSD serves for reduction of cortisone to the active glucocorticoid cortisol (in humans, type 1) and oxidation back to cortisone (type 2). Metabolic disorders (obesity, insulin-resistance in diabetes 2) caused by glucocorticoid excess or over-expression of 11β-HSD-1 could be treated by inhibiting this enzyme. Simple synthesis of a family of 11β-HSD inhibitors was published recently[255] and our methodology was exploited for preparing the enantioenriched amine unit.



Scheme 8.17. Synthesis of Thiazolone 11β-HSD Inhibitor from Amine **611**

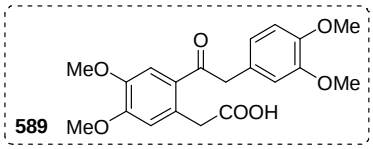
The free amine **611** was converted into the desired thiazolone **613** in three steps (Scheme 8.17). The first two steps were the formation of the *N*-benzoyl-*N*'-[1-(2'-fluorophenyl)ethyl]-thiourea **612a** and direct hydrolysis to the *N*-[1-(2'-

fluorophenyl)ethyl]-thiourea **612b**. The thiazolone ring was constructed by reaction of the crude thiourea material with racemic 2-bromopropionic acid. Thus, the final structure **613** was prepared from the free amine **611** in three steps in overall 47 % yield. It is noteworthy to say that **613** was obtained as a mixture of four isomers – a pair Ar-*C**-*N* epimers resulting from the enantioselective reduction (in 97.5:2.5 ratio) and a pair of *S*-*C**-*CO* epimers (in 1:1 ratio) as a result of the cyclisation with racemic 2-bromopropionic acid. Further derivatisation at the thiazolone *H*-*C**-CH_3 position would lead to a series of 11β-HSD inhibitors.[255]

8.3. Experimental Part (II)

8.3.1. Atracurium

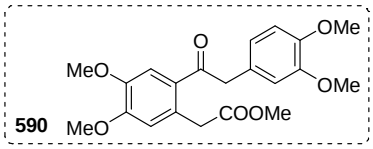
2-{2'-[2"-(3'",4'"-Dimethoxyphenyl)acetyl]-4',5'-dimethoxyphenyl}acetic acid (589), $C_{20}H_{22}O_7$, FW = 374.42



2-(3',4'-Dimethoxyphenyl)acetic acid (50.0 g, 255 mmol) was mixed into polyphosphoric acid (84 % P_2O_5, 1 kg) and the thick suspension was let to stand (with occasional stirring) for 24 h at room temperature.[252] Then the mixture was poured into cold water (4 L) and stirred occasionally. When the precipitation was finished (no brown oily material left), the yellow precipitate was filtered off and pre-dried with suction of air. The wet crude solid was crystallised from water-EtOH (2:1) mixture to afford **589** (18.9 g, 45.1 mmol, 35 %): yellowish crystals; **mp** 132-133 ºC (water: EtOH) [lit.[253] gives 135-136 ºC (water:EtOH)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.78 (s, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 4.19 (s, 2H), 6.75-6.83 (m, 4H), 7.37 (s, 1H); **^{13}C NMR** δ 41.03 (CH_2), 47.35 (CH_2), 55.90 (2 × CH_3), 56.20 (2 × CH_3), 111.43 (CH), 112.28 (CH), 113.12 (CH), 115.07 (CH), 121.47 (CH), 126.69 (C), 128.57 (C), 129.29 (C), 147.59 (C), 148.22 (C), 152.51 (C), 173.78 (C), 201.62 (C); **IR** (ATR) ν 2939, 2839, 1699, 1664, 1606, 1568, 1452, 1516, 1452, 1427, 1352, 1331, 1273, 1215 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 375 [$(M+H)^+$, 25],

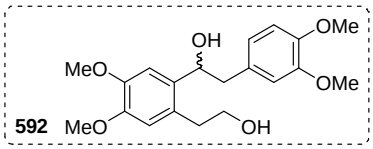
357 (25), 331 (50), 223 (45), 167 (55); **HRMS** (CI/isobutane) 375.1448 ($C_{20}H_{23}O_7$ requires 375.1444).

Methyl 2-{2'-[2"-(3'",4'"-dimethoxyphenyl)acetyl]-4',5'-dimethoxyphenyl}acetate (590), $C_{21}H_{24}O_7$, FW = 388.45



Methyl iodide (19.9 mL, 45.6 g, 321 mmol, 8 equiv) was added to a suspension of acid **589** (15.0 g, 40.1 mmol, 1 equiv) and potassium carbonate (22.1 g, 160 mmol, 4 equiv) in acetone (400 mL) and the mixture was heated to 50 ºC for 40 min.[253] Then solids were filtered off and the filtrate was concentrated *in vacuo*. The crude solid ester **590**[253] was used without further purification: yellowish crystals; **mp** 104-106 ºC (hexane) [lit.[253] gives 130-132 ºC (MeOH)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.89 (s, 2H), 3.92 (s, 3H), 4.16 (s, 2H), 6.71 (s, 1H), 6.76-6.83 (m, 3H), 7.39 (s, 1H); **^{13}C NMR** δ 40.08 (CH_2), 47.37 (CH_2), 51.85 (CH_3), 55.83 (CH_3), 55.88 (CH_3), 55.99 (CH_3), 56.15 (CH_3), 111.34 (CH), 112.39 (CH), 113.50 (CH), 115.37 (CH), 121.44 (CH), 127.51 (C), 128.62 (C), 129.71 (C), 147.26 (C), 147.98 (C), 151.70 (C), 172.13 (C), 199.06 (C); **IR** (ATR) ν 2951, 1736, 1605, 1522, 1462, 1339, 1265, 1234, 1126 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 389 [$(M+H)^+$, 30], 167 (25), 113 (32), 97 (45), 85 (70); **HRMS** (CI/isobutane) 389.1601 ($C_{21}H_{25}O_7$ requires 389.1600).

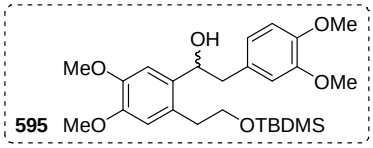
1-(2'-(2'-Hydroxyethyl)-4",5"-dimethoxyphenyl)-2-(3'",4'"-dimethoxyphenyl)ethanol (592), $C_{20}H_{26}O_6$, FW = 362.46



A solution of ester **590** (15.5 g, 41 mmol, 1 equiv) in anhydrous THF (300 mL) was added drop-wise to a suspension of lithium aluminium hydride (6.08 g, 160 mmol, 4 equiv) in THF (100 mL) under an argon atmosphere at 0 ºC. The mixture was allowed to warm to room temperature and then heated to reflux for 16 h. The mixture was then cooled down to 0 ºC and the excess of $LiAlH_4$ was quenched with ethyl acetate and water. The aqueous layer was neutralised and extracted with AcOEt (3 × 200 mL), the combined organic layers were washed with brine (200 mL), dried over $MgSO_4$ and evaporated. The crude solid was

crystallised from ethyl acetate to yield the alcohol **592** (10.3 g, 28.4 mmol, 71 % over two steps): off-white crystals; **mp** 122-123 ºC (AcOEt) [lit.[253] gives 135-136 ºC (AcOEt)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.60 (ddd, *J* = 15.8, 4.1, 4.0 Hz, 1H), 2.78-2.85 (m, 1H), 3.02 (dd, *J* = 14.3, 7.8 Hz, 1H), 3.10 (dd, *J* = 14.3, 4.7 Hz, 1H), 3.71-3.77 (m, 1H), 3.78 (s, 3H), 3.84 (s, 3H), 3.85 (s, 6H), 4.11 (ddd, *J* = 11.1, 4.8, 4.7 Hz, 1H), 4.94 (dd, *J* = 7.4, 4.8 Hz, 1H), 6.50 (s, 1H), 6.59 (s, 1H), 6.79 (s, 1H), 6.797 (s, 1H), 6.799 (s, 1H); **^{13}C NMR** δ 28.49 (CH_2), 42.19 (CH_2), 55.67 (CH_3), 55.71 (CH_3), 55.77 (CH_3), 55.80 (CH_3), 62.79 (CH_2), 76.19 (CH), 108.23 (CH), 110.93 (CH), 111.32 (CH), 112.63 (CH), 121.53 (CH), 126.15 (C), 129.35 (C), 131.09 (C), 147.04 (C), 147.35 (C), 147.42 (C), 148.46 (C); **IR** ν 3411, 3019, 2960, 2938, 1608, 1515, 1465, 1261, 1217 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 345 {$[M–OH)+H]^+$, 100}, 327 (15), 195 (20); **HRMS** (CI/isobutane) 345.1703 ($C_{20}H_{25}O_5$ requires 345.1702).

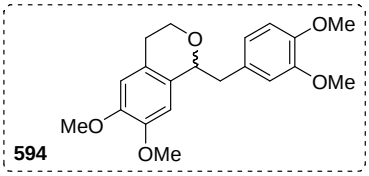
1-{2'-[2'-(*tert*-Butydimethylsilyloxy]ethyl]-4",5"-dimethoxyphenyl}-2-(3'",4'"-dimethoxyphenyl)ethanol (595), $C_{26}H_{40}O_6Si$, FW = 476.75



Neat *tert*-butyldimethylsilyl chloride (4.57 g, 30.4 mmol, 1.1 equiv) was added to a solution of diol **592** (10.0 g, 27.6 mmol, 1.0 equiv) and imidazole (4.12 g, 20.7 mmol, 2.2 equiv) in anhydrous CH_2Cl_2 (270 mL) under an argon atmosphere and the mixture was let to stir at room temperature for 3 h.[253] The reaction was quenched with water (400 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with water (100 mL), brine (200 mL), dried over $MgSO_4$ and evaporated. The crude oil was purified on a silica gel column (300 mL) with a gradient of petroleoum ether – ethyl acetate mixture (80:20 to 50:50) to afford mono-protected alcohol **595** (11.7 g, 24.5 mmol, 89 %): colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ –0.07 (s, 6H), 0.84 (s, 9H), 2.78 (dd, *J* = 6.8, 6.8 Hz, 2H), 2.96 (s, 1H), 2.98 (d, *J* = 2.7 Hz, 1H), 3.74 (dd, *J* = 6.7, 6.7 Hz, 2H), 3.80 (s, 3H), 3.84 (s, 3H), 3.849 (s, 3H), 3.854 (s, 3H), 5.05 (dd, *J* = 7.1, 6.0 Hz, 1H), 6.65 (s, 1H), 6.66 (s, 1H), 6.73 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.96 (s, 1H); **^{13}C NMR** δ –5.47 (2 × CH_3), 18.29 (C), 25.86 (3 × CH_3), 35.04 (CH_2), 44.56 (CH_2), 55.67 (CH_3), 55.71 (CH_3), 55.79 (CH_3), 55.87 (CH_3), 64.45 (CH_2), 71.59 (CH), 109.15 (CH), 111.08 (CH), 112.63 (CH), 112.91 (CH), 121.37 (CH), 128.37 (C), 130.86 (C), 134.27 (C), 147.50 (C), 147.60 (C), 147.94 (C), 148.65 (C); **IR** ν 3410, 3018, 2955,

2933, 2856, 1608, 1515, 1465, 1259 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 459 {[M–H_2O)+H]$^+$, 100}, 329 (50), 327 (95), 325 (40); **HRMS** (CI/isobutane) 459.2570 ($C_{26}H_{39}O_5Si$ requires 459.2567).

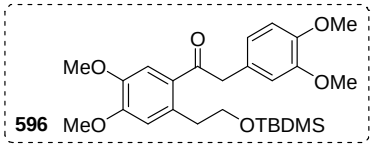
1-(3',4'-Dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isochromene (594), $C_{20}H_{24}O_5$, FW = 344.44



594

Manganese dioxide (959 mg, 11.0 mmol, 40 equiv) was added to a solution of diol **592** (100 mg, 0.276 mmol, 1 equiv) in anhydrous CH_2Cl_2 (5 mL) under an argon atmosphere and the mixture was let to stir at room temperature for 3 h. The solids were filtered off and the filtrate was concentrated *in vacuo*. The crude was purified on a silica gel column (20 mL) with a gradient of petroleum ether – ethyl acetate mixture (80:20 to 60:40) to afford the cyclised product **594**[253] (71 mg, 0.206 mmol, 75 %): colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.60 (ddd, *J* = 15.8, 4.1, 4.0 Hz, 1H), 2.77-2.84 (m, 1H), 3.02 (dd, *J* = 14.3, 7.7 Hz, 1H), 3.10 (dd, *J* = 14.3, 4.7 Hz, 1H), 3.71-3.77 (m, 1H), 3.78 (s, 3H), 3.84 (s, 3H), 3.85 (s, 6H), 4.11 (ddd, *J* = 11.2, 6.5, 4.7 Hz, 1H), 4.95 (dd, *J* = 7.4, 4.9 Hz, 1H), 6.50 (s, 1H), 6.58 (s, 1H), 6.78 (s, 1H), 6.79 (s, 1H), 6.80 (s, 1H); **^{13}C NMR** δ 28.55 (CH_2), 42.26 (CH_2), 55.72 (CH_3), 55.77 (CH_3), 55.79 (CH_3), 55.86 (CH_3), 62.85 (CH_2), 76.25 (CH), 108.28 (CH), 110.93 (CH), 111.36 (CH), 112.67 (CH), 121.52 (CH), 126.18 (C), 129.37 (C), 131.11 (C), 147.09 (C), 147.40 (C), 147.47 (C), 148.52 (C); **IR** ν 3002, 2934, 2834, 1609, 1516, 1465, 1259, 1217 cm^{-1}; **MS** (EI) *m/z* (%) 344 ($M^{\bullet+}$, 5), 193 (100), 151 (30); **HRMS** (EI) 344.1626 ($C_{20}H_{24}O_5$ requires 344.1624).

2-(3",4"-Dimethoxyphenyl)-2'-(2'"-hydroxyethyl)-4',5'-dimethoxyacetophenone (596), $C_{26}H_{38}O_6Si$, FW = 474.74

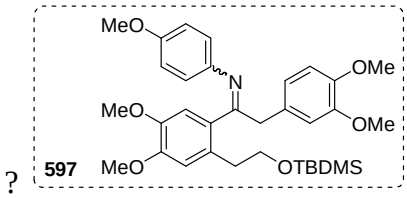


596

Oxidation of alcohol **595** with PCC according to general procedure in Chapter 6.2. The crude mixture was purified on a silica gel column (300 mL) with a gradient of petroleum ether – ethyl acetate mixture (80:20 to 70:30) to afford the ketone **596** (5.67 g, 11.9 mmol, 52 %): colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ –0.034 (s, 3H), –0.029 (s, 3H), 0.83

(s, 9H), 3.00 (t, *J* = 6.3 Hz, 2H), 3.80 (t, *J* = 6.3 Hz, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 4.12 (s, 2H), 6.75-6.78 (m, 2H), 6.80-6.82 (s, 2H), 7.264 (s, 1H); **^{13}C NMR** δ –5.39 (2 × CH_3), 18.31 (C), 25.96 (3 × CH_3), 37.59 (CH_2), 48.09 (CH_2), 55.81 (CH_3), 55.86 (2 × CH_3), 56.15 (CH_3), 64.21 (CH_2), 111.29 (CH), 112.30 (CH), 112.63 (CH), 115.44 (CH), 121.48 (CH), 127.46 (C), 129.22 (C), 135.14 (C), 146.46 (C), 147.95 (C), 149.02 (C), 151.06 (C), 199.70 (C); **IR** ν 2933, 2855, 1737, 1681, 1605, 1568, 1517, 1464, 1348, 1264 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 475 [$(M+H)^+$, 100], 417 (35), 343 (20), 323 (20); **HRMS** (CI/isobutane) 475.2514 ($C_{26}H_{39}O_6Si$ requires 475.2516).

_N_-(1-(2'-(2'"-(*tert*-Butyldimethylsilyloxy)ethyl)-4',5'-dimethoxyphenyl)-2-[3",4"-dimethoxyphenyl)ethylidene]-4-methoxyaniline (597), $C_{33}H_{45}O_6NSi$, FW = 579.88

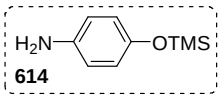


? **597** ?

597 prepared according general procedure for imination, Method C: semipurified sample, yellow foam; **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*/*Z*) isomers in ratio ca. 2:1, the minor one is marked *) δ –0.08* (s, 1.5H), –0.03 (s, 3H), 0.81* (s, 4.5 H), 0.85 (s, 9H), 2.54* (t, *J* = 6.7 Hz, 1H), 3.20 (t, *J* = 6.8 Hz, 2H), 3.705 (s, 3H), 3.713* (s, ?H), 3.74 (s, 3H), 3.75* (s, ?H), 3.86 (s, 4.5H), 3.89 (s, 3H), 3.91 (s, 3H), 3.95* (s, 1.5H), 3.97* (s, 1.5H), 6.65-6.78 (m, 6.5H), 6.82-6.96 (m, 6.5H), 7.34 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.77* (d, *J* = 1.9 Hz, 0.5H), 7.95* (dd, *J* = 8.4, 2.0 Hz, 0.5H); **IR** ν 3020, 2955, 2934, 2855, 1658, 1593, 1513, 1464, 1266 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 594 (80), 580 [$(M+H)^+$, 30], 475 (100), 446 (50), 272 (50), 183 (22), 124 (20).

8.3.2. Other Syntheses

4-(Trimethylsilyloxy)aniline (614), $C_9H_{15}NOSi$, FW = 181.34



614

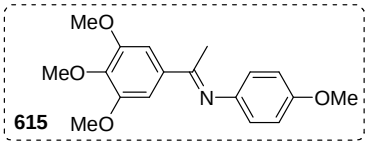
n-Butyllithium (1.6 M in hexane, 28.9 mL, 45.3 mmol, 1.01 equiv) was added drop-wise to a suspension of 4-aminophenol (5.00 g, 45.8 mmol, 1.00 equiv) in anhydrous THF (50 mL) at 0 ºC and let to stir at room temperature for 1 hour.[256] Then the solvent was evaporated *in*

vacuo, the solid residue was washed with hexane (3 × 20 mL) and re-dissolved in anhydrous THF (50 mL). Neat trimethylsilyl chloride was added drop-wise to the solution of the crude lithium phenolate and let to stir for 3.5 h at room temperature. Then the solvent was evaporated *in vacuo* and the residue was washed with hexane (3 × 20 mL). The crude silylether **614**[256] (5.99 g, 33.0 mmol, 72 %) was used without further purification: brown oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.22 (s, 9H), 3.42 (br s, 2H), 6.57-6.59 (m, 2H), 6.65-6.67 (m, 2H).

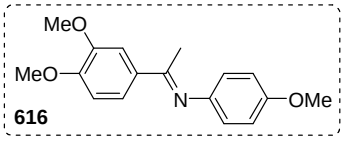
Imination of Ketones:

Table 8.3. Preparation of Imines from the Corresponding Ketones

Method	**Ketone** ***p*-substituted aniline** ***p*-TsOH (mg) or $TiCl_4$ (mL)**	**SiO_2 (mL)** **PE – EA**	**Imine**
B	500 mg, 2.38 mmol 322 mg, 2.62 mmol 45 mg, 0.238 mmol	20 mL 85:15	**615** (467 mg, 1.48 mmol, 62 %) 2:1 P:SM
C	500 mg, 2.38 mmol 876 mg, 7.11 mmol 2.4 mL, 0.238 mmol	20 mL 85:15	**615** (341 mg, 1.08 mmol, 46 %) 5:1 P:SM
B	1.00 g, 5.55 mmol 752 mg, 6.10 mmol 105 mg, 0.555 mmol	40 mL 85:15	**616** (824 mg, 2.89 mmol, 52 %) 3:1 P:SM
C	1.00 g, 5.55 mmol 2.05 g, 16.6 mmol 5.6 mL, 5.55 mmol	40 mL 85:15	**616** (596 mg, 2.09 mmol, 38 %) 9:1 P:SM
B	1.00 g, 8.32 mmol 1.27 g, 9.16 mmol 157 mg, 0.832 mmol	40 mL 95: 5	**617** (566 mg, 2.36 mmol, 28 %)
B	500 mg, 3.62 mmol 490 mg, 3.98 mmol 69 mg, 0.362 mmol	25 mL 99: 1 (PE:EA)	**231** (468 mg, 2.66 mmol, 74 %)

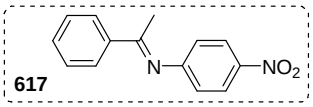


(*E*)-*N*-[1'-(3",4",5"-Trimethoxyphenyl)ethylidene]-4-methoxyaniline (615), $C_{17}H_{21}NO_3$, FW = 287.39: yellow solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.29 (br s, 3H), 3.82 (s, 3H), 3.91 (s, 3H), 3.95 (s, 6H), 6.84 (br s, 2H), 6.90-6.94 (m, 2H), 7.29 (br s, 2H). No further data provided as the imine was obtained only in a mixture with the corresponding ketone.



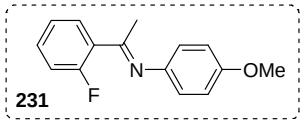
(*E*)-*N*-[1'-(3",4"-Dimethoxyphenyl)ethylidene]-4-methoxyaniline (616),[120] **$C_{17}H_{21}NO_3$, FW = 287.39**: yellow solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 3.81 (s,

3H), 3.93 (s, 3H), 3.97 (s, 3H), 6.75-6.78 (m, 2H), 6.87-6.92 (m, 3H), 7.44 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H). No further data provided as the imine was obtained only in a mixture with the corresponding ketone.



(*E*)-*N*-(1'-Phenylethylidene)-4-nitroaniline (617),[257] **$C_{14}H_{12}N_2O_2$, FW = 240.28**: yellow solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.85 (s, 3H), 7.05-7.08 (m, 2H), 7.47-7.51 (m, 3H), 7.97-7.98 (m, 2H), 8.18-8.22 (m, 2H). No further data provided as the imine was obtained only in a mixture with the corresponding ketone.

(*E*)-*N*-[1'-(2"-Fluorophenyl)ethylidene]-4-methoxyaniline (231), $C_{15}H_{14}NOF$, FW = 243.30



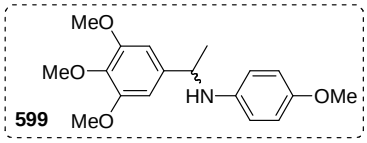
231[119,120] (Method B, Table 8.3): yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of (*E*,Z)- isomers in ratio ca. 5:1, the minor one is marked*) δ 2.27 (d, *J* = 3.5 Hz, 3H), 2.51* (d, *J* = 0.6 Hz, 0.6H), 3.68* (s, 0.6H), 3.81 (s, 3H), 6.62-6.65* (m, 0.4H), 6.65-6.67* (m, 0.4H), 6.78-6.82 (m, 2H), 6.90-6.94 (m, 2H), 6.94-6.97* (m, 0.6H), 7.10 (ddd, *J* = 11.4, 8.3, 1.0 Hz, 1H), 7.17-7.21* (m, 0.2H), 7.20 (ddd, *J* = 7.6, 7.4, 1.1 Hz, 1H), 7.39 (dddd, *J* = 8.2, 7.1, 5.1, 1.9 Hz, 1H), 7.83 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H); **^{13}C NMR** δ 20.69 (d, *J* = 6.6 Hz, CH_3), 28.54* (d, *J* = 1.2 Hz, CH_3), 55.10* (CH_3), 55.32 (CH_3), 113.59* (2 × CH), 114.15 (2 × CH), 115.60* (d, *J* = 21.8 Hz, CH), 116.07 (d, *J* = 22.9, CH), 120.66 (2 × CH), 121.57* (2 × CH), 123.90* (d, *J* = 3.4 Hz, CH), 124.14 (d, *J* = 3.4 Hz, CH), 126.63* (d, *J* = 18.0 Hz, C), 128.72* (d, *J* = 4.6 Hz, CH), 128.90* (d, *J* = 12.3 Hz, C), 129.90 (d, *J* = 3.6 Hz, CH), 130.06* (d, *J* = 8.0 Hz, CH), 131.29 (d, *J* = 8.6 Hz, CH), 143.39* (C), 143.65 (C), 155.96* (C), 156.07 (C), 158.41* (d, *J* = 247.0 Hz, CF), 160.91 (d, *J* = 250.3 Hz, CF), 161.95* (C), 162.15 (C), 164.86* (unresolved, C), 165.14 (d, *J* = 2.4 Hz, C); **^{19}F NMR** δ –113.44; **IR** (ATR) ν 2951, 2833, 1624, 1611, 1501, 1449, 1288, 1238, 1207 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 244 [$(M+H)^+$, 100], 102 (28); **HRMS** (CI/isobutane) 244.1141 ($C_{15}H_{15}NOF$ requires 244.1138).

Reduction of Imines:

Table 8.4. Reductions of Imines

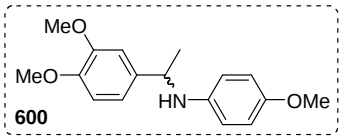
Imine	PE – EA	Amine
615 (630 mg)	85:15	**599rac** (424 mg, 1.34 mmol, 67 %)
616 (570 mg)	85:15	**600rac** (560 mg, 1.95 mmol, 97 %)
617 (361 mg)	90:10	**608rac** (49 mg, 0.202 mmol, 13 %)
615 (126 mg)	85:15	**599** (119 mg, 0.375 mmol, 94 %)
616 (114 mg)	85:15	**600** (100 mg, 0.348 mmol, 87 %)
617 (96.1 mg)	95:5 → 90:10	**608** (21 mg, 0.867 mmol, 22 %)
231 (243 mg)	98:2	**232rac** (225 mg, 0.917 mmol, 92 %)
231 (195 mg)	98:2	**232** (166 mg, 0.677 mmol, 85 %)

(+)-*N*-[1'-(3",4",5"-Trimethoxyphenyl)ethyl]-*N*-(4-methoxyphenyl)amine (599), $C_{18}H_{23}NO_4$, FW = 317.42



599: white crystals; **mp** 66-67 °C; **$[\alpha]_D$** +7.1 (*c* 1.0, $CHCl_3$), **$[\alpha]_{436}$** +17 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.51 (d, *J* = 6.7 Hz, 3H), 3.71 (s, 3H), 3.82 (s, 3H), 3.83 (s, 6H), 4.31 (q, *J* = 6.7 Hz, 1H), 6.51-6.54 (m, 2H), 6.60 (s, 2H), 6.70-6.72 (m, 2H); **^{13}C NMR** δ 24.80 (CH_3), 55.43 (CH_3), 55.66 (CH_3), 56.04 (2 × CH_3), 60.78 (CH), 102.70 (2 × CH), 114.63 (2 × CH), 114.75 (C), 115.22 (2 × CH), 136.62 (C), 140.81 (2 × C), 152.41 (C), 153.34 (2 × C); **IR** ν 3387, 2937, 2833, 1592, 1513, 1462, 1325, 1234 cm^{-1}; **MS** (EI) *m/z* (%) 317 ($M^{\bullet+}$, 42), 195 (100); **HRMS** (EI) 317.1628 ($C_{18}H_{23}NO_4$ requires 317.1627); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (87:13), 0.75 mL/min, t_{major} = 20.14 min, t_{minor} = 21.70 min) showed 86 % ee (not baseline separation).

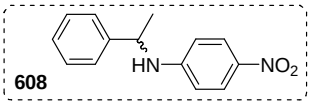
(–)-*N*-[1'-(3",4""-Dimethoxyphenyl)ethyl]-*N*-(4-methoxyphenyl)amine (600), $C_{17}H_{21}NO_3$, FW = 287.39



600:[120] white crystals; **mp** 116-118 °C; **$[\alpha]_D$** –5.7 (*c* 1.0, $CHCl_3$), **$[\alpha]_{436}$** –8.6 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.51 (d, *J* = 6.7 Hz, 3H), 3.70 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.35 (q, *J* = 6.7 Hz, 1H), 6.51-6.55 (m, 2H), 6.68-6.72 (m, 2H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.89 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.92 (d, *J* = 1.9 Hz, 1H); **^{13}C NMR** δ 24.80 (CH_3), 54.77 (CH_3), 55.74 (CH), 55.90 (2 × CH_3), 109.25 (CH), 111.19 (CH), 114.72 (2 × CH),

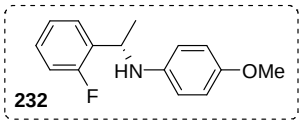
115.31 (2 × CH), 117.99 (CH), 137.55 (C), 140.82 (C), 147.91 (C), 149.16 (C), 152.42 (C); **IR** ν 3395, 2960, 2833, 1593, 1513, 1464, 1234 cm^{-1}; **MS** (EI) *m/z* (%) 287 ($M^{\bullet+}$, 48), 165 (100), 150 (30), 123 (42), 91 (40); **HRMS** (EI) 287.1523 ($C_{17}H_{21}NO_3$ requires 287.1521); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (87:13), 0.75 mL/min, t_{minor} = 16.492 min, t_{major} = 17.613 min) showed 94 % ee, [lit.[120] gives Chiralpak AS-H, heptane – propan-2-ol (90:10), 0.5 ml/min, t_{major} = 24.22 min, t_{minor} = 30.96 min showing 89 % ee].

(–)-*N*-(4-Nitrophenyl)-*N*-(1'-phenylethyl)amine (608), $C_{14}H_{14}N_2O_2$, FW = 242.30



608:[119] yellow oil; **[α]$_D$** –77 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.60 (d, *J* = 6.7 Hz, 3H), 4.59 (q, *J* = 6.7 Hz, 1H), 6.47-6.55 (m, 2H), 7.29-7.38 (m, 5H), 7.99-8.03 (m, 2H); **^{13}C NMR** δ 24.47 (CH_3), 53.65 (CH), 112.22 (2 × CH), 125.72 (2 × CH), 126.22 (2 × CH), 127.61 (CH), 129.01 (2 × CH), 138.40 (C), 143.04 (C), 152.06 (C); **IR** ν 3373, 3026, 2972, 2927, 1601, 1524, 1503, 1473, 1315, 1278, 1185 cm^{-1}; **MS** (EI) *m/z* (%) 242 ($M^{\bullet+}$, 20), 227 (20), 120 (20), 118 (22), 105 (60), 87 (85), 85 (100), 83 (100); **HRMS** (EI) 242.1056 ($C_{14}H_{14}N_2O_2$ requires 242.1055); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (94:6), 0.75 mL/min, t_{major} = 32.17 min, t_{minor} = 39.01 min) showed 88 % ee (negative peaks).

(–)-*N*-[1'-(2"-Fluorophenyl)ethyl]-*N*-(4-methoxyphenyl)amine (232), $C_{15}H_{16}NOF$, FW = 245.32



232[119,120] (Table 8.4): colourless oil; **[α]$_D$** –17.0 (*c* 1.0, $CHCl_3$), [lit.[119] gives **[α]$_D^{25}$** +8.4 (*c* 1.0, $CHCl_3$) for 84 % ee]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.56 (d, *J* = 6.7 Hz, 3H), 3.72 (s, 3H), 3.85 (br s, 1H), 4.80 (q, *J* = 6.7 Hz, 1H), 6.51-6.55 (m, 2H), 6.72-6.76 (m, 2H), 7.07 (ddd, *J* = 17.5, 8.1, 1.2 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 7.19-7.25 (m, 1H), 7.41 (ddd, *J* = 8.1, 7.5, 1.7 Hz, 1H); **^{13}C NMR** δ 23.27 (CH_3), 48.20 (d, *J* = 2.6 Hz, CH), 55.57 (CH_3), 114.47 (2 × CH), 114.69 (2 × CH), 115.34 (d, *J* = 21.9 Hz, CH), 124.27 (d, *J* = 3.4 Hz, CH), 127.19 (d, *J* = 4.8, CH), 128.14 (d, *J* = 8.2 Hz, CH), 131.79 (d, *J* = 13.2 Hz, C), 140.96 (C), 152.01 (C), 160.43 (d, *J* = 244.6 Hz, CF); **^{19}F NMR** δ –120.37; **IR** ν 3400, 2968, 2931, 2832, 1512, 1451, 1236 cm^{-1}; **MS** (EI) *m/z* (%) 245 ($M^{\bullet+}$, 65), 230 (78), 123

(65), 108 (30), 103 (25), 85 (55), 83 (100); **HRMS** (EI) 245.1218 ($C_{15}H_{16}NOF$ requires 245.1216); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (99:1), 0.75 mL/min, t_{minor} = 12.85 min, t_{major} = 14.63 min) showed 95 % ee or (Chiralcel OD-H, hexane – propan-2-ol (98:2), 0.60 mL/min, t_{minor} = 15.74 min, t_{major} = 18.79 min) showed 95 % ee, [lit.[119] gives Chiralcel OD-H, hexane – propan-2-ol (98:2), 0.60 mL/min, $t_{(+)\text{-major}}$ = 14.55 min, $t_{(–)\text{-minor}}$ = 17.24 min showing 84 % ee, lit.[120] gives Chiralcel OD-H, heptane – propan-2-ol (98:2), 0.50 mL/min, $t_{(R)\text{-minor}}$ = 15.58 min, $t_{(S)\text{-major}}$ = 18.11 min showing 85 % ee].

Deprotection of PMP-group:

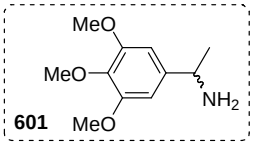
Method A: Periodic acid (1.0 equiv) was added portion-wise to a solution of amine (1.0 equiv) in a mixture of MeCN, water (both 10 mL per 1 mmol of amine) and diluted H_2SO_4 (1.0 M, 1 mL per 1 mmol of amine) at room temperature. The mixture was let to stir at this temperature for the time indicated. Then water was added (3 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The aqueous layer was basified to pH 10 (to pH 8 in the case of amino alcohols) and the precipitate was extracted into AcOEt (3 × 10 mL). The combined AcOEt layers were dried over $MgSO_4$ and evaporated affording crude free amine as off-white solid which was used without further purification.

Method B: Periodic acid (1.0 equiv) was added portion-wise to a solution of amine (1.0 equiv) in a mixture of MeCN (20 mL per 1 mmol of amine) and diluted H_2SO_4 (1.0 M, 10 mL per 1 mmol of amine) in 10:1 ratio at room temperature. The mixture was let to stir at room temperature for the time indicated. Work-up as in Method A.

Method C: Trichloroisocyanuric acid (TCCA, 0.5 equiv) was added portion-wise to a solution of amine (1.0 equiv) in a mixture of MeCN and water (both 10 mL per 1 mmol of amine) at room temperature. The mixture was let to stir at room temperature for the time indicated. Work-up as in Method A.

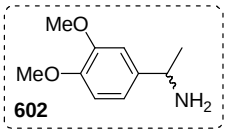
Table 8.5. PMP-deprotection of Amines

PMP-Amine	(Method) React. Time Oxidant	Free Amine
599rac (0.2 mmol, 63.5 mg) **600rac** (0.2 mmol, 57.5 mg)	(C) 1.5 h 23.2 mg, 0.1 mmol	**601rac** (~ 20 mg, 0.0947 mmol, 47 %) mix with unknown, P:U (2:1) **602rac** (21 mg, 0.116 mmol, 58 %)
599rac (0.2 mmol, 63.5 mg) **600rac** (0.2 mmol, 57.5 mg)	(A) 1.5 h 45.6 mg, 0.2 mmol	**601rac** (34 mg, 0.161 mmol, 80 %) **602rac** (24 mg, 0.132 mmol, 66 %)
599rac (0.2 mmol, 63.5 mg) **600rac** (0.2 mmol, 57.5 mg)	(B) 2 h 45.6 mg, 0.2 mmol)	**601rac** (22 mg, 0.104 mmol, 52 %) **602rac** (9 mg, 0.0492 mmol, 25 %) mix with SM, P:SM (5:1)
599 (0.1 mmol, 31.7 mg) **600** (0.1 mmol, 28.7 mg)	(A) 4 h 22.8 mg, 0.1 mmol	**601** (18 mg, 0.0852 mmol, 85 %) **602** (12 mg, 0.0662 mmol, 66 %)
476w rac (0.4 mmol, 143 mg)	(C) 0.5 h 0.1 mmol, 23.2 mg	**604rac** (15 mg, 0.0596 mmol, 15 %)
476w rac (0.4 mmol, 143 mg)	(A) 5.5 h 91.2 mg, 0.4 mmol	**603rac** (13 mg, 0.0948 mmol, 24 %)
476w rac (0.4 mmol, 143 mg)	(B) 6 h 91.2 mg, 0.4 mmol	**603rac** (41 mg, 0.299 mmol, 75 %)
476w (0.3 mmol, 107 mg)	(B) 12 h 68.4 mg, 0.3 mmol	**603** (14 mg, 0.102 mmol, 34 %)
232 (570 mg, 2.32 mmol)	(C) 3 h 270 mg, 1.16 mmol	**611** (228 mg, 1.64 mmol, 71 %)



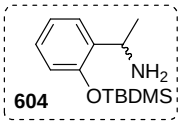
601

(–)-*N*-[1-(3',4',5'-Trimethoxyphenyl)ethyl]amine (601),[258] **$C_{11}H_{17}NO_3$, FW = 211.29**: white solid; **$[\alpha]_D$** –9.8 (*c* 0.5, $CHCl_3$); [lit.[258] gives **$[\alpha]_D^{25}$** +24.4 (*c* 1.06, $CHCl_3$) for (*S*)-enantiomer 96 % ee]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.39 (d, *J* = 6.6 Hz, 3H), 2.16 (br s, 2H), 3.83 (s, 3H), 3.86 (s, 6H), 4.09 (q, *J* = 6.6 Hz, 1H), 6.59 (s, 2H).



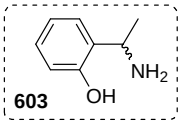
602

(–)-*N*-[1-(3',4',5'-Trimethoxyphenyl)ethyl]amine (602),[258] **$C_{10}H_{15}NO_2$, FW = 181.26**: white solid; **$[\alpha]_D$** –33 (*c* 0.5, $CHCl_3$); [lit.[258] gives **$[\alpha]_D^{25}$** –24.2 (*c* 1.01, $CHCl_3$) for (*S*)-enantiomer 82 % ee]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.38 (d, *J* = 6.6 Hz, 3H), 2.05 (br s, 1H), 3.85 (s, 3H), 3.89 (s, 3H), 4.09 (q, *J* = 6.6 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.87 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.92 (d, *J* = 1.9 Hz, 1H).

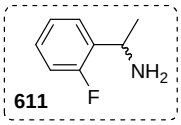


604

(±)-*N*-{1-[2'-(*tert*-Butyldimethylsilyloxy)phenyl]ethyl}amine (604), $C_{14}H_{25}NOSi$, FW = 251.49: white solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.19 (s, 6H), 0.98 (s, 9H), 1.47 (d, *J* = 6.6 Hz, 3H), 3.55 (br s, 2H), 4.15 (q, *J* = 6.6 Hz, 1H), 6.73 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.75 (dd, *J* = 2.5, 1.8 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 7.19 (dd, *J* = 7.9, 7.8 Hz, 1H).

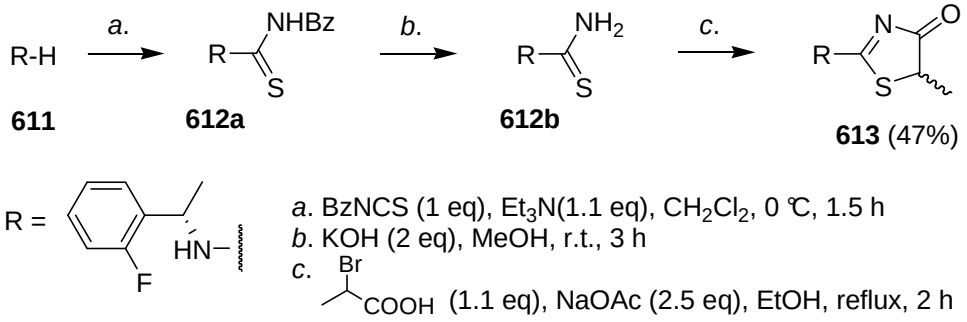


(–)-*N*-[1-(2'-Hydroxyphenyl)ethyl]amine, (–)-2-(1'-Aminoethyl)phenol (603),[259] **$C_8H_{11}NO$, FW = 137.20**: white solid; **$[\alpha]_{436}$** –80 (*c* 0.5, *l* 10 mm, MeOH); [lit.[259] gives **$[\alpha]_D$** –77.6 (*c* 1, MeOH) for (*S*)-enantiomer 95 % ee]; **^{1}H NMR** (400 MHz, MeOH-d_4) δ 1.38 (d, *J* = 6.7 Hz, 3H), 3.99 (q, *J* = 6.7 Hz, 1H), 6.67 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H), 6.77 (dd, *J* = 2.3, 1.8 Hz, 1H), 6.80-6.83 (m, 1H), 7.13 (dd, *J* = 7.8, 7.8 Hz, 1H).



(±)-*N*-[1'-(2"-Fluorophenyl)ethyl]amine (611),[260] **C_8H_9NF, FW = 138.18**: brown liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.44 (d, *J* = 6.7 Hz, 3H), 2.24 (br s, 2H), 4.42 (br q, *J* = 6.5 Hz, 1H), 7.01 (ddd, *J* = 10.8, 8.1, 1.2 Hz, 1H), 7.12 (d, *J* = 7.5, 7.5, 1.2 Hz, 1H), 7.18-7.24 (m, 1H), 7.42 (ddd, *J* = 7.6, 7.6, 1.8 Hz, 1H); **^{19}F NMR** δ –119.73.

Three-step Procedure for Synthesis of Thiazolone 399[255] **(Scheme 8.18):**



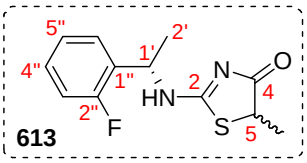
Scheme 8.18. Synthesis of Thiazolone 11β-HSD Inhibitor from Amine **611**

Benzoyl isothiocyanate (284 μL, 345 mg, 2.11 mmol, 1.0 equiv) was added drop-wise to a solution of amine **611** (294 mg, 2.11 mmol, 1.0 equiv) and triethylamine (324 μL, 235 mg, 2.32 mmol, 1.1 equiv) in anhydrous CH_2Cl_2 (3 mL) at 0 °C under an argon atmosphere. The reaction mixture was let to stir at 0 °C for 1.5 h and then quenched with water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with diluted HCl (7 %, 20 mL), saturated $NaHCO_3$ solution (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to provide crude *N*-benzoylthiourea **612a** which was used without further purification.

Crushed solid KOH (237 mg, 4.22 mmol, 2.0 equiv) was added in one portion to a solution of the crude *N*-benzoylthiourea **612a** (657 mg) in MeOH (3 mL). The reaction mixture was let to stir at room temperature for 3 h, then water (15 mL) was added and the mixture was let to stir for further 16 h at room temperature. The solution was diluted with CH_2Cl_2 (20 mL) and water (50 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with diluted KOH solution (1 M, 20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to furnish the crude thiourea derivative **612b** which was used without further purification.

2-Bromopropionic acid (211 µL, 359 mg, 2.32 mmol, 1.1 equiv) was added drop-wise to a solution of the crude thiourea derivative **612b** (372 mg) and sodium acetate (433 mg, 5.28 mmol, 2.5 equiv) in anhydrous EtOH (2.5 mL). The suspension was refluxed for 2 h, then cooled to room temperature and quenched with water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude thiazolone **399** was purified on a silica gel column (40 mL) with a gradient of dichloromethane – methanol mixture (100:0 to 98:2) to afford **613** as white foam (249 mg, 0.987 mmol, 47 %).

(+)-*N*-[1'-(2"-Fluorophenyl)ethyl]-*N*-(5-methylthiazol-4(*4H*)-on-2-yl)amine (613), $C_{12}H_{12}N_2OSF$, FW = 245.32



613: an inseparable mixture of (1'*S*,4*S*) and (1'*S*,4*R*) diastereoisomers in 1:1 ratio; white foam; **[α]$_D$** +14.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$, a mixture of 5-epimers in ca. 1:1 ratio, one is marked * and ^, unassigned signals are not marked) δ 1.58^ (d, *J* = 7.3 Hz, 3H, 5-CH- C*H*$_3$), 1.65* (d, *J* = 7.3 Hz, 3H, 5-CH-C*H*$_3$), 1.78^ (d, *J* = 6.8 Hz, 3H, 2'-C*H*$_3$), 1.79* (d, *J* = 6.8 Hz, 3H, 2'-C*H*$_3$), 4.04* (q, *J* = 7.3 Hz, 1H, 5-C*H*), 4.14^ (q, *J* = 7.3 Hz, 1H, 5-C*H*), 4.98* (q, *J* = 6.8 Hz, 1H, 1'-C*H*), 4.99^ (q, *J* = 6.8 Hz, 1H, 1'-C*H*), 7.02-7.05* (m, 1H, 3"-C*H*), 7.03-7.07^ (m, 1H, 3"-C*H*), 7.15* (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H, 4"-C*H*), 7.16^ (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H, 4"-C*H*), 7.23-7.27* (m, 1H, 5"-C*H*), 7.25-7.29^ (m, 1H, 5"-C*H*), 7.58* (ddd, *J* = 7.7, 7.6, 1.7 Hz, 1H, 6"-C*H*), 7.61^ (ddd, *J* = 7.7, 7.6, 1.7 Hz, 1H, 6"-C*H*); **^{13}C NMR** δ 18.51^ (5-CH_3), 18.88^ (2'-CH_3), 21.52* (5-CH_3), 21.60* (2'-CH_3), 49.20^ (5-CH), 49.26* (5-CH), 49.28 (2 × 1'-CH), 115.15 (d, *J* = 21.9, 2

× 3”-CH), 124.78* (d, *J* = 3.4 Hz, 5”-CH), 124.79^ (d, *J* = 3.4 Hz, 5”-CH), 127.98* (d, *J* = 3.5 Hz, 6”-CH), 128.05^ (d, *J* = 3.5 Hz, 6”-CH), 128.88 (d, *J* = 10.9 Hz, 1”-C), 129.02 (d, *J* = 10.9 Hz, 1”-C), 129.16* (d, *J* = 2.4 Hz, 4”-CH), 129.24^ (d, *J* = 2.4 Hz, 4”-CH), 159.13 (d, *J* = 246.0 Hz, 2 × 2”-CF), 181.62^ (2-C), 181.72* (2-C), 188.84 (4-C), 188.86 (4-C); **^{19}F NMR** δ –119.90, –119.97; **IR** ν 3192, 2979, 2933, 1686, 1599, 1583, 1492, 1450, 1251 cm^{-1}; **MS** (EI) *m/z* (%) 252 ($M^{\bullet+}$, 40), 237 (90), 149 (20), 123 (100), 103 (38), 91 (44), 83 (40), 77 (39); **HRMS** (EI) 252.0730 ($C_{12}H_{13}N_2OSF$ requires 252.0733); **HPLC** analysis (Chiralpak IB, hexane – propan-2-ol (85:15), 0.75 mL/min, $t_{1,\ major}$ = 16.96 min, $t_{1,\ minor}$ = 19.79 min, $t_{2,\ major}$ = 21.61 min, $t_{2,\ minor}$ = not resolved) showed 93 % ee for diastereomer 1 and >95 % ee for diastereomer 2 (not baseline separation).

9. References

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Appendix:

Publications