RHODIUM CATALYSED TRANSFER HYDROGENATION AND TRANSAMINATION

Thesis submitted in accordance with the requirements of the

University of Liverpool for the degree of Doctor in Philosophy

by

Zhenyu Chen

November 2021

To my dear family

致我亲爱的家人

ACKNOWLEDGMENTS

To start with, I would like to express my gratitude to my supervisor, Professor Jianliang Xiao, for his support, guidance and advice throughout my PhD study. His persistence and optimism in scientific research have deeply influenced me. It is never too late to act on an idea, even a naïve one. The smallest attempts you make today may lead to unexpected results.

I also thank the Department of Chemistry of Liverpool University for financial support, especially for their help and support during the COVID-19 pandemic. I would like to acknowledge Dr Konstantin Luzyanin for his important training in analytic instruments at the beginning of my research study and his help in NMR analysis with Dr Jonathan Iggo. Thanks go to Dr Christophe Aissa and Dr Andrew Carnell for their kind support during my first and second year viva. Dr Aissa greatly helped me during and after my final PhD viva on understanding the detailed mechanisms for the transamination reactions. I would also like to thank Dr Craig Robertson, Mrs Jean Ellis, Mrs Moya McCarron and all staff and technicians at the Department of Chemistry for their support and technical assistance for my work.

I would like to give special thanks to Dr Elliot Bennett, Dr Zhiliang Huang, Dr Prashant Kumar and Dr Ramachandran Gunasekar for their valuable advice and useful research techniques. Thanks also go to former PhD students in the Xiao group. When I joined lab G58, Ahmed Aboo was about to start writing his thesis

and he still spent his valuable time helping me in the lab. Naomi Ritchie helped me a lot with the synthesis of phosphine ligands, which can be tricky for beginners. The chocolates she shared with everyone at the group meeting before Christmas each year made me feel the joy of the festive even when I am abroad far from home.

Thanks all the buddies in the Xiao group, Liangliang Zhao, Guanhong Chen, Renpeng Guan, Sydney Williams and Leiming Qi, with whom I spent most of my time staying each day. They helped me with the problems I encountered in experiments. I enjoyed our discussion about food, culture, news, video games, music and films. Without them, my PhD would be difficult and boring.

Finally, I would like to say a big Thank You to my family for their unconditional love and support over the years. Even though they are thousands of miles away, I can still feel their love and care all the time. I am also grateful to all my friends who have always been there to listen, argue and laugh with me. Thanks for being part of my life.

ABSTRACT

Reduction of carbonyl and *N*-heteroaromatic compounds is a fundamental transformation in organic synthesis to produce valuable products in both academia and industry. Transfer hydrogenation using non-H_2 hydrogen source is a convenient and safe alternative to direct hydrogenation with hazardous hydrogen gas. Compared with other *N*-heterocyclic compounds, transfer hydrogenation of pyridine derivatives is less developed, especially in obtaining high enantioselectivity.

Chapter 1 provides a brief introduction of catalytic transfer hydrogenation and the use of formic acid and methanol as hydrogen sources. It also describes previous achievements on the TH of carbonyl and *N*-heteroaromatic compounds.

Chapter 2 extends our previously reported method for the preparation of chiral piperidines to more valuable chiral fluorinated piperidines with excellent enantioselectivities. A chiral amine is incorporated into the pyridine ring *via* transamination during the reduction process and induces the chirality on the ring.

Chapter 3 describes a simple and efficient method for the switchable synthesis of *N*-aryl piperidines and pyrrolidines from pyridinium salts, providing an alternative to the traditional C-N cross coupling methods. The key to the preparation of pyrrolidines is the introduction of a leaving group on the pyridine substrates, which leads to the ring contraction during the ring-closing step after transamination.

Chapter 4 demonstrates the preliminary attempts on the asymmetric transamination of pyridinium salts with achiral amines. Imidazoline iridacycle and rhodacycle have been found to be active for the reaction, although the enantioselectivity currently achieved still needs to be improved.

Chapter 5 presents a highly efficient cyclometaled rhodium complex for the transfer hydrogenation of various aldehydes at near room temperature using methanol as hydrogen source. The hydroxy functionality on the imino ligand is shown to be crucial for this remarkable activity.

Chapter 6 summarise all works covered in this thesis and provides an outlook for the future work.

LIST OF PUBLICATIONS

- **Methanol as Hydrogen Source: Transfer Hydrogenation of Aldehydes near Room Temperature**

  Z. Chen, G. Chen, A. H. Aboo, J. Iggo, J. Xiao, *Asian J. Org. Chem*. **2020**, *9*, 1174 – 1178.

- **Recent Development in the Synthesis and Catalytic Application of Iridacycles**

  Z. Chen, A. Kacmaz, J. Xiao, *Chem. Rec.* **2021**, *21*, 1506–1534.

- **Asymmetric Reductive Transamination: a New Reaction to Access Chiral Piperidines**

  J. Wu, **Z. Chen**, J. Barnard, C. Pu, X. Wu, S. Zhang, R. Gunasekar, J. Ruan, J. Xiao, *Nat Catal.* 2021, under revision

- **Switchable Synthesis of *N*-Aryl Piperidines and Pyrrolidines *via* Reductive Transamination**

  Z. Chen, R. Gunasekar, J. Xiao, manuscript in preparation

ABBREVIATIONS

α	Alpha
β	Beta
δ	NMR chemical shift
Å	Armstrong
Ac	Acyl
AH	Asymmetric hydrogenation
Aq	Aqueous
Ar	Aryl
ATH	Asymmetric transfer hydrogenation
atm	Atmosphere
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
brs	Broad singlet
°C	Celsius degree
^{13}C	Carbon 13
Cat.	Catalyst
CD_3OD	Deuterated methanol
CI	Chemical ionisation
COD	1,5-Cyclooctadiene
conv.	Conversion
Cp*	Pentamethylcyclopentadienyl

Cy	Cyclohexyl
d	Doublet
DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
ddq	Doublet of doublet of quartets
ddt	Doublet of doublet of triplets
dm	Doublet of multiplet
DME	Dimethoxyethane
DPEN	1,2-Diphenylethylenediamine
dq	Doublet of quartets
dt	Doublet of triplets
ee	Enantiomeric excess
equiv.	Equivalent(s)
Eq.	Equation
ESI	Electrospray ionisation
Et	Ethyl
et al.	And others
FT	Formic acid/triethylamine azeotrope
g	Gram(s)
h	Hour(s)
^{1}H	Proton
H_2	Molecular hydrogen

HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectroscopy
Hz	Hertz
i.e.	*id est* (that is to say)
IPA	Isopropanol
IR	Infrared
J	Coupling constant value
K	Kelvin degree
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
Me	Methyl
MeOH	Methanol
mg	Milligram(s)
min	Minute(s)
mL	Mililitre
mmol	Milimole(s)
MS	Mass spectrometry
MTBE	Methyl tert-butyl ether
m/z	Mass to charge ratio
NEt_3	Triethylamine
NHC	Nitrogen heterocyclic carbenes
NMR	Nuclear magnetic resonance
o	Ortho

p	Para
OAc	Acetate
Ph	Phenyl
PhMe	Toluene
PPh_3	Triphenylphosphine
ppm	Parts per million
q	Quartet
Rh	Rhodium
r. t.	Room temperature
s	Singlet
sept	Septet
t	Triplet
td	Triplet of doublets
TFE	2,2,2-Trifluoroethanol
TH	Transfer hydrogenation
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TOF	Turnover frequency
TON	Turnover number
t_R	Retention time
Ts	p-Toluenesulfonyl
TsDPEN	N-(p-toluenesulfonyl)-1,2-diphenylethylenediamine
tt	Triplet of triplets

CONTENTS

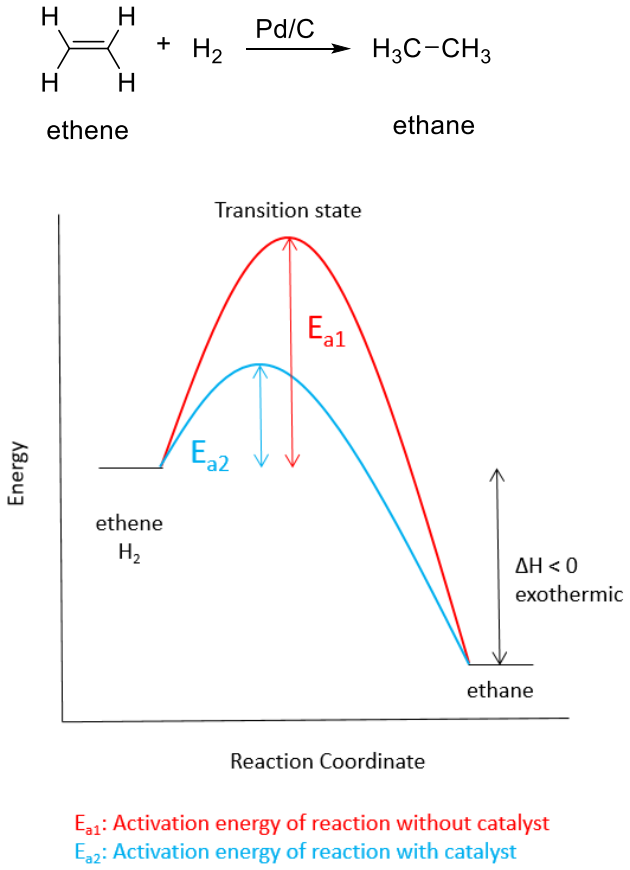
Chapter 1: Introduction - Transfer Hydrogenation of *N*-Heteroaromatics and Carbonyl Compounds

1.1 Introduction

In organic chemistry, hydrogenation reaction refers to the addition of pairs of hydrogen atoms towards double or triple bonds of unsaturated compounds, resulting in reduced or saturated organic compounds. It is one of the most important transformations in organic synthesis, and is widely carried out in both laboratory and industry.[1–3] Hydrogenation processes have profoundly affected the daily life of human society. For example, in the fats and oils industry, hydrogenation is used to convert liquid vegetable oils into solid or semi-solid fats products like shortenings, spreads and margarine, improving the oxidative stability of the oil.[4] In the petrochemical industry, hydrogenation is used as an essential process during hydrocracking to obtain lighter, valuable petroleum products, such as gasoline and diesel, from heavy crude with longer hydrocarbon chains.

Generally, hydrogenation reactions proceed in the presence of a metal catalyst, which is known as catalytic hydrogenation or catalytic reduction. Although a typical hydrogenation reaction of an alkene is thermodynamically favourable, it would not proceed without the addition of a catalyst, like Pd/C (Scheme 1.1). The catalyst lowers the activation energy required for the reactants to reach the transition state and thus enables the catalysis to occur. There are two main types of catalysts, namely homogeneous catalysts and heterogeneous catalysts. Homogeneous catalysts can dissolve in the solvent which also contains the unsaturated substrates. Noble metals are commonly used to generate highly

active catalysts which operate at lower pressures and temperatures, such as Wilkinson's catalyst[5] and Crabtree's catalyst.[6] However, heterogeneous catalysts are more common in industry. Precious metal catalysts are generally deposited on the support as fine powders and suspended in the solvent, such as Pd/C.



Scheme 1.1: Energy diagram for hydrogenation of ethene

1.2 Transfer hydrogenation

Apart from the choice of catalysts used in catalytic hydrogenation, there are two main strategies to perform hydrogenation reactions: direct hydrogenation with

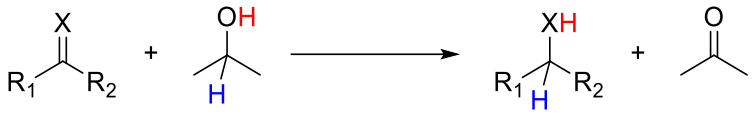
a pressure of gaseous H_2, and transfer hydrogenation (TH) using other hydrogen donors. Molecular hydrogen is commercially available from hydrocarbons by an industrial process called steam reforming and stored in pressurised cylinders. Hydrogenation reactions are normally performed under more than 1 atm of hydrogen gas, which requires special equipment and safe handling, as hydrogen gas is highly flammable when dispersed in air.[7] Compared with direct hydrogenation, TH is a robust and convenient method to produce saturated compounds using hydrogen sources other than hazardous and pressurised H_2, and thus no special operations are needed. The hydrogen sources for TH are usually inexpensive and readily available, like isopropanol and formic acid.[8,9] Therefore, TH has been widely investigated over the last few decades and has been extensively reported in organic synthesis.[9]

1.2.1 Hydrogen donors in TH

For transfer hydrogenation, hydrogen sources other than H_2 gas are employed. Various compounds such as hydrocarbons, alcohols, formic acid and its derivatives have been used as hydrogen donors in catalytic TH reactions. In practice, formic acid, and isopropanol (IPA) are the most commonly used hydrogen donors due to their easy availability and high activity.[7,10] In the presence of a suitable catalyst, two hydrogen atoms are transferred from hydrogen donor to unsaturated compounds, in which one hydrogen is transferred to the X atom on the C=X multiple bond as a proton, and the second hydrogen to the carbon as a hydride.

A general example of catalytic TH using IPA as hydrogen donor is shown in Scheme 1.2.

When isopropanol is used as hydrogen donor, a base, hydroxides or metal alkoxides, is usually required to extract protons from the donor. After losing two hydrogen atoms from isopropanol, acetone forms and accumulates in the reaction system. As a hydrogen acceptor, acetone competes with the unsaturated substrates in the TH reaction until an equilibrium is reached.[11] In order to promote the shift of the equilibrium in the direction of the desired product, an excessive amount of isopropanol is required according to Le Chatelier's principle, and thus isopropanol often takes the role of solvent in catalytic TH reactions.



Scheme 1.2: Catalytic transfer hydrogenation using isopropanol as hydrogen donor

1.2.2 Formic acid as hydrogen donor

Formic acid is considered as one of the most popular materials for hydrogen storage in a safe and dense form with a higher hydrogen content (53.4 g/L, 4.4 wt%) than molecular hydrogen gas (0.089 g/L at 0 °C, 1 atm).[12] The industrial production of formic acid is mainly based on fossil feedstock. Recent research revealed a great potential of sustainable synthesis of formic acid from renewable sources, namely biomass[13] and CO_2 hydrogenation.[14] In the presence of a suitable catalyst, formic acid could be readily decomposed into CO_2 and H_2 ($\Delta G°$

= -32.8 kJ/mol), which makes it preferred as an *in situ* H_2 source in catalytic reactions.[15]

The dehydrogenation product, carbon dioxide, could easily escape from the reaction system, making the catalytic TH reaction irreversible. In addition, only a weak base like trimethylamine is sufficient to activate formic acid, and sometimes it could be used in an aqueous solution.[16–18] The commercially available formic acid/trimethylamine azeotrope (F/T) also shows a high solubility in various solvents at a wide range of temperatures (20 to 60 °C). However, the major drawback of using F/T azeotrope is that the acidity of formic acid can easily decompose or deactivate metal complexes, leading to the loss of their catalytic activities.[10]

1.2.3 Methanol as hydrogen donor

Methanol, also known as methyl alcohol, is the simplest aliphatic alcohol. In 1661, methanol was first produced by Sir Robert Boyle through the destructive distillation of wood materials. Later, the composition of this new compound was independently determined by Justus von Liebig and J. B. A. Dumas, and the term "methyl" was introduced to the Chemistry Society in 1835. Since then, the so-called "wood alcohol" or methyl alcohol was mainly obtained from the method of distillation until the 1920s. Nowadays, methanol is mainly produced industrially from syngas (H_2, CO) and CO_2. The conversion of syngas and CO_2 into crude methanol is shown in the equations below.

$$CO + 2H_2 \rightleftharpoons CH_3OH \quad \text{(Eq. 1.1)}$$

$$CO_2 + 3H_2 \rightleftharpoons CH_3OH + H_2O \quad \text{(Eq. 1.2)}$$

With a global production capacity of more than 110 million tons annually,[19] methanol is one of the most important chemical industry materials. At ambient conditions, methanol is a colourless, polar and volatile liquid. It is miscible with various organic solvents and water, making methanol a popular organic solvent being able to dissolve compounds with high polarity. In fact, around 85% of methanol produced is consumed as solvent or the starting material in the chemical industry for the synthesis of other commodity chemicals, such as formaldehyde, methyl *tert*-butyl ether (MTBE), acetic acid, dimethyl ether (DME), etc., in order of importance. The remaining share is used in the energy and fuel areas.[20]

Methanol is a promising alternative to replace a large number of traditional petroleum-based fuels in terms of efficient combustion, low cost and abundance.[21] Its high hydrogen storage capacity of 12.5 wt% has resulted in increased interest in the development of methods for using methanol as hydrogen source. However, from the thermodynamic point of view, methanol, as a primary alcohol, is considered unfavourable to undergo dehydrogenation to generate H_2 or metal hydride (Scheme 1.3),[22] although several studies on dehydrogenation of methanol at low temperature have been reported.[23–27] In contrast, isopropanol shows a great

advantage for conversion to acetone *via* dehydrogenation. Thus dehydrogenation of methanol generally requires a higher energy input, impeding its applications in catalytic TH.

$$CH_3OH\ (l) \longrightarrow H_2CO\ (g) + H_2\ (g) \qquad \Delta H^\circ_{298} = 129.8\ kJ/mol,\ \Delta G^\circ_{298} = 63.5\ kJ/mol$$

$$i\text{-PrOH}\ (l) \longrightarrow Me_2CO\ (l) + H_2\ (g) \qquad \Delta H^\circ_{298} = 68.6\ kJ/mol,\ \Delta G^\circ_{298} = -3.3\ kJ/mol$$

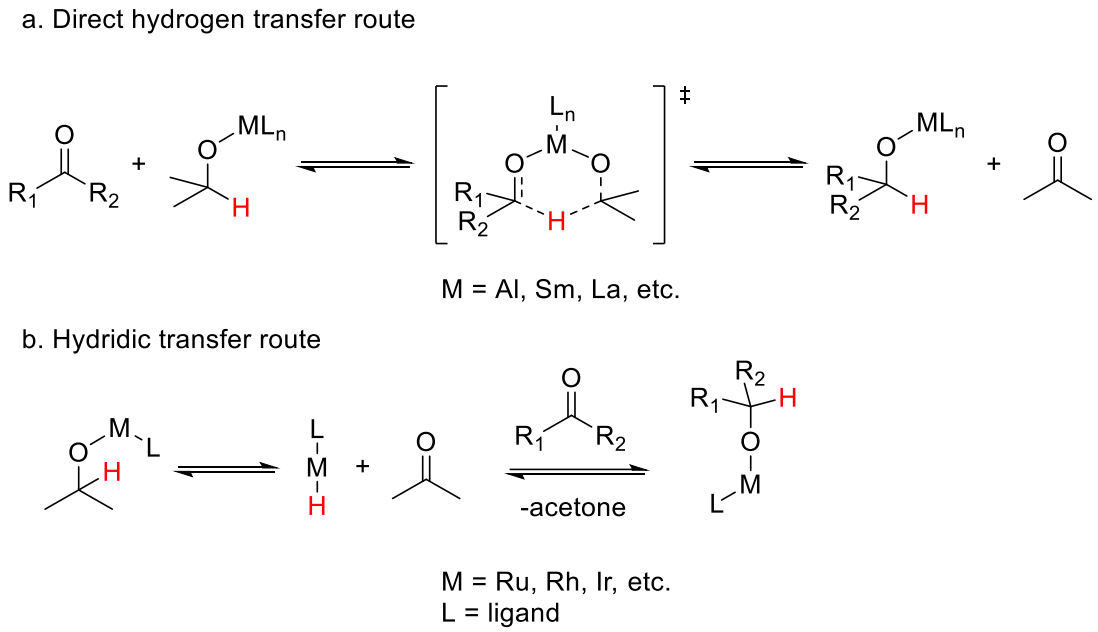
Scheme 1.3: Thermodynamic data for methanol and isopropanol dehydrogenation

Both theoretical and experimental studies have shown that it is challenging to achieve low temperature dehydrogenation of methanol.[22–27] Furthermore, secondary or primary alcohols, generated from the TH reaction of carbonyl compounds like ketones or aldehydes, are more easily to be dehydrogenated than methanol. In this thesis, we will show the TH of aldehydes using methanol as hydrogen source near room temperature.

1.2.4 Mechanism of catalytic TH

The mechanism of catalytic TH reactions depends on the choice of metal catalysts and substrates. Generally, the TH reactions can be classified into two main mechanisms: (i) the direct transfer mechanism in which the hydrogen is transferred directly from the hydrogen donor to the substrate (acceptor) without the involvement of metal hydrides (Scheme 1.4a); and (ii) the indirect or hydridic

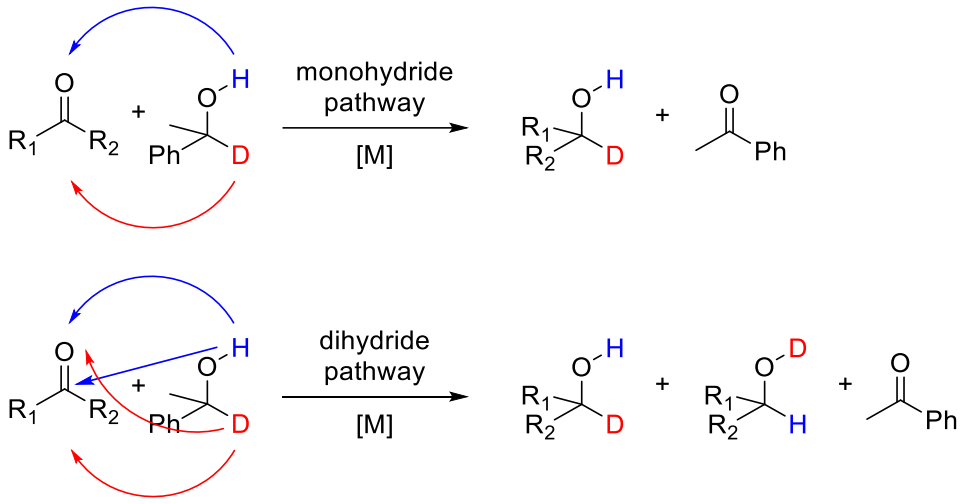
transfer mechanism in which the hydride is transferred from the donor to the acceptor *via* the active metal hydride intermediate (Scheme 1.4b).[28]



Scheme 1.4: General representation of the two main hydrogen transfer mechanisms

In the direct transfer mechanism, both hydrogen donor and acceptor are coordinated to the metal ion, enhancing polarisation and geometric proximity of the substrates, thereby allowing an intramolecular transfer of hydrogen in a concerted process without the formation of metal hydrides. The metal catalyst plays a role in enhancing the electrophiles of the carbonyl group, making hydride to be accepted more favourable. For example, in the traditional Meerwein-Ponndorf-Verley (MPV) reduction, the reaction is believed to undergo a catalytic cycle with the involvement of a six-member ring transition state caused by a hard Lewis acid Al(III) ion (Scheme 1.4a).[29]

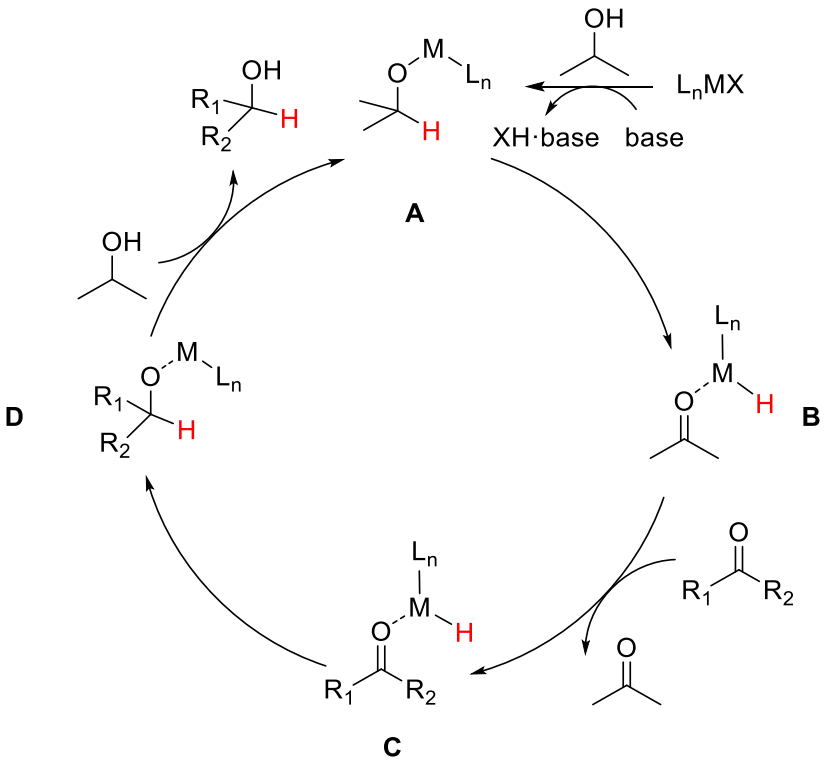
On the other hand, the hydridic route usually occurs in the presence of transition metal complexes. A hydride is first transferred from the donor molecule to the metal catalyst, generating a metal hydride. The hydride is then transferred to the substrate (acceptor) molecule. Weak Lewis acids with high hydride affinity, like Ru, Rh and Ir, are typical examples for the hydridic transfer mechanism. The catalytic TH reaction using Ru, Rh and Ir metal complexes were shown to proceed either *via* a monohydride or a dihydride intermediate (Scheme 1.5).[30] In both cases, the hydrogen donor and acceptor interact separately with the metal species in the catalytic cycle. Bäckvall *et al*. conducted an experiment to determine whether the hydridic mechanism proceeds through a monohydride or a dihydride pathway.[31] A hydrogen donor, α-deuterated α-phenylethanol, was used to easily track the destination of the hydrogen transfer process to ketone substrates. In the monohydridic route, the α-C−D deuterium of the donor is the origin of the metal deuteride, which is transferred to the carbonyl carbon, whereas the O−H hydrogen of the donor is transferred as a proton to the carbonyl oxygen, keeping their identity through the catalytic reaction. On the contrary, both α-C−D deuterium and O−H hydrogen atoms of the donor are transferred to the metal in the dihydride pathway, yielding a metal dihydride species. Then, both hydrogens are transferred to the carbonyl functionality of the acceptor randomly.



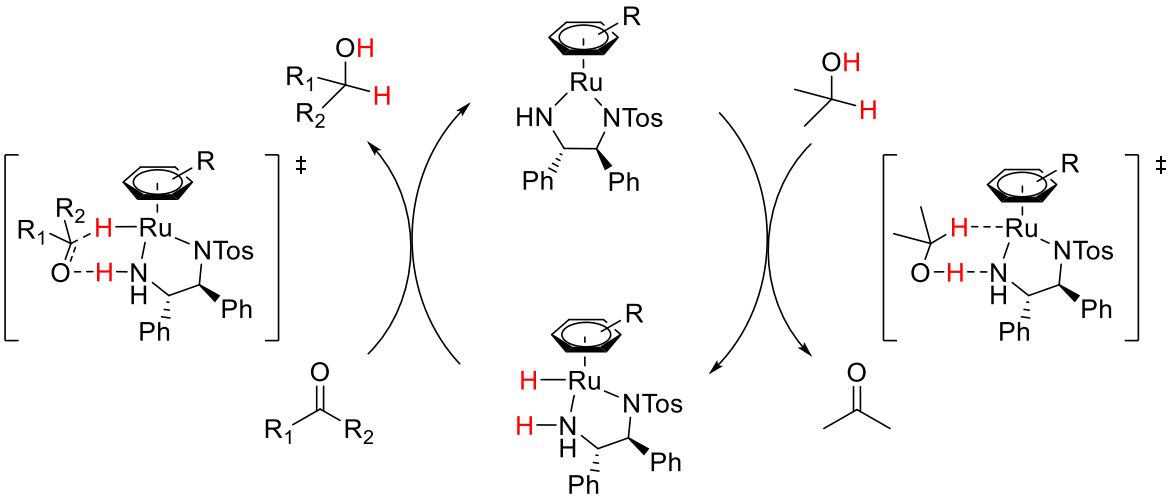
Scheme 1.5: Monohydride and dihydride pathway for catalytic TH of ketones

The catalytic TH reaction mechanisms can also be classified according to the condition of the substrate in the coordination sphere of the metal catalyst. Thus, the reaction route proceeding through the coordination of the substrate to the metal is called inner-sphere mechanism; whereas the route without direct coordination is called outer-sphere mechanism. A typical example of an inner-sphere mechanism for TH of ketones is shown in Scheme 1.6. The reaction between a metal precursor and isopropanol forms the active metal species **A**, which generates the metal hydride **B** *via* intramolecular β-hydride elimination. Acetone is formed and replaced with a carbonyl substrate to give complex **C**. The migratory insertion of the carbonyl to the metal-hydride bond results in intermediate **D**. Finally, protonolysis of the alkoxy group by additional isopropanol molecule generates the desired alcohol product and closes the catalytic cycle. The outer-sphere mechanism was proposed by Noyori and co-workers in their study on the monohydride

pathway.[32] In this case, the proton of the diamine ligand of the Ru complex played an important role in the catalytic mechanism. When the hydride is transferred from the monohydride species to the substrate, the other hydrogen is provided by the N-H from the diamine in the ligand (Scheme 1.7); thus this mechanism is also known as "metal-ligand bifunctional catalysis".[33]



Scheme 1.6: Schematic illustration of the inner-sphere mechanism for TH of ketones

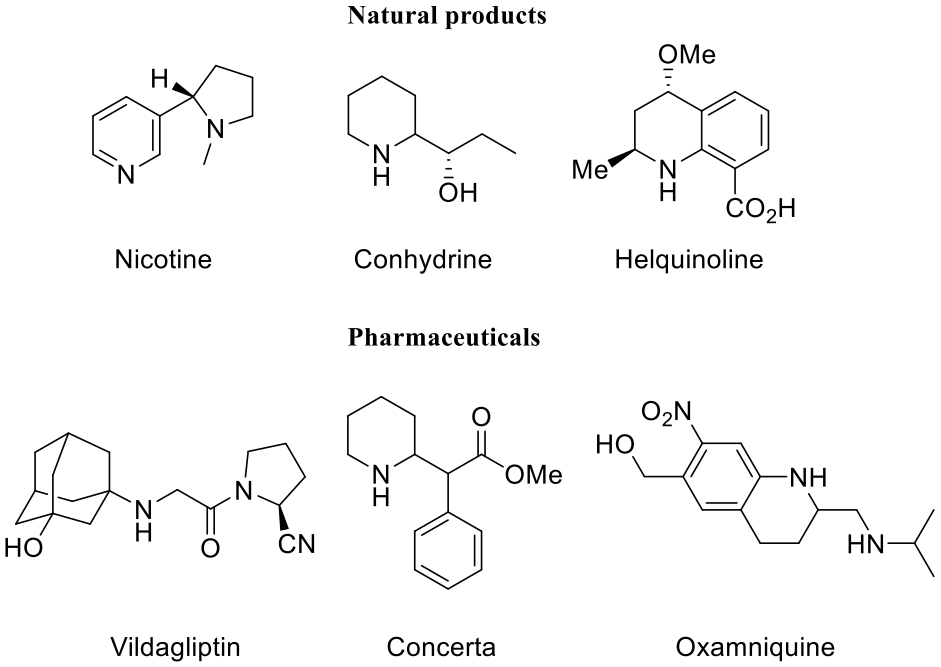


Scheme 1.7: Schematic illustration of the outer-sphere mechanism for TH of ketones

1.3 TH of *N*-heteroaromatics

Aromatic compounds with at least one non-carbon atom (e.g. O, N, S) in the ring are called heteroaromatics. The reduction of heteroaromatics leads to their corresponding saturated compounds. Among these, saturated nitrogen heterocycles are valuable and abundant in both natural products and pharmaceuticals (Scheme 1.8).[34–39] For instance, nicotine, a chiral alkaloid, is a natural product mostly found in tobacco, and can be used as a stimulant or as a drug for smoking cessation. Conhydrine is another alkaloid found in poison hemlock and can convert into *L*-coniine by reacting with hydroiodic acid and phosphorus. Helquinoline is a new type of antibiotic and is classified as tetrahydroquinoline. Vildagliptin, Concerta and Oxamniquine are all FDA-approved drugs that exhibit diverse biological

activities and excellent medicinal applications. Therefore, various methods have been developed for the synthesis of saturated *N*-heterocycles.[40–43] TH of *N*-heteroaromatics have shown great advantages over direct hydrogenation in terms of safety and easy operation;[9,44–48] however it has been much less studied.



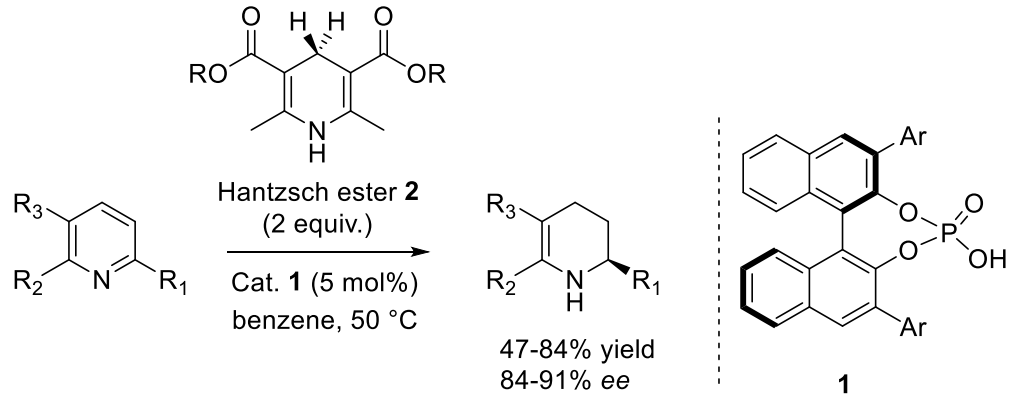
Scheme 1.8: Representative examples of saturated nitrogen heterocycles

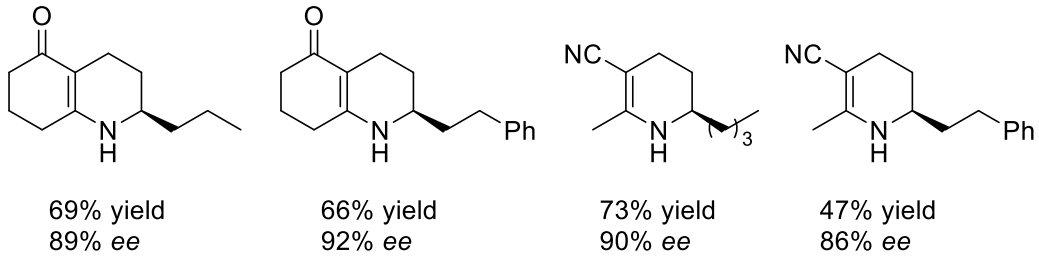
1.3.1 TH of pyridines

Piperidines are ubiquitous in natural products, biologically active compounds, and pharmaceuticals.[49] The catalytic hydrogenation of pyridines offers a straightforward method to access the desired piperidine products, and has been well-studied over the past decades.[45,50–58] The representative examples on asymmetric transfer hydrogenation (ATH) of pyridines are summarised in Chapter

4. Whilst the TH method is an attractive alternative to direct hydrogenation since it does not require hazardous pressurised H_2 gas and special equipment, so far, only limited studies have demonstrated the reduction of pyridines. In this section, studies on TH of pyridines will be highlighted.

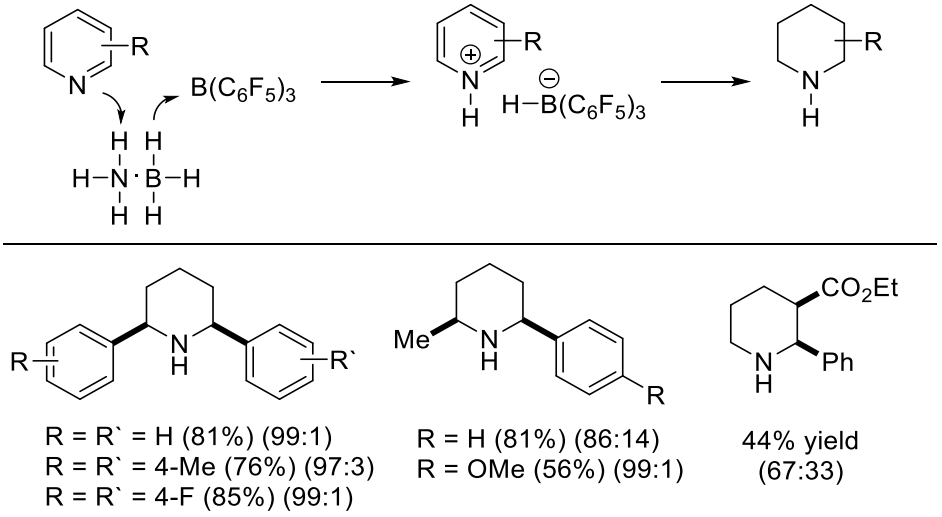
In 2007, Rueping and co-workers developed the first example of metal-free ATH of pyridines using Hantzsch esters as hydrogen source (Scheme 1.9).[59] In the presence of 5 mol% of the phosphoric acid **1** and 2 equiv. of Hantzsch dihydropyridine **2**, a variety of trisubstituted pyridines were reduced to the corresponding tetrahydropyridines in good yields (66-84%) and excellent enantioselectivities (up to 92% *ee*).





Scheme 1.9: Organocatalytic enantioselective TH of pyridines with Hantzsch esters

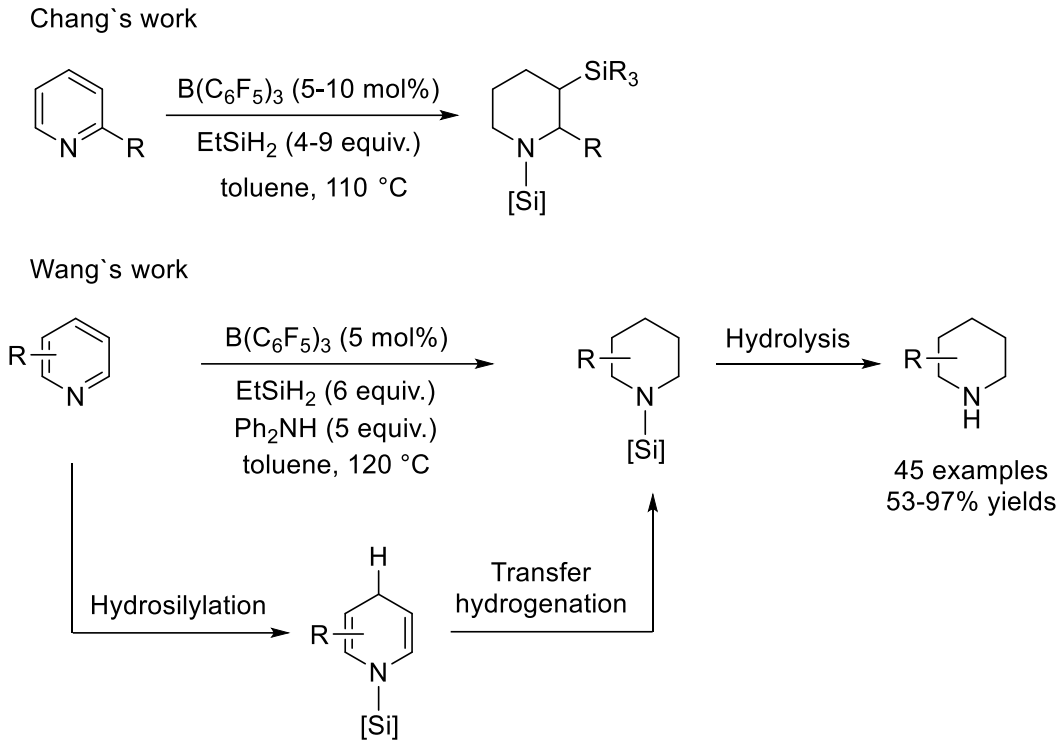
Frustrated Lewis pairs (FLPs) are a compound containing both a Lewis acid and a Lewis base, which, due to steric hindrance, cannot form the classical acid-base adducts. FLPs have emerged as a promising class of catalysts for metal-free homogeneous hydrogenation of unsaturated compounds since the discovery of hydrogen splitting with FLPs by Stephan and co-workers in 2006.[60] In 2016, the Du group demonstrated a metal-free method for borane-catalysed TH of pyridines using ammonia borane as hydrogen donor.[61] They proposed that the FLPs formed from pyridine and $B(C_6F_5)_3$ can split the N-H and B-H bonds of ammonia borane to produce zwitterion species, followed by the subsequent reduction to obtain piperidine products (Scheme 1.10).



Scheme 1.10: Proposed pathway for the FLPs-catalysed TH of pyridines with ammonia borane and selected piperidine products

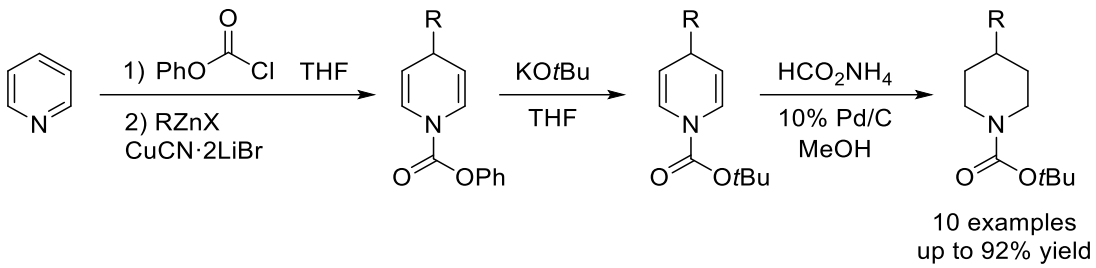
Similarly, the Chang[62] and Wang[63] groups developed the $B(C_6F_5)_3$ catalysed TH of pyridines using Et_2SiH_2 or $PhMe_2SiH$ as reducing reagents.

Although various substituted pyridines can be reduced to corresponding piperidines with these methods (Scheme 1.11), they are limited in substrate scope, e.g. unsuitable for reducible functional groups due to the harsh reaction conditions (over 100 °C) and suffer from the use of expensive hydrogen donors.



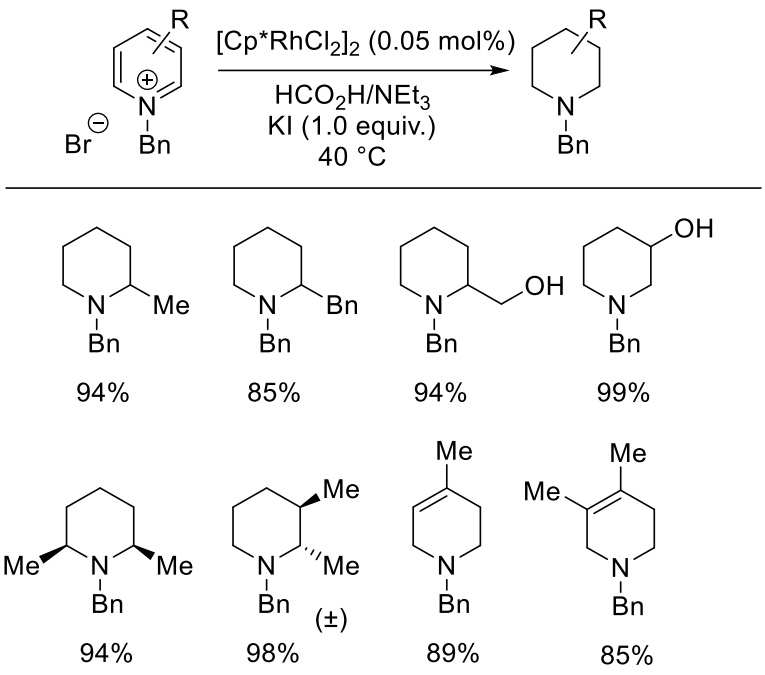
Scheme 1.11: Selected examples for the borane-catalysed TH of pyridines

In 2003, Olsson and co-workers reported the synthesis of 4-substituted *N*-protected piperidines *via* CuCN·2LiBr-catalysed organozinc additions and subsequent TH (Scheme 1.12).[64] The *N*-phenoxycarbonyl group can be readily converted to *N*-Boc by addition of KO*t*Bu, which allows for the further deprotection strategies.



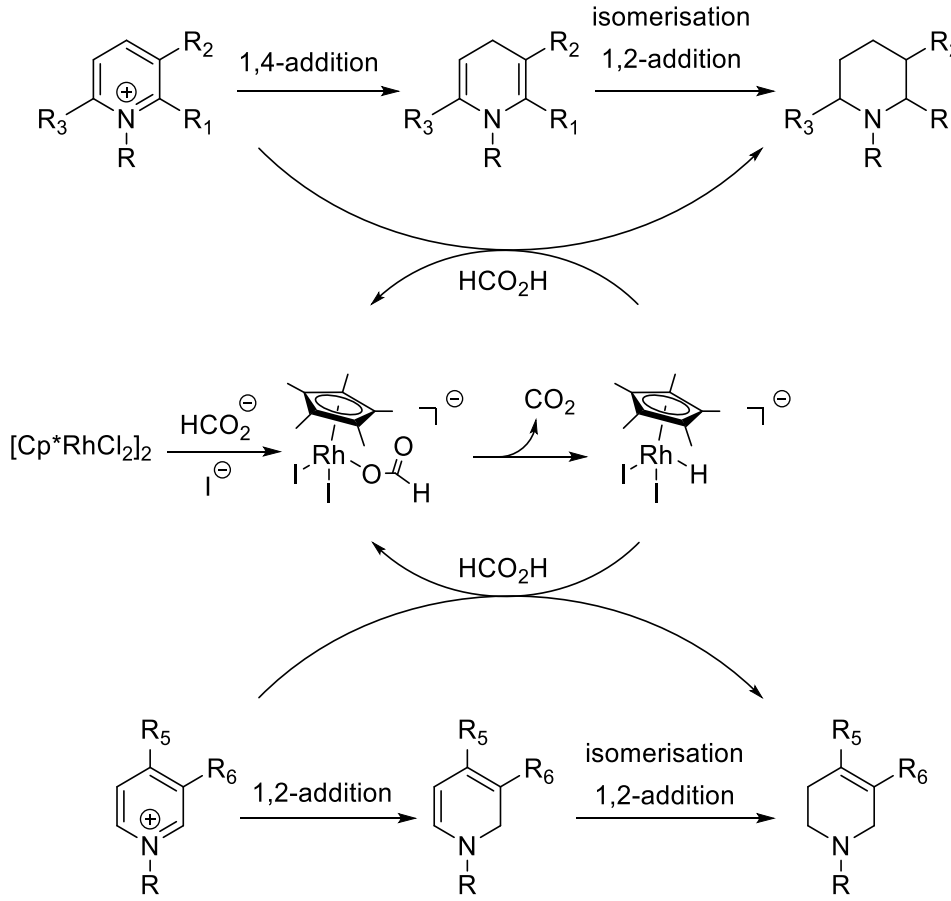
Scheme 1.12: Synthesis of 4-substituted *N*-Boc-protected piperidines

In 2012, our group reported iodide-promoted, simple rhodium complex $[Cp^*RhCl_2]_2$ (Cp* = pentamethylcyclopentadiene) catalysed TH of *N*-heteroaromatics such as quinolines and isoquinolines using F/T azeotrope as hydrogen source.[65] Later on, we successfully applied this catalytic protocol to the TH of pyridines.[66] Various pyridinium salts, obtained from simple quaternisation with benzyl halide, can be reduced to corresponding piperidines or tetrahydropyridines under mild reaction conditions (Scheme 1.13).



Scheme 1.13: Selected examples of Rh-catalysed TH of pyridinium salts

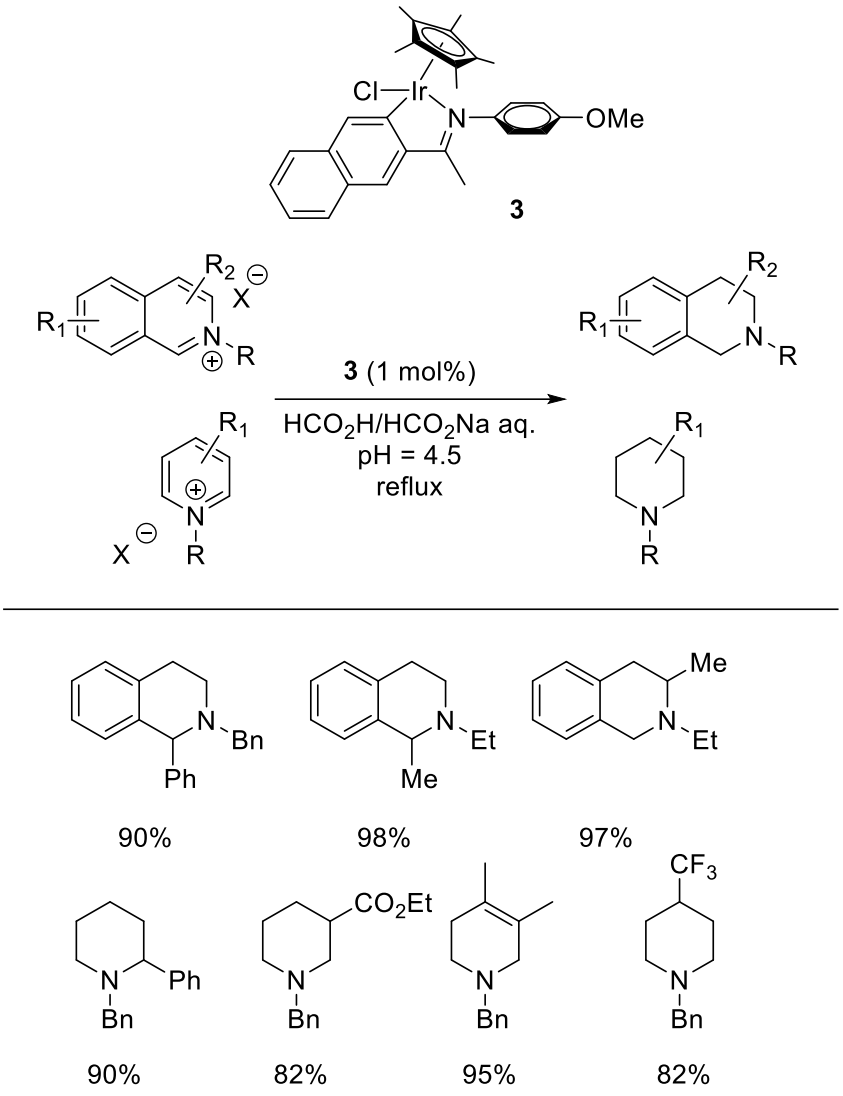
A plausible mechanism is shown in Scheme 1.14 to explain the effect of iodide during the catalysis. The substrate is possibly reduced by the active diiodo rhodium hydride species. The excessive amount of iodide salt takes the role of suppressing the dissociation of iodide ions from the hydride species.[66] The substrates without substituents at C4 position would undergo a 1,4-addition first, and then reduced to piperidines *via* a 1,2-addition. In the presence of C4-substituent, 1,2-addition takes place, giving 1,2-dihydropyridines, followed by another 1,2-addition to produce tetrahydropyridines. These unsaturated piperidines can be further transformed into other high value products *via* a number of well-established reactions, such as asymmetric hydrogenation, asymmetric epoxidation[67] and allylic substitution,[68] etc.



Scheme 1.14: Proposed mechanism for Rh-catalysed TH of pyridinium salts

Previously, our group had developed a series of cyclometalated iridium complexes, called iridacycles, for the TH of a wide range of carbonyl compounds and for the reductive amination of ketones in aqueous conditions.[69–73] The robust iridium complex **3** exhibited efficient catalytic activity in reduction of various *N*-heterocycles, including quinolones, isoquinolines, indoles and pyridinium salts, in a HCO_2H/HCO_2Na aqueous solution (Scheme 1.15).[74] This work marks the first example of homogeneous catalytic TH of *N*-heterocycles in water. We also achieved ATH of pyridinium salts with iridacycles using F/T in isopropanol.[75] In

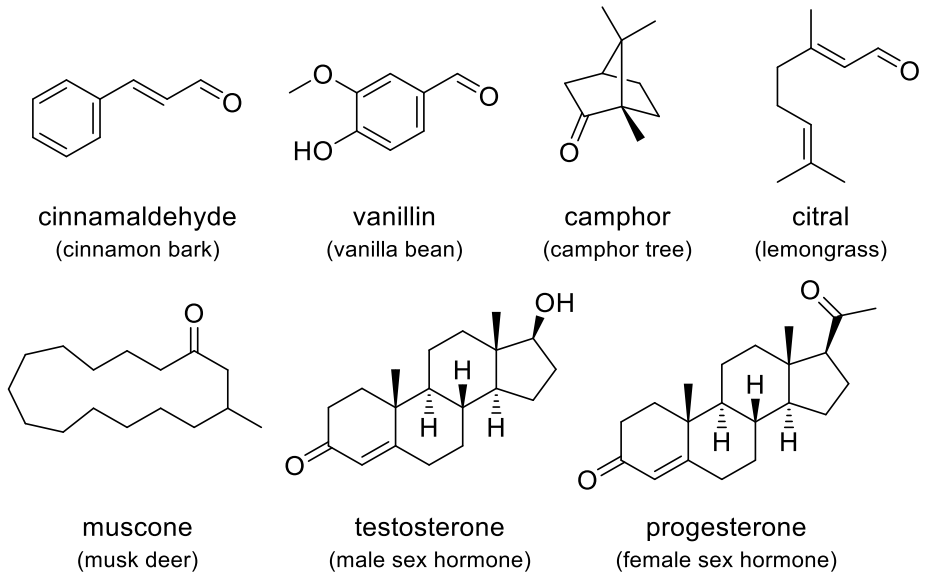
this thesis, the TH of pyridinium salts will be discussed in the context of a process called “reductive transamination”.



Scheme 1.15: Selected examples of cyclometalated iridium complex catalysed TH of *N*-heterocycles

1.4 TH of carbonyl compounds

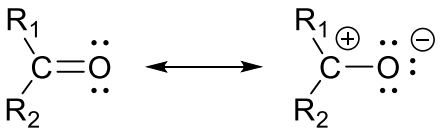
The carbonyl group is a functional group composed of a carbon atom and an oxygen atom connected by a double bond. Carbonyl compounds, like aldehydes and ketones, are ubiquitous in nature (Scheme 1.16).



Scheme 1.16: Examples of carbonyl compounds in nature

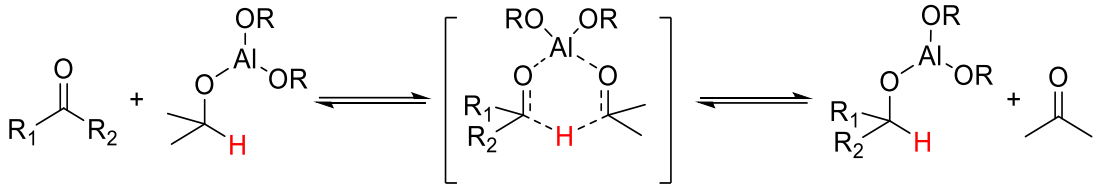
Both alkenes (C=C) and carbonyl groups have a double bond; but the physical properties and reactivity are largely different from each other. The high electronegativity of the oxygen draws the electron density away from the carbon, making the carbon atom slightly positive (Scheme 1.17). As a consequence of the charge separation, the dipole-dipole interaction dramatically affects the boiling point of carbonyl compounds. Generally, the carbonyl compounds have a higher boiling point than alkenes and other hydrocarbons with a similar molecular

weight.[76] In this thesis, we focus on the reduction reaction which happens at the carbonyl group.



Scheme 1.17: The resonance structures of the carbonyl group

Metal-catalysed hydrogenation of aldehydes and ketones is an efficient way to produce primary and secondary alcohols, respectively, which are valuable building blocks in fine chemicals and pharmaceutical industry.[7] Transfer hydrogenation of those carbonyl compounds is a safer, cheaper, and easier method by avoiding the use of hazardous hydrogen gas and the equipment for high-pressure conditions in the direct hydrogenation.[9] In 1920s, the Meerwein-Ponndorf-Verley (MPV) reduction demonstrated TH of ketones, which is catalysed by stoichiometric aluminium isopropoxide with isopropanol as hydrogen source.[77–80] The reduction happens through a direct hydrogen transfer route *via* the formation of a six-membered transition state (Scheme 1.18). In the late 1930s, Burg and co-workers reported the first application of hydrides for the reduction of aldehydes and ketones using di-borane as a reducing agent.[77] In the 1940s, under improved methods, alkali metal hydrides, like sodium borohydride and lithium aluminium hydride, were discovered and brought a profound change in the procedures for the reduction of functional groups in organic molecules.[81]

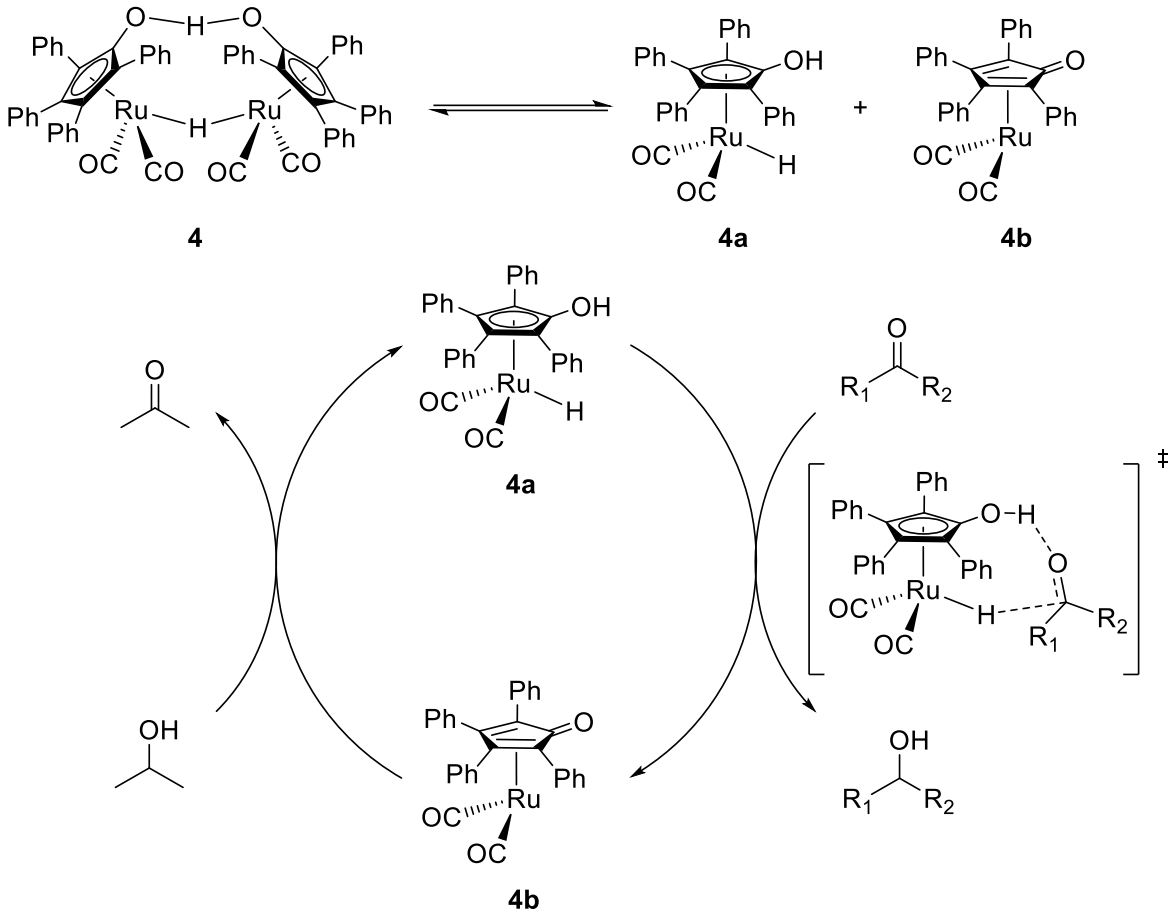


Scheme 1.18: Mechanism of MPV reduction of ketones

1.4.1 Ru-, Rh- and Ir-catalysed TH of carbonyl compounds

From economic and environmental points of view, catalytic TH has a great advantage over stoichiometric reduction. MPV reduction requires considerable aluminium reagent and produces undesired by-products. The first example of transition metal catalysed TH of ketones was reported by Mitchell and co-workers in the 1960s. Cyclohexanone is reduced to cyclohexanol catalysed by an iridium complex in the presence of isopropanol.[82] In 1975, Sasson and Blum demonstrated dichlorotris(triphenylphosphine)ruthenium, $[RuCl_2(PPh_3)_3]$, catalysed TH of various saturated and α,β-unsaturated ketones.[83] Later, the reactivity of the ruthenium complex was significantly improved by the addition of a catalytic amount of a strong base, sodium hydroxide (2.4 mol% NaOH), as co-catalyst. The new ruthenium-based system efficiently catalysed both aliphatic and aromatic ketones by isopropanol with a highest turnover rate of 900 per hour.[84] In the presence of base, the displacement of the chloride by isopropanol takes place first and followed by β-elimination to give the active ruthenium dihydride species $[RuH_2(PPh_3)_3]$.

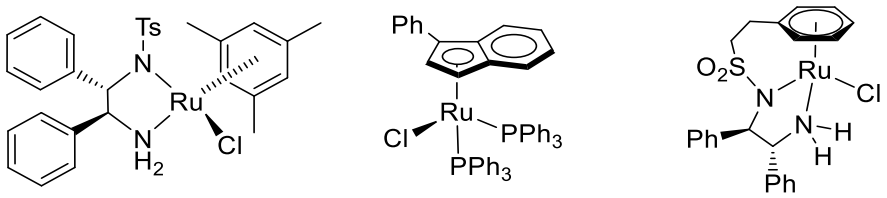
In 1986, Shvo and co-workers reported the synthesis of a new ruthenium complex **4**, now called Shvo's catalyst, and its applications in both hydrogenation and TH of ketones.[85] Upon heating, the dinuclear complex **4** dissociates into an 18-electron ruthenium hydride complex **4a** and a 16-electron cyclopentadienone complex **4b** (Scheme 1.19). The hydride from the ruthenium centre and the proton from the η^5-hydroxycyclopentadienyl group transfer into the ketone substrate *via* an outer-sphere mechanism. The dehydrogenation of isopropanol, the hydrogen donor, regenerates the active ruthenium catalyst **4a** to close the catalytic cycle. The ruthenium catalyst reported by Shvo *et al*. was the first example of "ligand-metal bifunctional catalyst". Later in 1995, Noyori, the Nobel laureate in 2001, reported the unprecedented ATH of aromatic ketones using a Ru-TsDPEN catalyst (TsDPEN = *N*-tosyl-1,2-diphenylethylene-1,2-diamine).[86]



Scheme 1.19: TH mechanism for Shvo's catalyst

The catalytic activity of a wide range of half-sandwich ruthenium complexes have been investigated for TH reactions (Scheme 1.20).[9] Complex **5** is known as Noyori's catalyst, often *in situ* generated from $[RuCl_2(mesitylene)]_2$ and (*S*,*S*)-TsDPEN in the presence of potassium hydroxide, giving high yields of aromatic alcohol products with excellent enantiomeric excess (*ee*).[86] Except for Cp, Cp* and arene group, the indenyl structure is also employed as a coordinating ligand in ruthenium half-sandwich complexes. The Ru phenylindenyl complex **6** is

a highly efficient catalyst in TH of ketones and aldehydes. In most of the cases, the desired alcohol products were obtained with excellent yields in isopropanol at 89 °C, exceeding the catalytic activity of Shvo's catalyst **4**.[87] The Wills group reported the first "tethered" Ru(II) catalyst **7** for ATH of aromatic ketones in F/T azeotrope. Various ketones were reduced in quantitative yields and with *ee* up to 98%.[88]

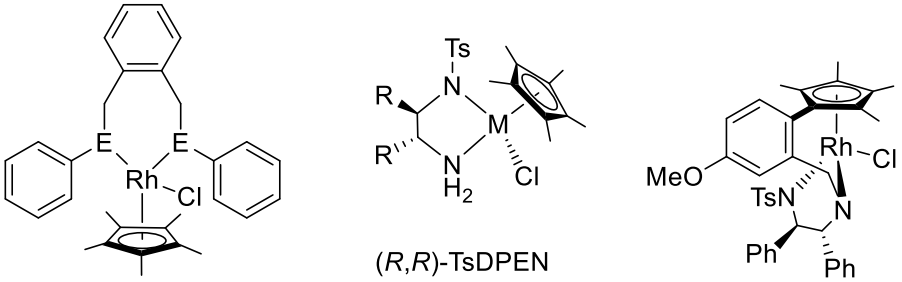


5 **6** **7**

Scheme 1.20: Selected ruthenium complexes for TH reactions

The half-sandwich rhodium complexes are also the most widely used catalysts for TH of carbonyl compounds (Scheme 1.21). Complex **8** was the first example of rhodium catalyst with (S, S) and (Se, Se) ligands capable of TH in glycerol, a cheap, non-hazardous, biodegradable hydrogen source. Complex **8b** with (Se, Se) ligand exhibited higher catalytic efficiency than the (S, S) analogue **8a**.[89] Tani, Ikariya and co-workers reported the synthesis of new chiral rhodium and iridium complexes **9** with chiral diamines and applications for efficient ATH of ketones inspired by the high selectivity of Noyori's catalyst.[11,90,91] The Ratovelomanana-Vidal group reported the synthesis of a novel "tethered" half-sandwich rhodium complex **10** using TsDPEN ligand and the functionalised Cp*

moiety, which catalysed ATH of ketones using F/T azeotrope as hydrogen source. Various alcohol products were obtained with excellent yields and enantiomeric excess at room temperature.[92]



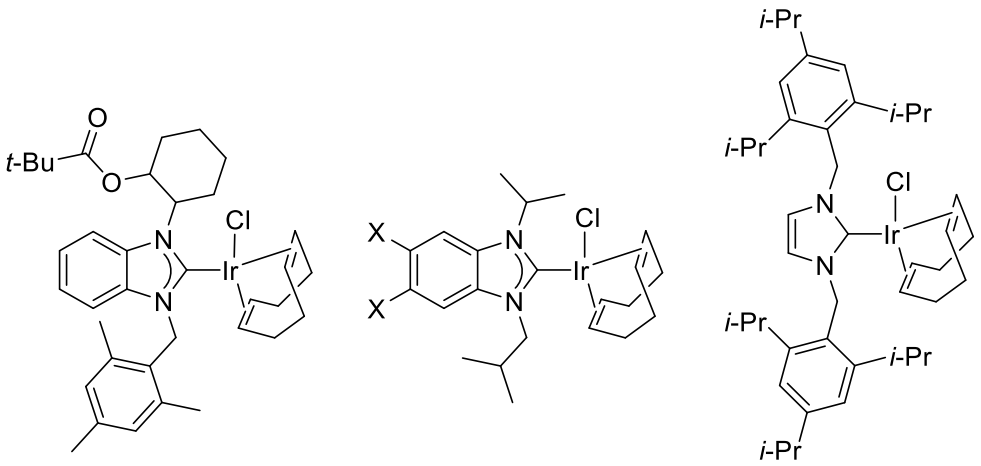
8a: E = S
8b: E = Se

(*R*,*R*)-TsDPEN
(*R*,*R*)-TsCYDN
M = Rh, Ir
9

10

Scheme 1.21: Selected rhodium complexes for TH reactions

Iridium catalysts are the most active catalysts in TH reactions, and have attracted much attention from researchers since the pioneering work on TH of ketones reported by Mestroni and co-workers.[93] In particular, Ir-NHC (*N*-heterocyclic carbene) type complexes are the most prominent examples of iridium-based catalysts. The Gülcemal group reported several iridium-NHC complexes which were synthesised *via* transmetalation from *in situ* generated silver(I)-NHC derivatives (Scheme 1.22). Over 99% conversions were obtained for the TH of carbonyls using only 0.1 mol% of iridium (I) complex **11** as the catalyst.[94] The TH of carbonyls catalysed by complexes **12** and **13** was completed in 2 min, reaching 12000 h^{-1} TOF (turnover frequency).[95] This study showed the influence of substituents on the catalytic reactivity of the iridium-NHC complexes.

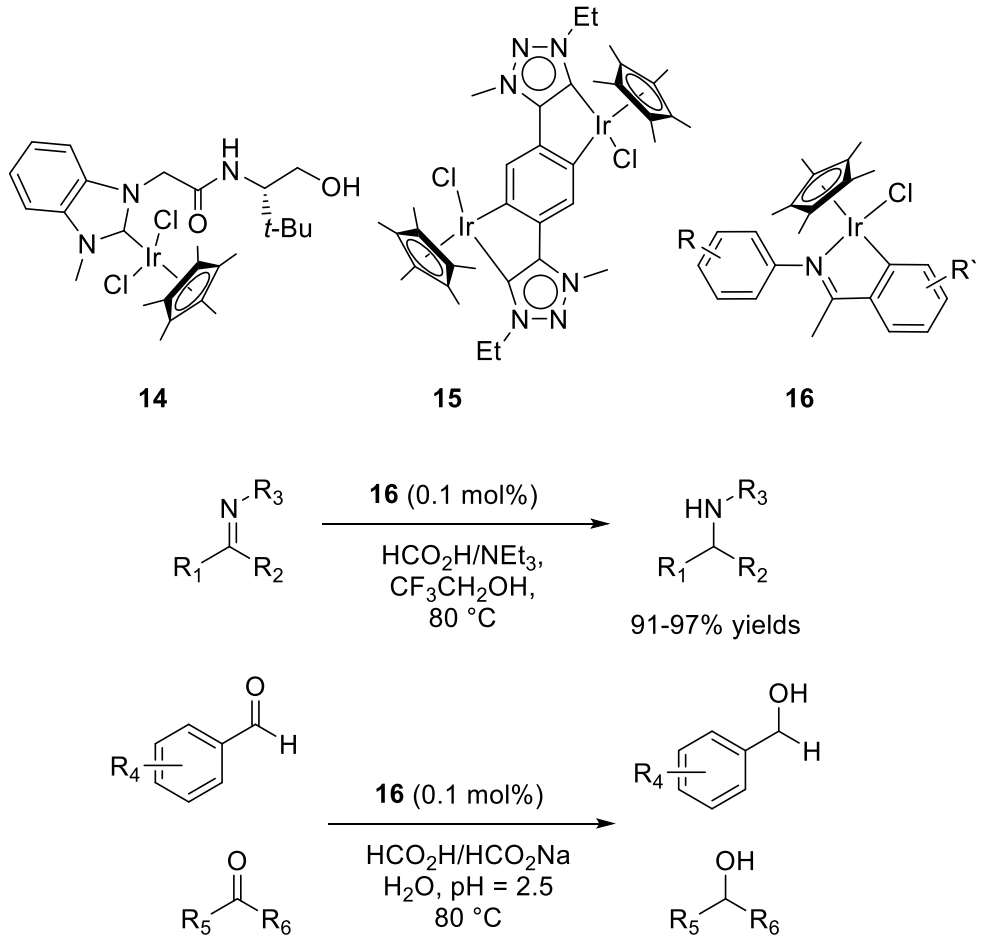


11 **12a**: X = H **12b**: X = CH_3 **13**

Scheme 1.22: Selected Ir-NHC complexes by the Gülcemal group

The iridium complexes of half-sandwich structure have been shown to be active in TH reactions.[71,96,97] Recent examples of half-sandwich iridium catalysts incorporated a wide range of coordinating ligands based on elements like N, P, and C, such as mono-NHC, bis-NHC, pyridyl, triazolyl and TsDPEN (Scheme 1.23). A monodentate iridium(III) complex **14** bearing a tunable chiral hydroxyamide functionalised NHC ligand was found to act as a catalyst precursor for ATH of acetophenone even at room temperature.[98] Iridium complexes with triazolyl moieties have been widely investigated due to their high activities, stabilities and easy modifications. The dinuclear iridium complex **15** with both a Cp* ring and a triazolyl fragment showed higher activity in TH of carbonyls than its mononuclear counterpart.[99] Our group also reported the synthesis of a family of cyclometalated iridium complexes, such as **3** and **16** using imino chelating ligand, and their applications in several TH reactions.[71,72] These complexes can be efficiently

employed in TH of carbonyls,[69,100] and imines[101] in aqueous medium or in organic solvents. Our studies showed that the pH values are critical for the TH reactions to be performed in high reactivity and selectivity.



Scheme 1.23: Selected half-sandwich iridium complexes as TH catalysts

1.5 Conclusion and aims of the thesis

Hydrogenation is one of the most fundamental reactions in organic synthesis. Its valuable products span from laboratory research to industrial applications, like pharmaceuticals and agrochemicals. Compared with direct hydrogenation using high-pressure H_2, transfer hydrogenation employs non-H_2 hydrogen donors, avoiding the use of special equipment, which is safer and easier to handle. Therefore TH provides a green, safe and environmentally friendly solution and has become a rapidly growing research hotspot in the context of high demand for sustainable and green chemistry. Lots of ligands and metal complexes have been synthesised and investigated to find the suitable catalytic system where various carbonyl compounds, imines and *N*-heterocycles can be reduced to desired hydrogenated products.

As summarised in previous sections, there are limited catalysts and methods for the efficient ATH of *N*-heterocyclic compounds, particularly, pyridines. Chiral piperidines are one of the most important cyclic amines, which are ubiquitous in natural products, bioactive molecules, and pharmaceutical compounds. The need for high catalyst loading and harsh reaction conditions limits the potential for industrial applications. In addition, the use of excessive amount of reducing agents, like Et_2SiH_2 or $PhMe_2SiH$, leads to abundant waste by-products and economic costs (£13/mL for Et_2SiH_2, £25.40/500mL for formic acid and £25.2/L for methanol, results obtained from Sigma-Aldrich, as of Sep 2021). However, the use

of cheaper and greener hydrogen source like formic acid and methanol are less explored.

The main aim of this thesis is to develop more efficient and greener methods for TH of *N*-heterocycles and carbonyls. Chapter 2 extends the previous study on reductive transamination of mono-substituted pyridines to di-substituted pyridines, more specifically, fluorinated pyridines, generating highly valuable fluorinated piperidines with high yields and excellent enantioselectivities. Chapter 3 reports a new protocol for the TH of pyridines with (hetero) arylamines to access *N*-arylated piperidines, bypassing the limitation of traditional C-N cross couplings. The reaction can be switched to producing five-membered pyrrolidines by introducing a leaving group at the pyridine structure. Chapter 4 demonstrates the preliminary attempts on the asymmetric transamination of pyridinium salts with achiral amines. Chapter 5 presents the rhodium-catalysed TH of saturated and α,β-unsaturated aldehydes with methanol as hydrogen source near room temperature.

1.6 References

[1] L. Cerveny, *Catalytic Hydrogenation*, Elsevier, **1978**.

[2] J. G. de Vries, C. J. Elsevier, *The Handbook of Homogeneous Hydrogenation*, Wiley-VCH: Weinheim, **2007**.

[3] P. G. Andersson, I. J. Munslow, *Modern Reduction Methods*, Wiley-VCH

Verlag GmbH & Co. KGaA: Weinheim, **2008**.

[4] A. J. Dijkstra, R. J. Hamilton, W. Hamm, *Trans Fatty Acids*, Wiley-Blackwell, **2008**.

[5] J. A. Osborn, G. Wilkinson, J. J. Mrowca, *Inorg. Synth.* **1967**, 67–71.

[6] R. H. Crabtree, M. W. Davis, *Organometallics* **1983**, *2*, 681–682.

[7] R. A. W. Johnstone, A. H. Wilby, I. D. Entwistle, *Chem. Rev.* **1985**, *85*, 129–170.

[8] G. Brieger, T. J. Nestrick, *Chem. Rev.* **1974**, *74*, 567–580.

[9] D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621–6686.

[10] S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226–236.

[11] T. Ikariya, A. J. Blacker, *Acc. Chem. Res.* **2007**, *40*, 1300–1308.

[12] I. Schmidt, K. Müller, W. Arlt, *Energy Fuels* **2014**, *28*, 6540–6544.

[13] D. J. Hayes, S. Fitzpatrick, M. H. B. Hayes, J. R. H. Ross, in *Biorefineries-Industrial Processess and Products*, WILEY-VCH Verlag GmbH & Co. KGaA, **2005**, pp. 139–164.

[14] G. Centi, S. Perathoner, *Catal. Today* **2009**, *148*, 191–205.

[15] M. Grasemann, G. Laurenczy, *Energy Environ. Sci.* **2012**, *5*, 8171–8181.

[16] X. Wu, X. Li, F. King, J. Xiao, *Angew. Chem. Int. Ed.* **2005**, *44*, 3407–

3411.

[17] X. Wu, X. Li, A. Zanotti-Gerosa, A. Pettman, J. Liu, A. J. Mills, J. Xiao, *Chem. Eur. J.* **2008**, *14*, 2209–2222.

[18] C. Wang, C. Li, X. Wu, A. Pettman, J. Xiao, *Angew. Chem. Int. Ed.* **2009**, *48*, 6524–6528.

[19] The Methanol Industry by Methanol Institute, http://www.methanol.org/the-methanol-industry/, accessed Sep 2021.

[20] F. Dalena, A. Senatore, A. Marino, A. Gordano, M. Basile, A. Basile, *Methanol Production and Applications: An Overview*, Elsevier, **2018**.

[21] G. A. Olah, A. Goeppert, G. K. S. Prakash, *Beyond Oil and Gas: The Methanol Economy, 3rd Ed.*, John Wiley & Sons, **2018**.

[22] R. H. Crabtree, *Chem. Rev.* **2017**, *117*, 9228–9246.

[23] M. Nielsen, E. Alberico, W. Baumann, H.-J. Drexler, H. Junge, S. Gladiali, M. Beller, *Nature* **2013**, *495*, 85–89.

[24] R. E. Rodríguez-Lugo, M. Trincado, M. Vogt, F. Tewes, G. Santiso-Quinones, H. Grützmacher, *Nat. Chem.* **2013**, *5*, 342–347.

[25] M. Wakizaka, T. Matsumoto, R. Tanaka, H.-C. Chang, *Nat. Commun.* **2016**, *7*, 12333.

[26] F. F. van de Watering, M. Lutz, W. I. Dzik, B. de Bruin, J. N. H. Reek,

ChemCatChem **2016**, *8*, 2752–2756.

[27] Y. Shen, Y. Zhan, S. Li, F. Ning, Y. Du, Y. Huang, T. He, X. Zhou, *Chem. Sci.* **2017**, *8*, 7498–7504.

[28] D. Klomp, U. Hanefeld, J. A. Peters, in *The Handbook of Homogeneous Hydrogenation, 1st Ed.*, WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, **2007**, pp. 585–630.

[29] R. Cohen, C. R. Graves, S. T. Nguyen, J. M. L. Martin, M. A. Ratner, *J. Am. Chem. Soc.* **2004**, *126*, 14796–14803.

[30] J.-E. Bäckvall, *J. Organomet. Chem.* **2002**, *652*, 105–111.

[31] Y. R. S. Laxmi, J.-E. Bäckvall, *Chem. Commun.* **2000**, 611–612.

[32] K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed.* **1997**, *36*, 285–288.

[33] T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393–406.

[34] D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435–446.

[35] J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669–1730.

[36] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.

[37] V. Sridharan, P. A. Suryavanshi, J. C. Menéndez, *Chem. Rev.* **2011**, *111*, 7157–7259.

[38] R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845–5859.

[39] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.

[40] D. M. Schultz, J. P. Wolfe, *Synthesis* **2012**, *44*, 351–361.

[41] C.-V. T. Vo, J. W. Bode, *J. Org. Chem.* **2014**, *79*, 2809–2815.

[42] G. J. Tanoury, *Synthesis* **2016**, *48*, 2009–2025.

[43] M. Chrzanowska, A. Grajewska, M. D. Rozwadowska, *Chem. Rev.* **2016**, *116*, 12369–12465.

[44] C. Wang, X. Wu, J. Xiao, *Chem. Asian J.* **2008**, *3*, 1750–1770.

[45] D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557–2590.

[46] A. N. Kim, B. M. Stoltz, *ACS Catal.* **2020**, *10*, 13834–13851.

[47] Y.-G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357–1366.

[48] M. P. Wiesenfeldt, Z. Nairoukh, T. Dalton, F. Glorius, *Angew. Chem. Int. Ed.* **2019**, *58*, 10460–10476.

[49] M. Rubiralta, E. Giralt, A. Diez, *Piperidine: Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and Its Derivatives*, Elsevier: Amsterdam, **1991**.

[50] F. Glorius, *Org. Biomol. Chem.* **2005**, *3*, 4171–4175.

[51] C. Y. Legault, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 8966–8967.

[52] W.-J. Tang, J. Tan, L.-J. Xu, K.-H. Lam, Q.-H. Fan, A. S. C. Chan, *Adv. Synth. Catal.* **2010**, *352*, 1055–1062.

[53] Z.-S. Ye, M.-W. Chen, Q.-A. Chen, L. Shi, Y. Duan, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2012**, *51*, 10181–10184.

[54] M. Chang, Y. Huang, S. Liu, Y. Chen, S. W. Krska, I. W. Davies, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 12761–12764.

[55] W.-X. Huang, B. Wu, X. Gao, M.-W. Chen, B. Wang, Y.-G. Zhou, *Org. Lett.* **2015**, *17*, 1640–1643.

[56] A. Karakulina, A. Gopakumar, İ. Akçok, B. L. Roulier, T. LaGrange, S. A. Katsyuba, S. Das, P. J. Dyson, *Angew. Chem. Int. Ed.* **2016**, *55*, 292–296.

[57] W.-X. Huang, C.-B. Yu, Y. Ji, L.-J. Liu, Y.-G. Zhou, *ACS Catal.* **2016**, *6*, 2368–2371.

[58] Z. Yu, W. Jin, Q. Jiang, *Angew. Chem. Int. Ed.* **2012**, *51*, 6060–6072.

[59] M. Rueping, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2007**, *46*, 4562–4565.

[60] G. C. Welch, R. R. S. Juan, J. D. Masuda, D. W. Stephan, *Science* **2006**, *314*, 1124–1126.

[61] Q. Zhou, L. Zhang, W. Meng, X. Feng, J. Yang, H. Du, *Org. Lett.* **2016**, *18*, 5189–5191.

[62] N. Gandhamsetty, S. Park, S. Chang, *J. Am. Chem. Soc.* **2015**, *137*, 15176–15184.

[63] Z.-Y. Liu, Z.-H. Wen, X.-C. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 5817–5820.

[64] X. Wang, A. M. Kauppi, R. Olsson, F. Almqvist, *Eur. J. Org. Chem.* **2003**, *2003*, 4586–4592.

[65] J. Wu, C. Wang, W. Tang, A. Pettman, J. Xiao, *Chem. Eur. J.* **2012**, *18*, 9525–9529.

[66] J. Wu, W. Tang, A. Pettman, J. Xiao, *Adv. Synth. Catal.* **2013**, *355*, 35–40.

[67] Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu, K.-X. Su, *Chem. Rev.* **2005**, *105*, 1603–1662.

[68] C. G. Frost, J. Howarth, J. M. J. Williams, *Tetrahedron: Asymmetry* **1992**, *3*, 1089–1122.

[69] D. Talwar, X. Wu, O. Saidi, N. P. Salguero, J. Xiao, *Chem. Eur. J.* **2014**, *20*, 12835–12842.

[70] Q. Lei, Y. Wei, D. Talwar, C. Wang, D. Xue, J. Xiao, *Chem. Eur. J.* **2013**, *19*, 4021–4029.

[71] Z. Chen, A. Kacmaz, J. Xiao, *Chem. Rec.* **2021**, *21*, 1506–1534.

[72] C. Wang, J. Xiao, *Chem. Commun.* **2017**, *53*, 3399–3411.

[73] C. Michon, K. MacIntyre, Y. Corre, F. Agbossou-Niedercorn, *ChemCatChem* **2016**, *8*, 1755–1762.

[74] D. Talwar, H. Y. Li, E. Durham, J. Xiao, *Chem. Eur. J.* **2015**, *21*, 5370–5379.

[75] J. Smith, A. Kacmaz, C. Wang, B. Villa-Marcos, J. Xiao, *Org. Biomol. Chem.* **2021**, *19*, 279–284.

[76] S. Patai, *The Chemistry of the Carbonyl Group*, John Wiley & Sons Ltd, New York, **1966**.

[77] A. L. Wilds, *Org. React.* **2011**, 178–223.

[78] K. Nishide, M. Node, *Chirality* **2002**, *14*, 759–767.

[79] D. Klomp, T. Maschmeyer, U. Hanefeld, J. A. Peters, *Chem. Eur. J.* **2004**, *10*, 2088–2093.

[80] J. S. Cha, *Org. Process Res. Dev.* **2006**, *10*, 1032–1053.

[81] H. C. Brown, S. Krishnamurthy, *Tetrahedron* **1979**, *35*, 567–607.

[82] Y. M. Y. Haddad, H. B. Henbest, J. Husbands, T. R. B. Mitchell, *Proc. Chem. Soc.* **1964**, 361.

[83] Y. Sasson, J. Blum, *J. Org. Chem.* **1975**, *40*, 1887–1896.

[84] R. L. Chowdhury, J.-E. Bäckvall, *J. Chem. Soc. Chem. Commun.* **1991**, 1063–1064.

[85] Y. Shvo, D. Czarkie, Y. Rahamim, D. F. Chodosh, *J. Am. Chem. Soc.* **1986**, *108*, 7400–7402.

[86] S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563.

[87] S. Manzini, C. A. U. Blanco, S. P. Nolan, *Adv. Synth. Catal.* **2012**, *354*, 3036–3044.

[88] J. Hannedouche, G. J. Clarkson, M. Wills, *J. Am. Chem. Soc.* **2004**, *126*, 986–987.

[89] O. Prakash, K. N. Sharma, H. Joshi, P. L. Gupta, A. K. Singh, *Organometallics* **2014**, *33*, 2535–2543.

[90] K. Murata, T. Ikariya, R. Noyori, *J. Org. Chem.* **1999**, *64*, 2186–2187.

[91] K. Mashima, T. Abe, K. Tani, *Chem. Lett.* **1998**, *27*, 1201–1202.

[92] P.-G. Echeverria, C. Férard, P. Phansavath, V. Ratovelomanana-Vidal, *Catal. Commun.* **2015**, *62*, 95–99.

[93] G. Mestroni, G. Zassinovich, A. Camus, *J. Organomet. Chem.* **1977**, *140*, 63–72.

[94] D. Gülcemal, A. G. Gökçe, S. Gülcemal, B. Çetinkaya, *RSC Adv.* **2014**, *4*, 26222–26230.

[95] S. Gülcemal, A. G. Gökçe, B. Çetinkaya, *Dalton Trans.* **2013**, *42*, 7305–7311.

[96] J. Liu, X. Wu, J. A. Iggo, J. Xiao, *Coord. Chem. Rev.* **2008**, *252*, 782–809.

[97] Y.-F. Han, G.-X. Jin, *Chem. Soc. Rev.* **2014**, *43*, 2799–2823.

[98] H. Chiyojima, S. Sakaguchi, *Tetrahedron Lett.* **2011**, *52*, 6788–6791.

[99] R. Maity, S. Hohloch, C.-Y. Su, M. van der Meer, B. Sarkar, *Chem. Eur. J.* **2014**, *20*, 9952–9961.

[100] Y. Wei, D. Xue, Q. Lei, C. Wang, J. Xiao, *Green Chem.* **2013**, *15*, 629–634.

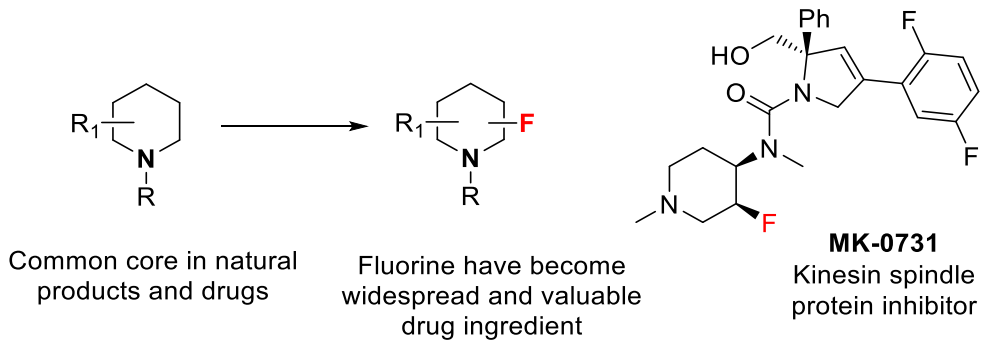
[101] C. Wang, A. Pettman, J. Bacsa, J. Xiao, *Angew. Chem. Int. Ed.* **2010**, *49*, 7548–7552.

Chapter 2: Synthesis of Chiral Fluorinated Piperidines *via* Asymmetric Reductive Transamination

2.1 Introduction

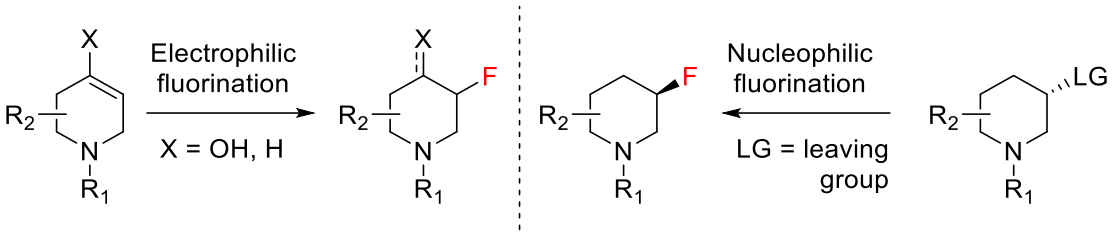
Reduction of *N*-heteroaromatics is a fundamental strategy in synthetic chemistry because of their broad applications in the synthesis of natural products, biologically active compounds and pharmaceuticals.[1] In fact, around 60% of FDA-approved drugs contain at least one *N*-heterocyclic compound, of which piperidine accounts for the majority.[2] Although progress has been made in the area of asymmetric hydrogenation of *N*-heterocycles like quinolines and isoquinolines,[3–9] studies on the asymmetric reduction of pyridine and derivatives remain rare.[10–13] There are a few reasons that make hydrogenation of pyridines a challenge: 1) high aromatic stabilisation energies; 2) the tendency to poison and/or deactivate catalysts by the strong coordination between the metal centres and the heteroatoms. Significant advances in this field over the past decade have relied on the employment of efficient catalysts and the applications of substrate activation strategies.[14]

Fluorine, as a small atom with high electronegativity, can dramatically affect the bioavailability and pharmacokinetic properties of a drug candidate.[15,16] A recent analysis revealed that 20% of all commercially available medicines contain fluorine atoms.[17] Therefore, the incorporation of fluorine into the piperidine scaffold provides an attractive opportunity for easier access to potential drug molecules (Scheme 2.1).[15,18,19]

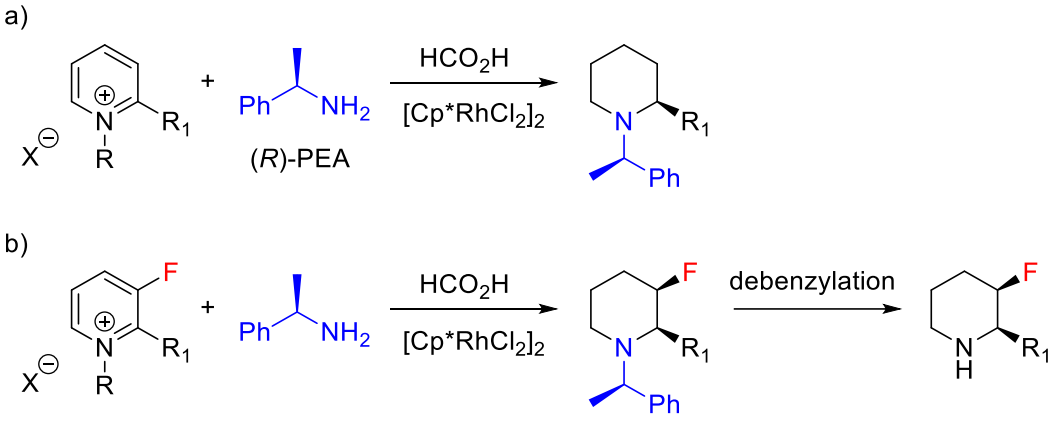


Scheme 2.1: Incorporation of fluorine into piperidine derivatives, and an example of fluorinated piperidine

Despite the importance of both fluorine and piperidine in pharmaceuticals, methods for the synthesis of simple monofluorinated piperidines are mainly based on either electrophilic fluorination[20] or nucleophilic fluorination[21,22] (Scheme 2.2). Both methods require elaborate predefined precursors, leading to chirally-enriched fluoropiperidines being limited in variety and expensive. For example, an online search shows that the retail price of a simple fluoropiperidine, (*R*)-3-fluoropiperidine hydrochloride (CAS No. 787564-37-8), is £995.5/g (as of Sep 2021, Sigma-Aldrich). Currently, the only stereoselective synthesis of fluoropiperidines *via* the hydrogenation of pyridines is seen in two recent reports from Glorius and co-workers, which discloses Rh- and Pd-catalysed hydrogenation reactions to access all *cis*-(multi)fluoropiperidines. However, the reaction cannot be used for the enantioselective hydrogenation of fluoropyridines.[23,24]



Scheme 2.2: Commonly used synthetic approaches to access fluorinated piperidines



Scheme 2.3: ART approach to access a) chiral piperidines and b) fluorinated ones

Our group has previously developed a new approach to access chiral piperidines *via* asymmetric reductive transamination (ART).[25] The key to this novel reduction of pyridine derivatives is the introduction of a chiral secondary amine under reducing conditions. The amine undergoes transamination and replaces the original nitrogen moiety, inducing chirality on ring (Scheme 2.3a). Although ethyl amine is more nucleophilic than (*R*)-PEA, based on their pKa values (10.7 vs 9.7), (*R*)-PEA has ten equivalents relative to ethylamine and is therefore more likely for condensation with the ring-opened intermediate. The result was also verified by a 6.1:1 ratio of the transamination product to *N*-ethyl

piperidine, ca. 14% of *N*-ethyl piperidine was observed in the crude sample (Figure 2.1).

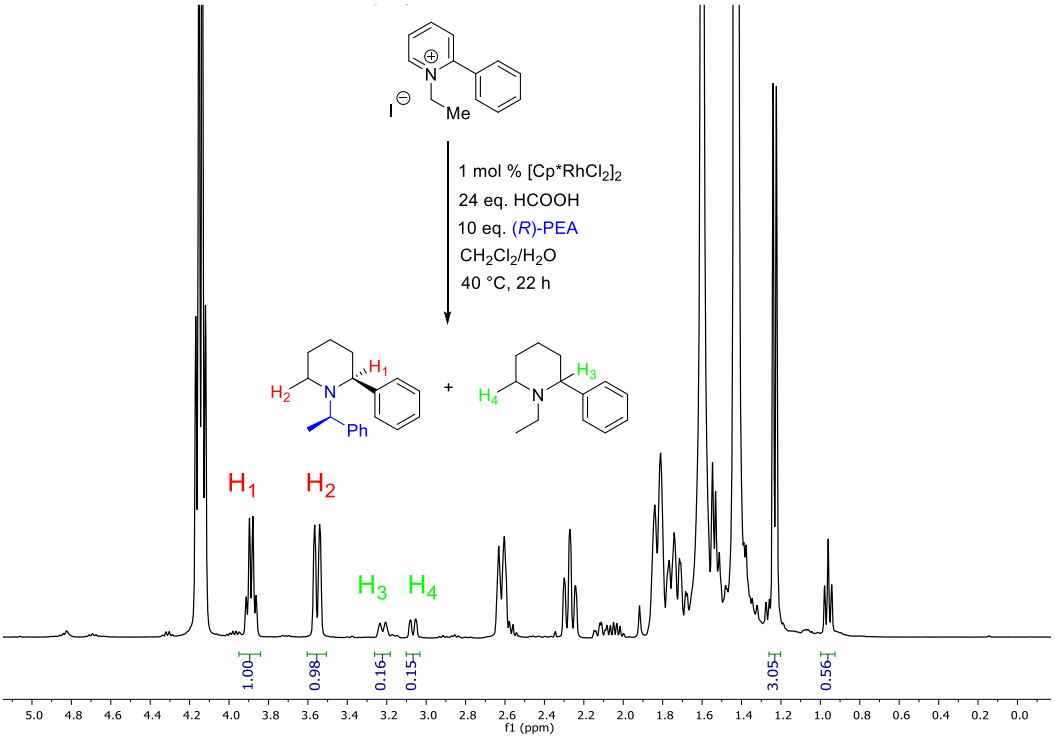


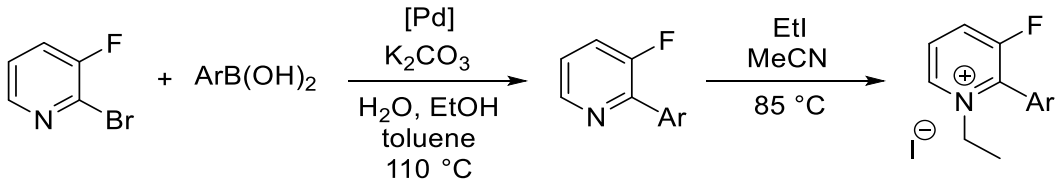
Figure 2.1: ^{1}H NMR spectrum of crude reaction mixture resulting from the reaction of *N*-ethyl-2-phenylpyrdinium iodide with (*R*)-PEA under the standard conditions.

Various 2-substituted pyridinium salts were reduced to their corresponding chiral piperidines with the exchange of ethylimido fragment by (*R*)-1-phenylethylimido. We hypothesised that the chiral amine could be used to induce chirality for an additionally substituted pyridines. The reaction could provide a straightforward catalytic route to access chiral fluorinated piperidine from its pyridine precursor (Scheme 2.3b).

2.2 Results and discussion

2.2.1 Structural identification of fluorinated piperidines

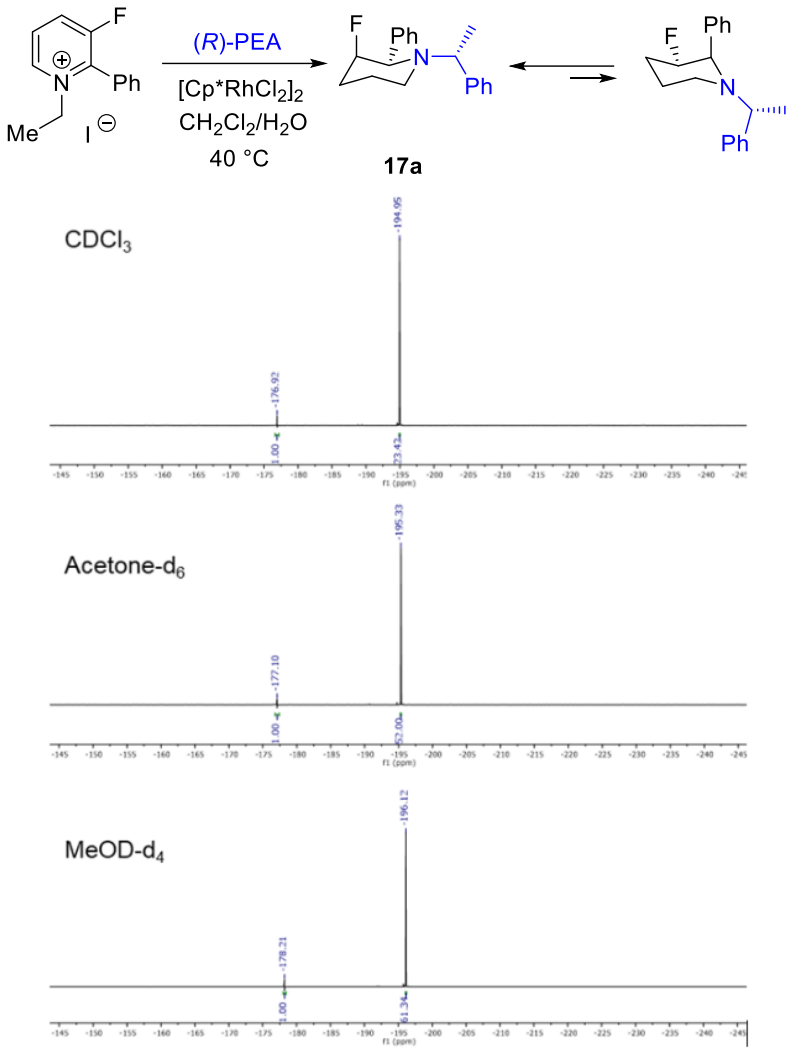
Our investigations began by synthesising 3-fluorinated pyridinium salts as starting materials from cheap and commercially available 2-bromo-3-fluoro pyridine *via* efficient Suzuki-Miyaura coupling reactions, followed by quaternisation with ethyl iodide to afford the crystalline solids (Scheme 2.4). All substrates were satisfactorily characterised by ^{1}H NMR spectra.



Scheme 2.4: General procedures for the preparation of pyridinium salts

The initial attempt to produce chiral piperidines were conducted using formic acid as hydrogen donor, $[Cp^*RhCl_2]_2$ as the catalyst for the ART of 2-phenyl-3-fluoropyridinium salt in CH_2Cl_2/H_2O mixture at 40 °C. These are the conditions that have been developed for the ART of 2-arylpyridinium salts.[25] The desired piperidine **17a** was obtained in a high yield of 80%. As shown in the $^{19}F\{^{1}H\}$ spectra, this compound exists as two equilibrating conformational isomers observable in solution (Scheme 2.5). The spectra show two singlets with a ratio varied with deuterated solutions, 1:23 in $CDCl_3$, 1:52 in acetone-d_6 and 1:61 in MeOD-d_4. The formation of two conformers can be verified by conducting

variable-temperature NMR analysis. At elevated temperatures, interconversion among conformers is accelerated, resulting in an averaged signal from equivalent peaks, whilst the integration of peaks from different diastereomers would be unaffected.



Scheme 2.5: ART to form piperidine **17a** and its conformational isomers revealed by $^{19}F\{^{1}H\}$ NMR spectrum

The X-ray spectroscopy shows that compound **17a** has a *cis* configuration between the phenyl and fluorine substituents. The orientation of the fluorine in the major isomer is assigned as axial due to the large value of $^{3}J_{H\text{-}F}$ in the ^{1}H NMR spectrum,[23,24] and this is also supported by a 2D-FH-HOESY analysis and is consistent with the solid-state X-ray structure (Figure 2.2). When 99% *ee* of (*R*)-PEA was used, the debenzylation of **17a** yielded (*2R,3R*)-3-fluoro-2-phenylpiperidine in 98% *ee*, showing the ART to be highly diastereoselective.

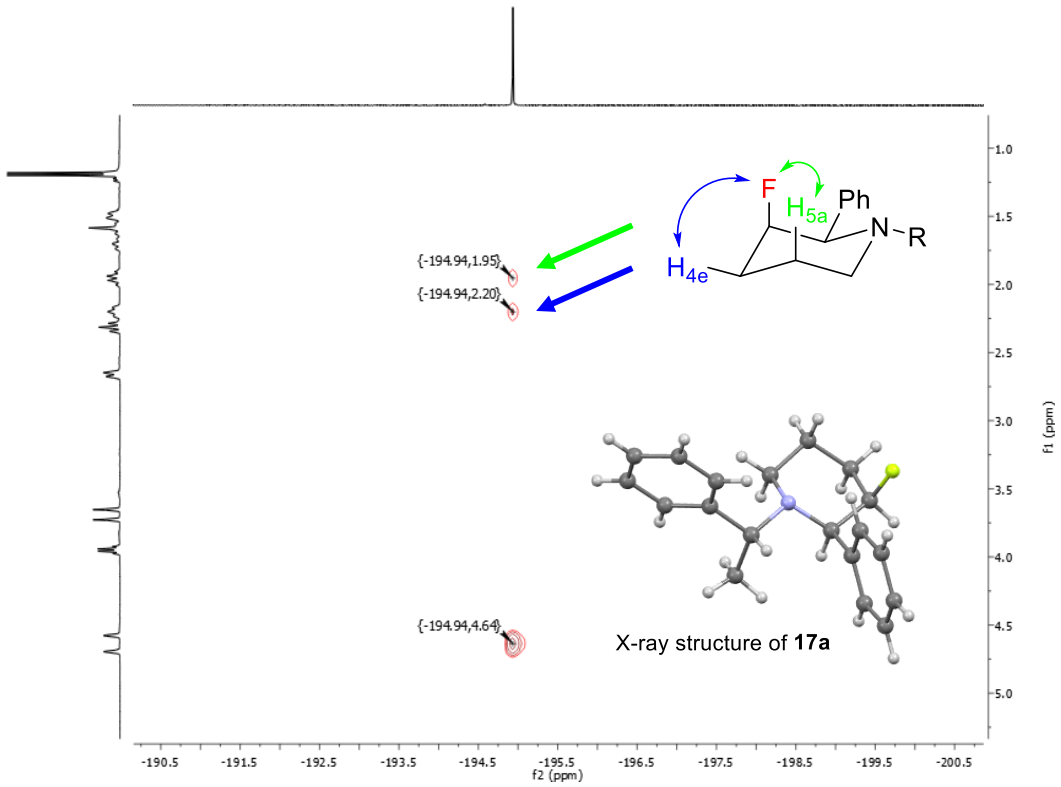


Figure 2.2: 2D FH-HOESY spectrum and X-ray structure of compound **17a**

2.2.2 Substrate scope

Under the standard conditions, the reaction proceeded smoothly with functionalised pyridinium salts bearing fluorine substituent, affording the corresponding fluorinated piperidines in good yields. The results are shown in Table 2.1. A series of potentially reducible functional groups were well-tolerated in the reduction process, such as halide, cyano (**17e**), nitro (**17g**), ketone (**17m**), ester (**17n**) and alkene (**17o**). Heterocyclic substituents like furan (**17v**) and thiophene (**17w**) also gave good yields. Furthermore, 5-fluorinated piperidines (**17x**, **y**) also could be obtained, albeit in diminished yields, from their pyridinium salts under the standard conditions. The addition of $Mg(OMe)_2$ as an additive to the reaction system has been found beneficial for the production of the desired products. The similar effect has also been recorded by Donohoe and co-workers when they conducted reductive C3 functionalisation of pyridinium salts.[26] The diastereomers of the fluorinated piperidines can be distinguished from $^{19}F\{^1H\}$ NMR spectra as they only show singlets for products studied, which can be unambiguously assigned and integrated with high accuracy. All the 3-fluoropiperidines show two observable singlets between -170 and -200 ppm in the $^{19}F\{^1H\}$ NMR spectra, one small and one significantly bigger. This has been assigned to equilibrating conformational isomers (see Scheme 2.5). The absence of other peaks in this region is also a good indication of the high diastereoselectivity of the reaction.

However, the reaction was less stereoselective for 5-fluorinated piperidines, affording mixtures of several isomeric products with over 70% yields. The major isomers **17x** and **17y** were isolated in *ca.* 40% yield. Taking **17x** as an example, the crude NMR spectra show three possible diastereomers with ratios of 4:2.2:1 in the $^{19}F\{^{1}H\}$ NMR and 3.6:2.4:1 in the ^{1}H NMR (proton at C5 position). The singlet peak at -188 ppm in the $^{19}F\{^{1}H\}$ NMR spectrum represents the major *cis* (2*S*,5*S*) piperidine (Figure 2.3, right). This assignment is supported by NMR analysis after isolation and is consistent with the solid-state X-ray structure (see appendix section). The minor product at -178 ppm, which was isolated in 18% yield, could be assigned to the *trans* (2*S*,5*R*) piperidine based on NMR analysis. The ^{3}J(H-H) couplings at around 10 Hz indicate the axial orientations for both H_{2a} and H_{5a}. Therefore, both fluorine and phenyl substituents are in the equatorial positions (Figure 2.3, left). The third product could not be isolated due to its low yield (< 10%). The similar splitting and chemical shifts from the crude ^{1}H and $^{19}F\{^{1}H\}$ NMR spectra between the major and this unknown product suggest an axial orientation of fluorine and an equatorial orientation of the phenyl substituent in the latter, meaning the formation of a *cis* (2*R*,5*R*) product (Figure 2.3, middle). The formation of this possible minor product is disfavoured by the 1,3-allylic strain in the transition state, which may explain the low yield. A possible fourth diastereomer, *trans* (2*R*,5*S*) piperidine, was not observed, possibly due to an even less favourable transition state (Scheme 2.6). Compounds **17y** showed similar results to **17x** by NMR analysis.

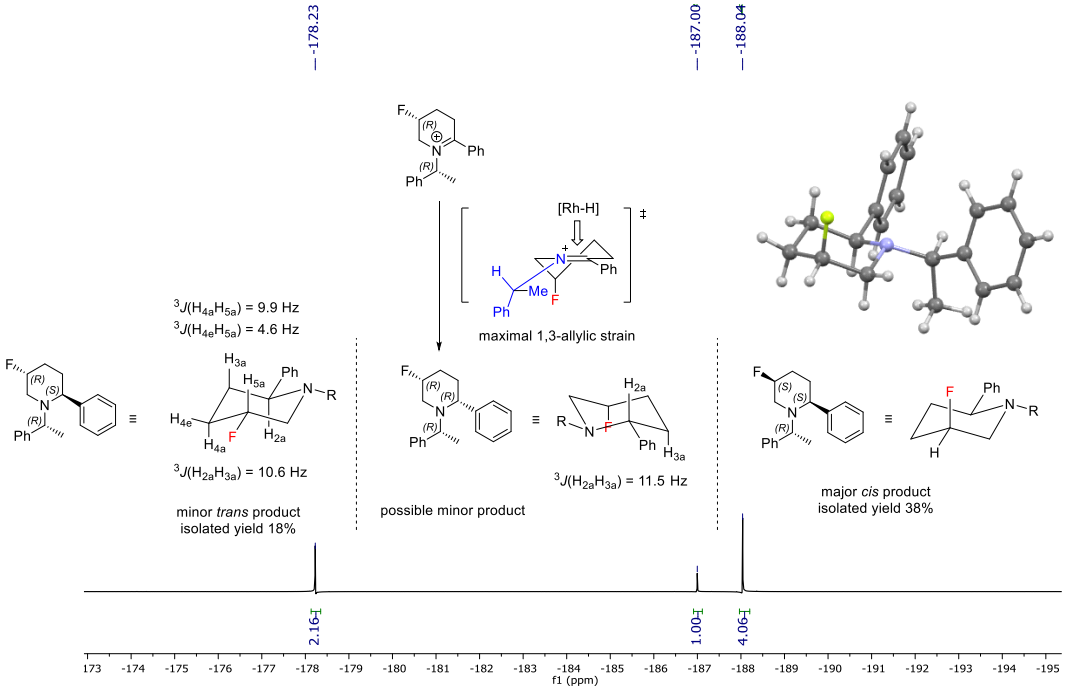
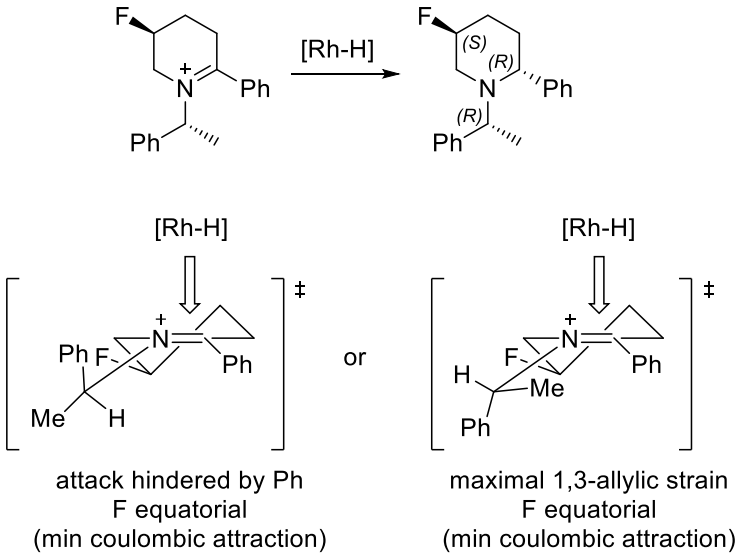


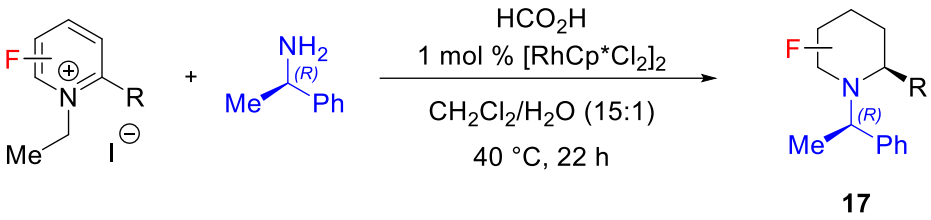
Figure 2.3: Structural analysis of diastereomers of **17x**



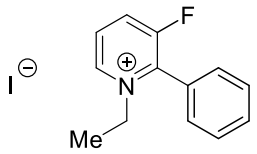
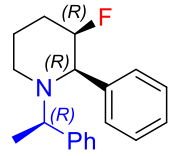
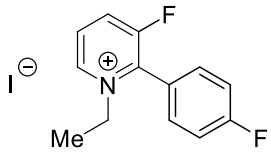
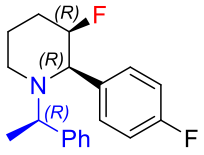
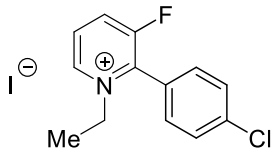
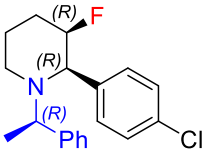
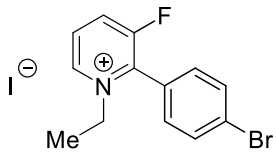
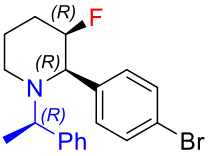
Scheme 2.6: The possible transition states of the disfavoured *trans* (2*R*,5*S*) diastereomer

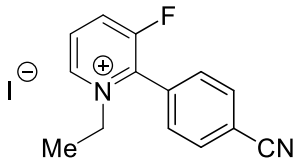
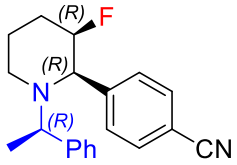
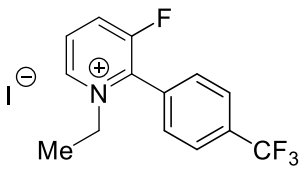
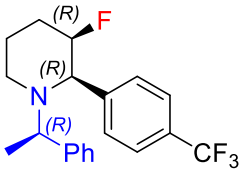
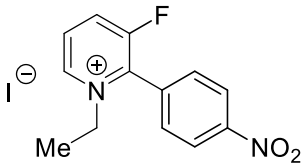
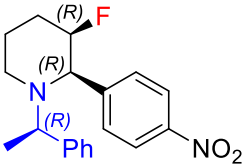
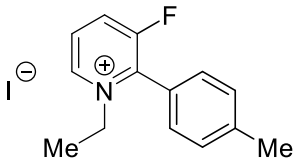
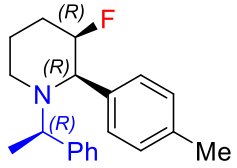
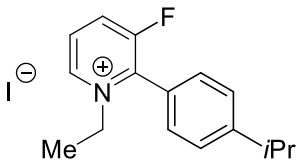
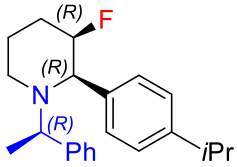
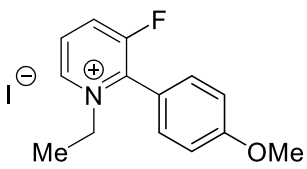
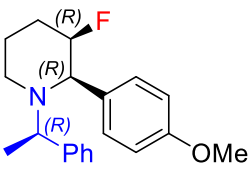
Overall, the ART reaction provides an novel and effective approach of introducing fluorine into piperidine core, including drug candidates or analogues of current medicines, such as MK-0731,[27] Bradykinin B1 antagonist (Merck),[28] NK1 receptor antagonist[29] and PARP-1/-2 inhibitor (Abbott).[30]

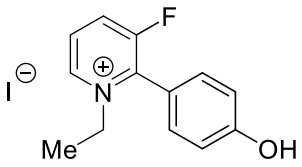
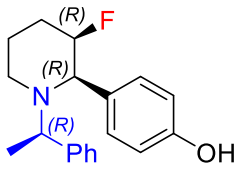
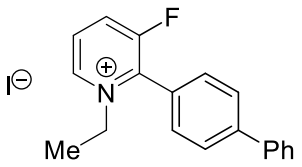
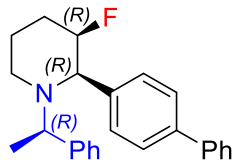
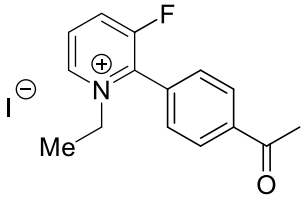
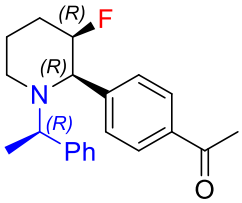
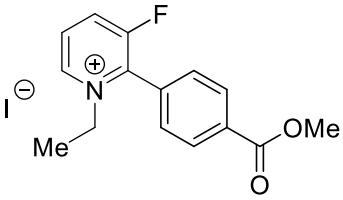
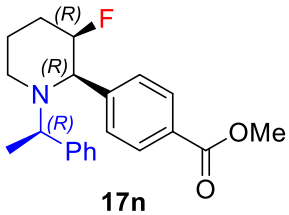
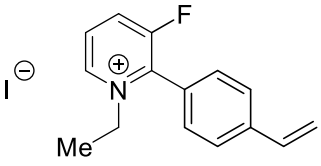
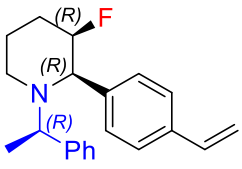
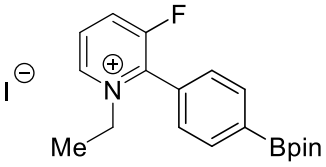
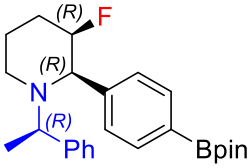
Table 2.1: Asymmetric reductive transamination to access fluorinated piperidines[a]

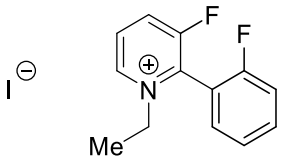
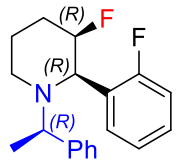
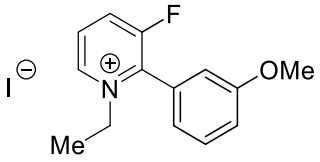
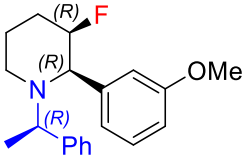
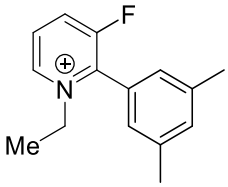
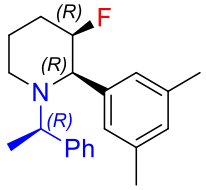
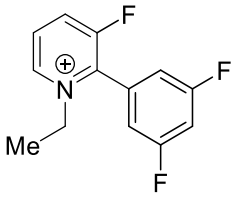
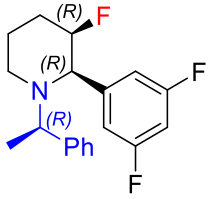
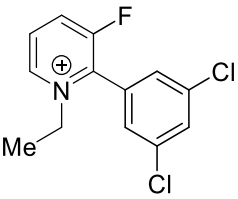
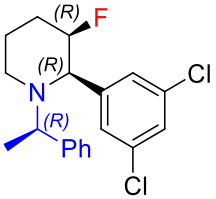
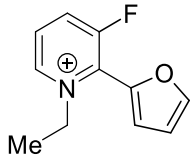
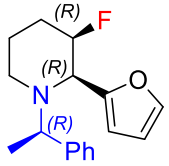


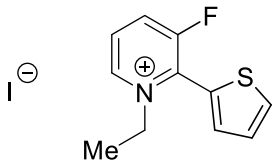
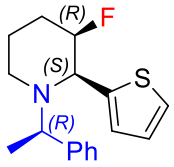
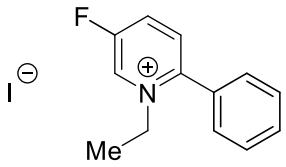
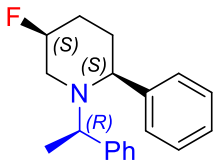
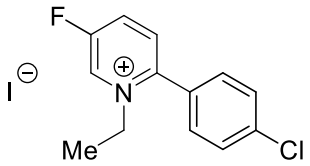
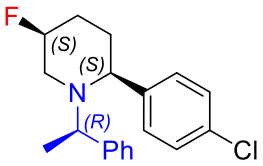
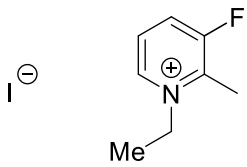
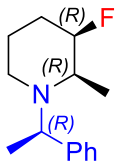
17

Entry	Substrate	Product	Yield (%)[b]
1		 **17a**	80
2		 **17b**	83
3		 **17c**	67
4		 **17d**	80

Entry	Substrate	Product	Yield (%)[b]
5		 **17e**	34
6		 **17f**	66
7		 **17g**	30
8		 **17h**	83
9		 **17i**	99
10		 **17j**	86

Entry	Substrate	Product	Yield (%)[b]
11		 **17k**	98
12		 **17l**	76
13		 **17m**	35
14		 **17n**	40
15		 **17o**	75[c]
16		 **17p**	51

Entry	Substrate	Product	Yield (%)[b]
17		 **17q**	62
18		 **17r**	91
19		 **17s**	83
20		 **17t**	51
21		 **17u**	32
22		 **17v**	67

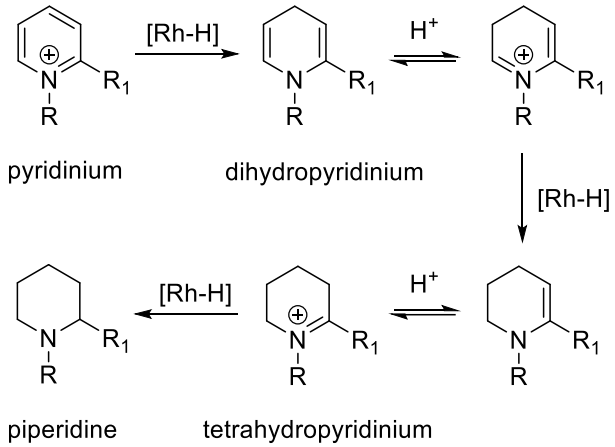
Entry	Substrate	Product	Yield (%)[b]
23		 **17w**	76
24		 **17x**	38[d] d.r. 4:2.2:1[e]
25		 **17y**	42[d] d.r. 4:2:1[e]
26		 **17z**	64

[a] All reactions were carried out under the standard conditions: substrate (0.5 mmol), $[Cp^*RhCl_2]_2$ (1 mol%), HCO_2H (12 mmol), (*R*)-PEA (5 mmol), CH_2Cl_2/H_2O = 15:1 (4.0 mL), 40 °C, 22 h, in air. [b] Isolated yields. [c] Reaction performed for 12 h. [d] 1 equiv. of $Mg(OMe)_2$ added. [e] The d.r. values were determined by the integration of peaks from different diastereomers in the $^{19}F\{^1H\}$ NMR spectra.

2.2.3 Mechanistic investigations

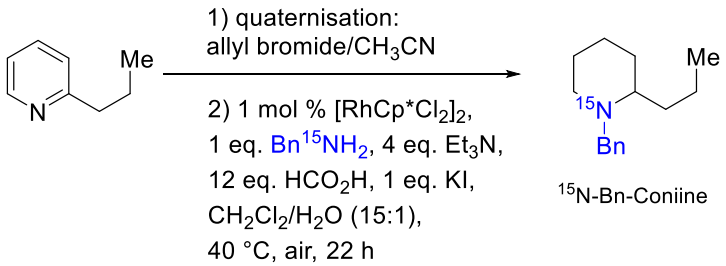
Based on the previous study [31] and earlier mechanistic investigations,[32,33] the TH of pyridinium salts catalysed by $[Cp^*RhCl_2]_2$ is likely to start with a 1,4-

addition of a rhodium hydride to produce 1,4-dihydropyridinium, followed by enamine isomerisation to an iminium species which is then reduced *via* a 1,2-addition to generate piperidines (Scheme 2.7).



Scheme 2.7: Rhodium catalysed TH of pyridinium salts with the hydride derived from formate

The retention of chirality from (*R*)-PEA and the experiment on the incorporation of ^{15}N-benzylamine to the hydrogenated piperidine ring clearly point out that the mechanism must involve a transamination process in which the imido fragment is exchanged with the new amine source (Scheme 2.8).



Scheme 2.8: The incorporation of ^{15}N into piperidine during reductive transamination (prepared by Dr. Xiaofeng Wu)

A control reaction also demonstrates the significance of water during the catalysis. The key step for the transamination mechanism involves the interception of the dihydropyridinium ion by water, which leads to ring opening of the dihydropyridine and then subsequent amine exchange. In addition, under the reducing conditions, the NMR analysis shows that a possible intermediate **18** (prepared by Dr. Jianjun Wu) is in equilibrium with its ring-opening form **19** in the presence of adventitious water in the solvent. Mass spectrum also supports the existence of compound **19** with a mass peak as *m/z* 206.18 (Figure 2.4). Experiments showed that **18** can be reduced but cannot undergo ART. Thus, the amine exchange must occur in a previous step (dihydropyridinium). The formation of **19** shows that water can ring-open the six-membered ring.

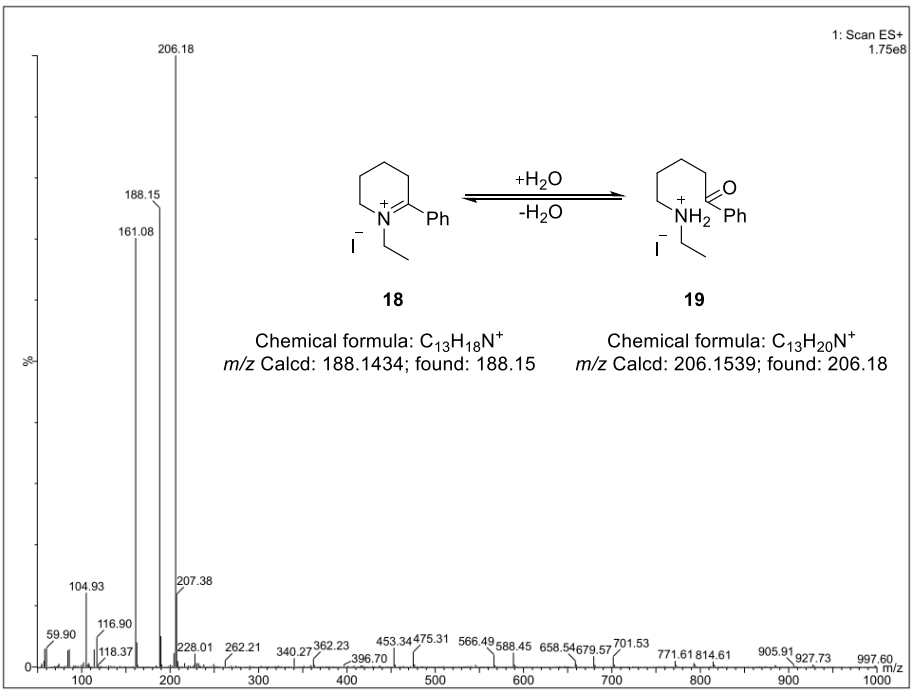


Figure 2.4: Mass spectrum of intermediate **18** and its ring-opening form **19**

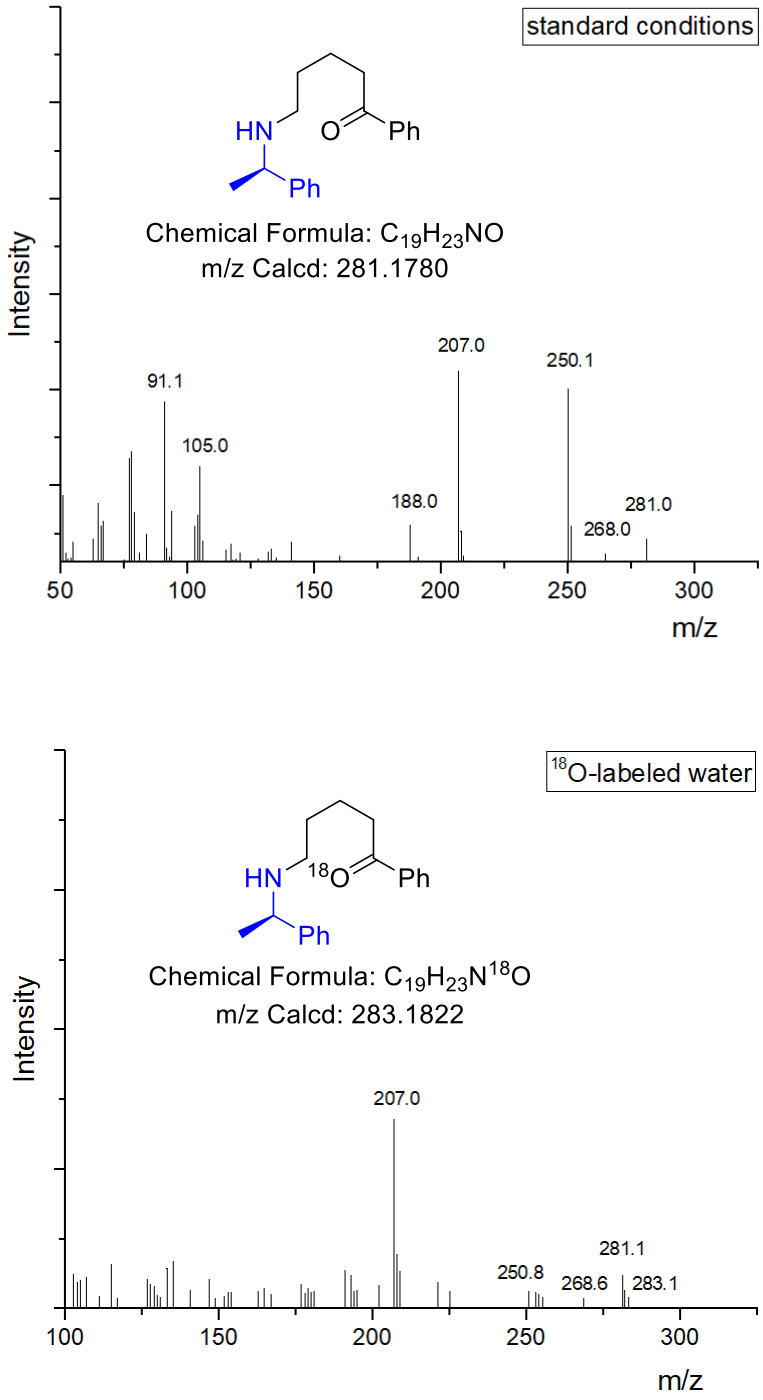
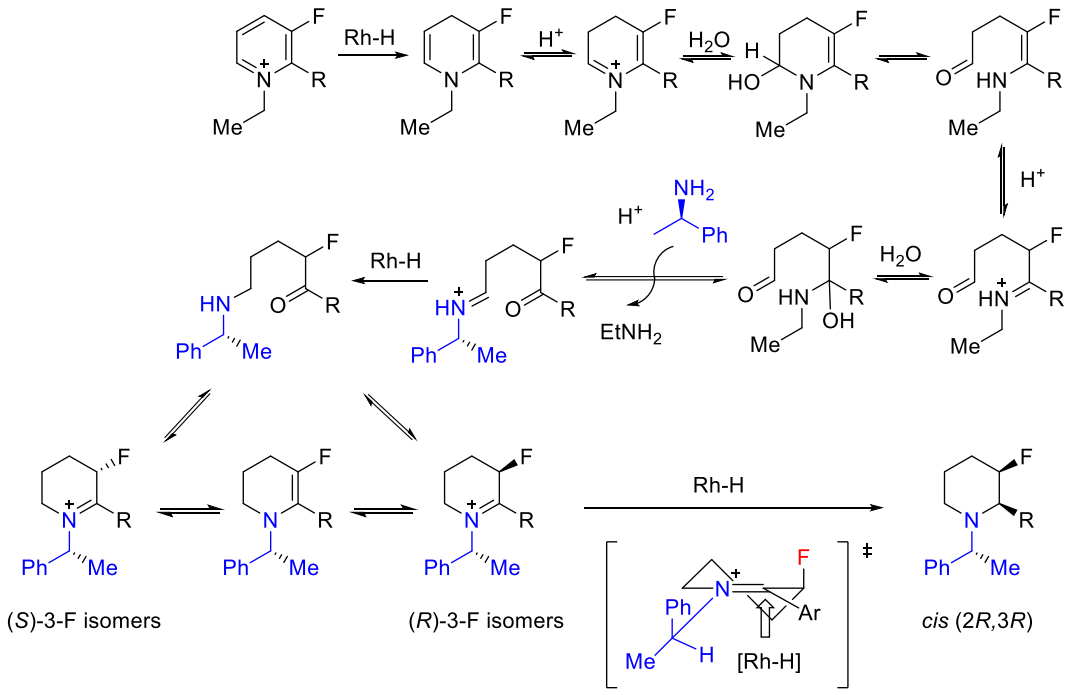


Figure 2.5: MS spectra of reaction intermediate under standard conditions (above) and ^{18}O-labeled water (below).

Under the ART conditions, two further experiments were performed, one using normal water and the other using ^{18}O-labeled water, and the reactions were stopped in 45 min. Both reaction mixtures were analysed with GC-MS. The MS spectra are shown in Figure 2.5, which support the formation of the suggested amino ketone intermediate. In the case of $H_2{}^{18}O$, the peak at *m/z* 281.1 results mostly likely from H_2O in the system.

In the light of the above observations, a mechanism for the ART of fluorinated pyridinium salts is proposed (Scheme 2.9). Under the reducing conditions, the substrate undergoes 1,4-addition by the Rh-H hydride species, and the resulting enamine isomerises to an iminium species. In the presence of water, dihydropyridine becomes its ring-opened form and extrudes the ethylamine fragment *via* acid-assisted hydrolysis. Condensation of the new amine (*R*)-PEA with the ring-opened compound occurs, and following the ring closure, reduction give the desired piperidine products. A dynamic kinetic resolution process *via* fast iminium-enamine isomerisation is proposed to occur at the final stage, providing access to both the (*R*)-3-F and (*S*)-3-F isomers. Out of the possible modes of hydride addition to the two equilibrating iminium diastereomers, the transition state suggested in Scheme 2.8 is of lowest energy barrier, which involves a minimal 1,3-allylic strain while provides maximal coulombic attraction.[34,35] As is clear, the metal hydride attacks opposite the axial fluorine, yielding the *cis* (2*R*,3*R*)diastereomer.



Scheme 2.9: Proposed mechanism for Rh-catalysed ART of fluorinated pyridinium salts

2.3 Conclusion

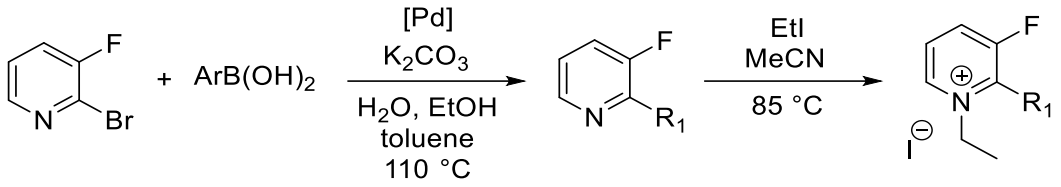
We have extended our new approach, ART reaction, to the synthesis of chiral fluorinated piperidines from easily available pyridinium salts. The reaction tolerates a wide range of substituents, even potentially reducible functionalities, and is operationally simple by using an air- and moisture-stable catalyst, affording valuable chiral fluorinated piperidines with excellent enantiomeric excess. The mild reaction conditions provide a great opportunity for the synthesis of potential fluoro- and piperidine-containing drug candidates or the late-stage modification of existing pharmaceuticals.

2.4 Experimental

2.4.1 General information

Unless otherwise specified, the chemicals were purchased from commercial suppliers (Sigma-Aldrich, Alfa Aesar, Fluorochem, Apollo Scientific and TCI) and used without further purification. Dichloromethane was used as purchased. Silica gel plates (GF254) were used for TLC monitoring and silica gel (230-400 mesh) was used for running column chromatography. NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer with TMS as the internal standard. The mass spectra were obtained by chemical ionization (CI). The mass spectra were obtained using a Thermo Finnigan Trio-1000 Mass spectrometer. HPLC analysis was performed on Gilson UV/VIS-151 or Shimadzu LC-20A UV/VIS equipped with an OJ-H or AD-H or OX-H column purchased from Daicel Chemical Industries. The configurations of selected products were assigned by X-ray diffraction and/or NMR analysis and those of the rest by analogy.

2.4.2 Preparation of fluorinated pyridinium salts



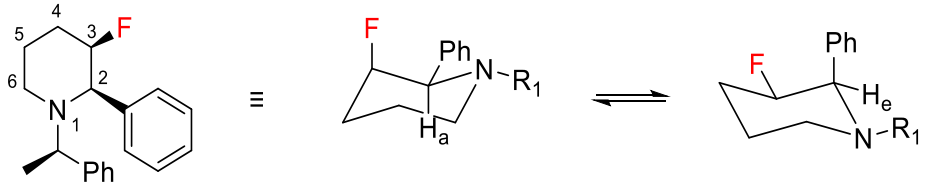
Suzuki-Miyaura coupling procedure: To a two-necked flask containing 2-bromo-3-fluoropyridine (4.0 mmol) was added arylboronic acid (5.0 mmol) followed by addition of $(PdPPh_3)_4$ (3 mol%) and K_2CO_3 (12 mmol). The resulting mixture was dissolved in toluene (7 mL), water (7 mL) and EtOH (1.5 mL) under N_2 atmosphere, and refluxed overnight. After completion, the reaction mixture was cooled to room temperature, and NH_4Cl aqueous solution was added to the flask. The reaction mixture was extracted with EtOAc for three times, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and purified by flash chromatography on silica gel with hexane/EtOAc.

Pyridinium salts preparation procedure: To a carousel reaction tube containing a substituted pyridine (3.0 mmol) was added ethyl iodide (6.0 mmol) followed by introducing acetonitrile (4.0 mL). The mixture was stirred at 85 °C in the dark for 18-24 h. After completion, the solvent was removed under reduced pressure, followed by addition of ethyl acetate. The resulting suspension was filtered, and the solid was washed with diethyl ether and dried under vacuum to give the *N*-ethyl pyridinium iodide salt as crystalline solid.

2.4.3 General procedure for ART of fluorinated pyridiniums

To a carousel reaction tube containing a magnetic stirring bar and (*R*)-1-phenylethylamine (615 mg, 5 mmol) was added formic acid (564 mg, 12 mmol) dropwise at room temperature. After stirring the amine/acid mixture for 10 min, a pyridinium salt, *N*-ethyl-2-phenyl-3-fluoropyridinium iodide (157 mg, 0.5 mmol), $[Cp^*RhCl_2]_2$ (3.1 mg, 5 μmol), 3.75 mL of CH_2Cl_2 and 0.25 mL of distilled H_2O were introduced into the mixture. The reaction system was placed in a carousel reactor. The mixture was stirred at 40 °C for 22 h, cooled to room temperature and then basified with an aqueous solution of KOH. The resulting mixture was extracted with ethyl acetate (3×10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane) to give the desired product.

2.5 Analytic data of isolated products



(2*R*,3*R*)-3-Fluoro-2-phenyl-1-((*R*)-1-phenylethyl)piperidine (17a):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (113.3 mg, 80%) after column

chromatography (silica gel, eluent: n-hexane/EtOAc 40:1). The compound exists as two conformational isomers, as indicated by the $^{19}F\{^{1}H\}$ spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of $^{3}J(F, H_a)$.[23,24]

[^{3}J**(3-F, 2-H$_a$) = 29.8 Hz**]

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.57 (d, *J* = 7.5 Hz, 2H), 7.51 (d, *J* = 7.8 Hz, 2H), 7.42-7.28 (m, 5H), 7.25-7.17 (m, 1H), 4.61 (d, *J* = 47.5 Hz, 1H), 3.92 (q, *J* = 6.8 Hz, 1H), 3.66 (d, *J* = 29.8 Hz, 1H), 2.66 (dm, *J* = 10.6 Hz, 1H), 2.38-2.26 (m, 1H), 2.26-2.14 (m, 1H), 1.95 (dm, *J* = 12.8 Hz, 1H), 1.77-1.54 (m, 1H), 1.50 (dm, *J* = 12.4 Hz, 1H), 1.16 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ (ppm):** -194.95; **^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm):** 144.16, 139.81, 129.17 (d, *J* = 2.3 Hz), 128.28, 127.90, 127.61, 127.46, 126.22, 90.44 (d, *J* = 180.5 Hz), 68.30 (d, *J* = 16.4 Hz), 54.72, 44.71, 30.39 (d, *J* = 22.3 Hz), 20.33, 7.78; **HRMS for C$_{19}$H$_{23}$FN [M+H]$^+$:** m/z calcd 284.1809, found 284.1808.

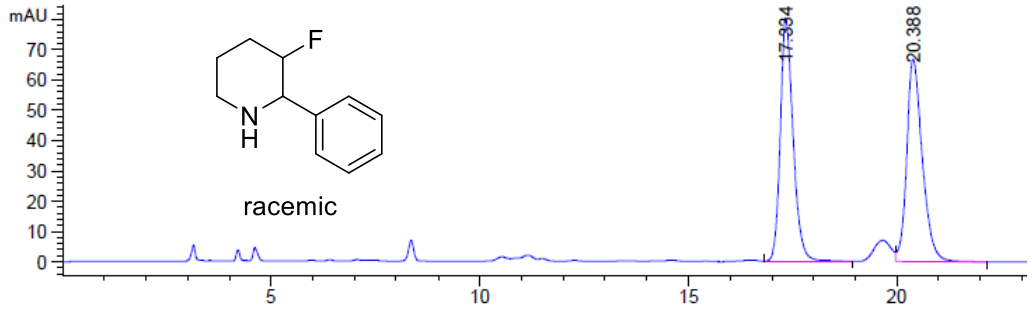
Debenzylation of 17a

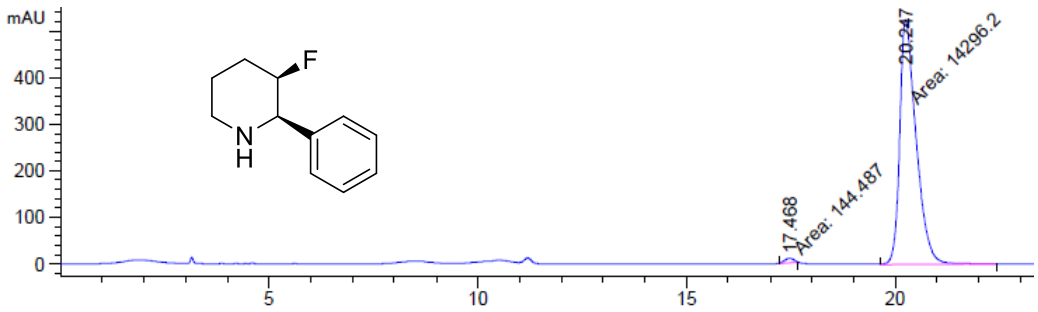
A mixture of **17a** (141.6 mg, 0.5 mmol), Pd/C (14.2 mg, 10 wt%), EtOH (5 mL) and 6N HCl aq. (0.2 mL) was stirred at 60 °C under H_2 balloon (1 atm) for overnight. After carefully releasing the hydrogen, the reaction mixture was filtered over celite and the filtrate was concentrated in vacuum. The residue was basified with an aqueous solution of KOH, extracted with DCM, washed with brine and

dried over Na_2SO_4. The solvent was removed in vacuum to afford the debenzylated product.

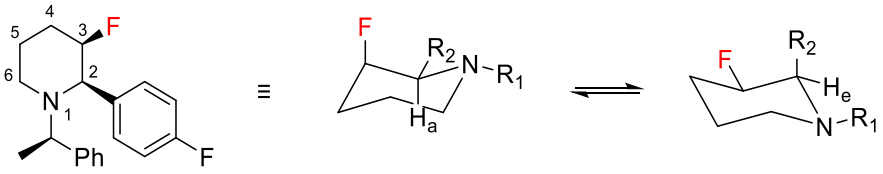
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.48 – 7.31 (m, 5H), 4.81 (d, *J* = 47.5 Hz, 1H), 3.87 (d, *J* = 30.7 Hz, 1H), 3.33 (dm, *J* = 12.7 Hz, 1H), 2.91 (tm, *J* = 11.8 Hz, 1H), 2.38 – 2.11 (m, 2H), 1.97 – 1.69 (m, 2H), 1.66 – 1.53 (m, 1H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -200.71; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 139.94, 128.54, 127.77, 127.39 (d, *J* = 1.5 Hz), 89.14 (d, *J* = 177.6 Hz), 63.14 (d, *J* = 18.4 Hz), 46.35, 29.93 (d, *J* = 21.9 Hz), 20.02; **HRMS for $C_{11}H_{15}FN$ $[M+H]^+$:** m/z calcd 180.1183, found 180.1186.

The enantiomeric excess, 98% *ee* (99% *ee* PEA used), was determined by HPLC analysis: Chiralpak OJ-H column, n-hexane/*i*-propanol = 95:5, flow rate = 1.0 mL/min, 220 nm UV detector, t = 17.47 min (minor), t = 20.39 min (major).





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.466	MM	0.2700	42.17005	2.60274	1.1240
2	20.246	BB	0.4005	3709.61230	136.75410	98.8760

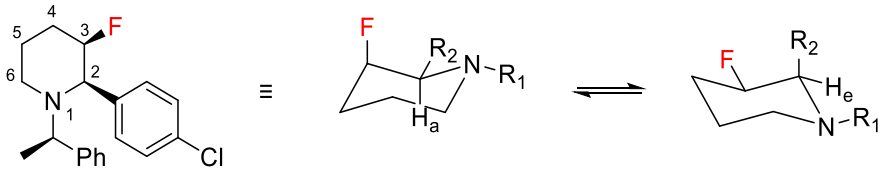


(2*R*,3*R*)-3-Fluoro-2-(4-fluorophenyl)-1-((*R*)-1-phenylethyl)piperidine (17b):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (124.9 mg, 83%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 35:1). The compound exists as two conformational isomers, as indicated by the $^{19}F\{^{1}H\}$ spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of $^{3}J(F, H_a)$.

[^{3}J(3-F, 2-H$_a$) = 29.6 Hz]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.59-7.52 (m, 2H), 7.49 (d, *J* = 7.7 Hz, 2H), 7.36-7.29 (m, 2H), 7.26-7.20 (m, 1H), 7.09-6.99 (m, 2H), 4.58 (d, *J* = 47.5 Hz, 1H), 3.87 (q, *J* = 6.9 Hz, 1H), 3.66 (d, *J* = 29.6 Hz, 1H), 2.69-2.58 (m, 1H), 2.35-2.24 (m, 1H), 2.24-2.11 (m, 1H), 2.00-1.84 (m, 1H), 1.74-1.53 (m, 1H), 1.47 (dm, *J* = 13.2 Hz, 1H), 1.17 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -114.96, -195.16; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 162.28 (d, *J* = 245.6 Hz), 143.95, 135.50 (d, *J* = 3.2 Hz), 130.61 (dd, *J* = 8.0, 2.6 Hz), 127.97, 127.40, 126.32, 115.15 (d, *J* = 21.2 Hz), 90.42 (d, *J* = 180.4 Hz), 67.41 (d, *J* = 16.5 Hz), 54.68, 44.68, 30.31 (d, *J* = 22.3 Hz), 20.26, 7.79; **HRMS for $C_{19}H_{22}F_2N$ $[M+H]^+$:** m/z calcd 302.1715, found 302.1717.

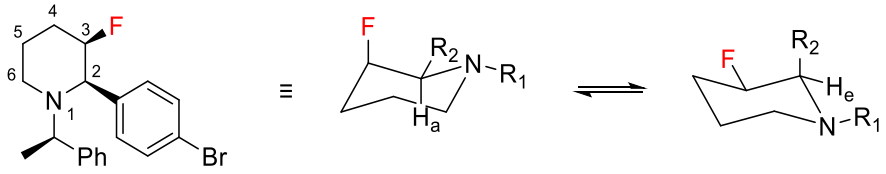


(2*R*,3*R*)-2-(4-Chlorophenyl)-3-fluoro-1-((*R*)-1-phenylethyl)piperidine (17c):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (106.2 mg, 67%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 35:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H_a).

[^{3}J(3-F, 2-H_a) = 29.4 Hz]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.51 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.37-7.29 (m, 4H), 7.27-7.18 (m, 1H), 4.57 (d, *J* = 46.8 Hz, 1H), 3.86 (q, *J* = 6.8 Hz, 1H), 3.65 (d, *J* = 29.4 Hz, 1H), 2.63 (dm, *J* = 11.2 Hz, 1H), 2.34-2.23 (m, 1H), 2.23-2.10 (m, 1H), 1.91 (dm, *J* = 12.8 Hz, 1H), 1.73-1.51 (m, 1H), 1.47 (dm, *J* = 12.9 Hz, 1H), 1.16 (d, *J* = 6.9 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -195.08; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 143.81, 138.32, 133.30, 130.45 (d, *J* = 2.7 Hz), 128.50, 127.98, 127.38, 126.35, 90.24 (d, *J* = 180.7 Hz), 67.53 (d, *J* = 16.3 Hz), 54.80, 44.61, 30.26 (d, *J* = 22.3 Hz), 20.21, 7.83; **HRMS for $C_{19}H_{22}{}^{35}ClFN$ $[M+H]^+$:** m/z calcd 318.1419, found 318.1418.

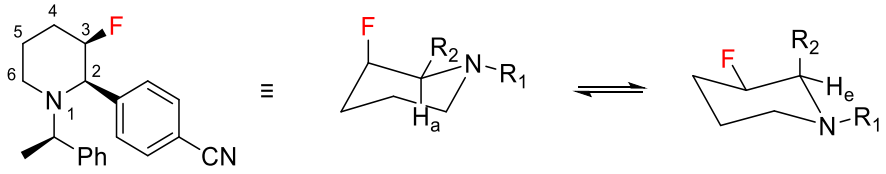


(2*R*,3*R*)-2-(4-Bromophenyl)-3-fluoro-1-((*R*)-1-phenylethyl)piperidine (17d):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (144.4 mg, 80%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 35:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H_a).

[**^{3}J(3-F, 2-H_a) = 29.4 Hz**]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.52-7.43 (m, 6H), 7.36-7.29 (m, 2H), 7.25-7.19 (m, 1H), 4.57 (d, *J* = 47.5 Hz, 1H), 3.86 (q, *J* = 6.9 Hz, 1H), 3.64 (d, *J* = 29.4 Hz, 1H), 2.70-2.57 (m, 1H), 2.32-2.23 (m, 1H), 2.23-2.10 (m, 1H), 1.91 (dm, *J* = 12.7 Hz, 1H), 1.76-1.51 (m, 1H), 1.50-1.39 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -195.07; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 144.22, 139.30, 131.90, 131.27 (d, *J* = 2.6 Hz), 128.43, 127.82, 126.80, 121.89, 90.60 (d, *J* = 180.8 Hz), 68.04 (d, *J* = 16.5 Hz), 55.27, 45.04, 30.68 (d, *J* = 22.1 Hz), 20.64, 8.28; **HRMS for $C_{19}H_{22}BrFN$ $[M+H]^+$:** m/z calcd 362.0914 and 364.0894, found 362.0913 and 364.0897.



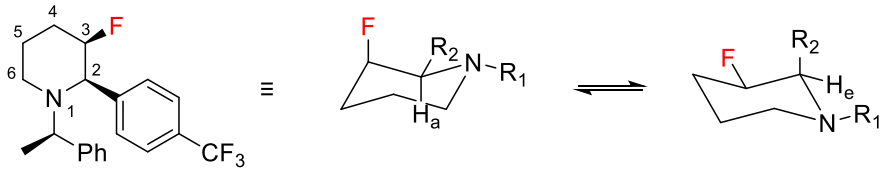
4-((2*R*,3*R*)-3-Fluoro-1-((*R*)-1-phenylethyl)piperidin-2-yl)benzonitrile (17e):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (52.4 mg, 34%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 30:1).The orientation of the fluorine atom is assigned as axial due to the large value of ^{3}J(F, H_a).

[**^{3}J(3-F, 2-H_a) = 25.2 Hz**]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.74-7.59 (m, 4H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.37-7.30 (m, 2H), 7.25-7.20 (m, 1H), 4.57 (d, *J* = 47.5 Hz, 1H), 3.78 (q, *J* = 6.8 Hz, 1H), 3.73 (d, *J* = 25.2 Hz, 1H), 2.72-2.57 (m, 1H), 2.34-2.25 (m, 1H), 2.23-

2.13 (m, 1H), 1.92 (dm, *J* = 12.8 Hz, 1H), 1.75-1.53 (m, 1H), 1.52-1.45 (m, 1H), 1.17 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ (ppm):** -194.87; **^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm):** 145.42, 143.31, 132.14, 129.87 (d, *J* = 2.4 Hz), 128.09, 127.27, 126.55, 118.83, 111.54, 89.79 (d, *J* = 181.6 Hz), 67.91 (d, *J* = 16.5 Hz), 55.16, 44.43, 30.09 (d, *J* = 22.2 Hz), 20.01, 7.98; **HRMS for $C_{20}H_{22}FN_2$ [M+H]$^+$:** m/z calcd 309.1762, found 309.1761.



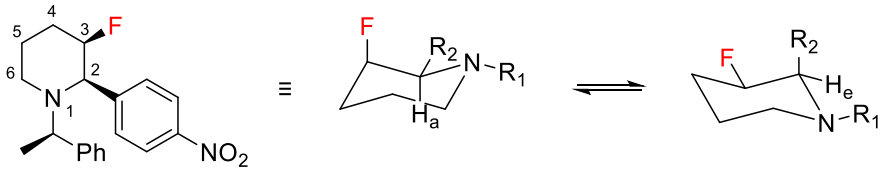
(2*R*,3*R*)-3-Fluoro-1-((*R*)-1-phenylethyl)-2-(4(trifluoromethyl)phenyl) piperidine (17f):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a brown solid (115.9 mg, 66%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 35:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H$_a$).

[**^{3}J(3-F, 2-H$_a$) = 29.5 Hz**]

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.61 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 7.7 Hz, 2H), 7.28-7.21 (m, 2H), 7.17-7.11 (m, 1H), 4.50 (d, *J* = 47.9 Hz, 1H), 3.74 (q, *J* = 6.9 Hz, 1H), 3.67 (d, *J* = 29.5 Hz, 1H), 2.63-2.52 (m,

1H), 2.27-2.17 (m, 1H), 2.15-2.05 (m, 1H), 1.84 (dm, *J* = 12.7 Hz, 1H), 1.67-1.45 (m, 1H), 1.44-1.32 (m, 1H), 1.09 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -62.48, -194.95; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 143.94, 143.59, 129.87 (q, *J* = 32.3 Hz), 129.46 (d, *J* = 2.5 Hz), 128.03, 127.34, 126.45, 125.25 (q, *J* = 3.8 Hz), 124.19 (q, *J* = 271.8 Hz), 90.00 (d, *J* = 181.2 Hz), 67.86 (d, *J* = 16.5 Hz), 54.98, 44.53, 30.19 (d, *J* = 22.2 Hz), 20.13, 7.87; **HRMS for $C_{20}H_{22}F_4N$ $[M+H]^+$:** m/z calcd 352.1683, found 352.1696.



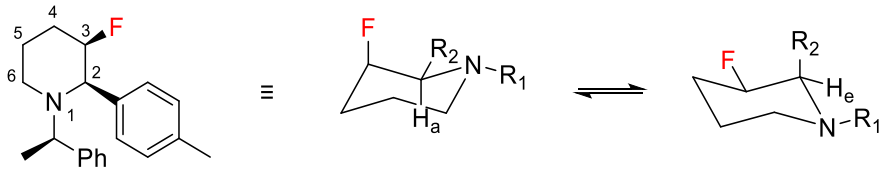
(2*R*,3*R*)-3-Fluoro-2-(4-nitrophenyl)-1-((*R*)-1-phenylethyl)piperidine (17g):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (49.2 mg, 30%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 10:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H_a).

[**^{3}J(3-F, 2-H_a) = 28.3 Hz**]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.14 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 7.9 Hz, 2H), 7.39 (d, *J* = 7.7 Hz, 2H), 7.31-7.22 (m, 2H), 7.18-7.10 (m, 1H), 4.50 (d, *J* = 47.8 Hz, 1H), 3.73 (d, *J* = 28.3 Hz, 1H), 3.69 (q, *J* = 6.9 Hz, 1H), 2.64-2.53 (m,

1H), 2.30-2.17 (m, 1H), 2.17-2.06 (m, 1H), 1.85 (dm, *J* = 12.8 Hz, 1H), 1.68-1.49 (m, 1H), 1.47-1.37 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -194.74; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 147.51, 143.21, 142.99, 129.95 (d, *J* = 2.6 Hz), 128.12, 127.27, 126.60, 123.55, 89.72 (d, *J* = 181.6 Hz), 67.63 (d, *J* = 16.5 Hz), 55.27, 44.41, 30.07 (d, *J* = 22.1 Hz), 19.99, 8.01; **HRMS for $C_{19}H_{22}FN_2O_2$ $[M+H]^+$:** m/z calcd 329.1660, found 329.1670.



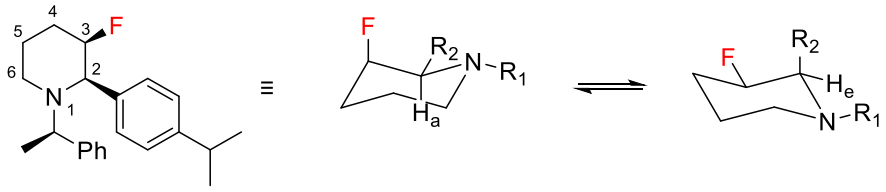
(2*R*,3*R*)-3-Fluoro-1-((*R*)-1-phenylethyl)-2-(p-tolyl)piperidine (17h):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (123.3 mg, 83%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 35:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H_a).

[**^{3}J(3-F, 2-H_a) = 30.0 Hz**]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.52 (d, *J* = 7.4 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.38-7.29 (m, 2H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 4.61 (d, *J* = 47.5 Hz, 1H), 3.95 (q, *J* = 6.8 Hz, 1H), 3.65 (d, *J* = 30.0 Hz, 1H), 2.73-2.60

(m, 1H), 2.36 (s, 3H), 2.34-2.25 (m, 1H), 2.24-2.12 (m, 1H), 1.93 (dm, *J* = 12.8 Hz, 1H), 1.75-1.52 (m, 1H), 1.50-1.43 (m, 1H), 1.17 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -194.85; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 144.27, 137.24, 136.81, 129.06 (d, *J* = 2.3 Hz), 129.01, 127.90, 127.49, 126.20, 90.63 (d, *J* = 180.2 Hz), 67.97 (d, *J* = 16.5 Hz), 54.68, 44.76, 30.44 (d, *J* = 22.4 Hz), 21.18, 20.39, 7.80; **HRMS for $C_{20}H_{25}FN$ $[M+H]^+$:** m/z calcd 298.1966, found 298.1974.



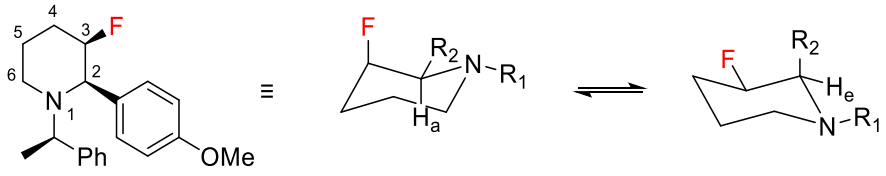
(2*R*,3*R*)-3-Fluoro-2-(4-isopropylphenyl)-1-((*R*)-1-phenylethyl)piperidine (17i):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (160.9 mg, 99%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 35:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H_a).

[**^{3}J(3-F, 2-H_a) = 29.8 Hz**]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.53 (d, *J* = 7.7 Hz, 2H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.37-7.30 (m, 2H), 7.24-7.18 (m, 3H), 4.61 (d, *J* = 47.5 Hz, 1H), 3.94 (q,

J = 6.8 Hz, 1H), 3.64 (d, *J* = 29.8 Hz, 1H), 2.90 (hept, *J* = 7.0 Hz, 1H), 2.68-2.55 (m, 1H), 2.35-2.23 (m, 1H), 2.23-2.11 (m, 1H), 1.93 (dm, *J* = 12.7 Hz, 1H), 1.74-1.51 (m, 1H), 1.50-1.41 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 6H), 1.17 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -194.77; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 148.07, 144.38, 137.05, 129.01 (d, *J* = 2.3 Hz), 127.89, 127.49, 126.32, 126.18, 90.60 (d, *J* = 180.2 Hz), 68.00 (d, *J* = 16.4 Hz), 54.61, 44.80, 33.79, 30.45 (d, *J* = 22.3 Hz), 24.00 (d, *J* = 4.3 Hz), 20.39, 7.79; **HRMS for $C_{22}H_{29}FN$ $[M+H]^+$:** m/z calcd: 326.2279, found 326.2278.



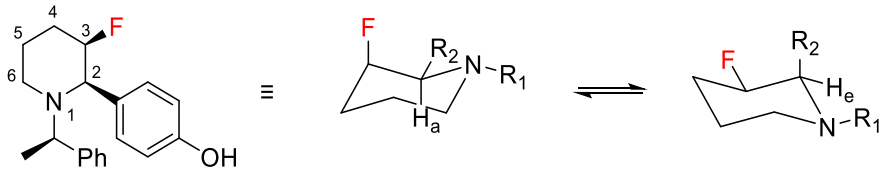
(2*R*,3*R*)-3-Fluoro-2-(4-methoxyphenyl)-1-((*R*)-1-phenylethyl)piperidine (17j):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a brown solid (134.7 mg, 86%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 30:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H_a).

[**^{3}J(3-F, 2-H_a) = 30.0 Hz**]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49 (d, *J* = 7.2 Hz, 4H), 7.36-7.29 (m, 2H), 7.25-7.16 (m, 1H), 6.93-6.86 (m, 2H), 4.58 (d, *J* = 47.5 Hz, 1H), 3.91 (q, *J* = 6.8

Hz, 1H), 3.79 (s, 3H), 3.61 (d, *J* = 30.0 Hz, 1H), 2.72-2.53 (m, 1H), 2.34-2.22 (m, 1H), 2.21-2.11 (m, 1H), 1.97-1.83 (m, 1H), 1.73-1.53 (m, 1H), 1.49-1.41 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H). **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -195.01; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 159.04, 144.29, 131.88, 130.15 (d, *J* = 2.5 Hz), 127.89, 127.45, 126.18, 113.68, 90.74 (d, *J* = 179.9 Hz), 67.50 (d, *J* = 16.4 Hz), 55.22, 54.58, 44.79, 30.42 (d, *J* = 22.3 Hz), 20.38, 7.78; **HRMS for $C_{20}H_{25}FNO$ [M+H]$^+$:** m/z calcd 314.1915, found 314.1920.



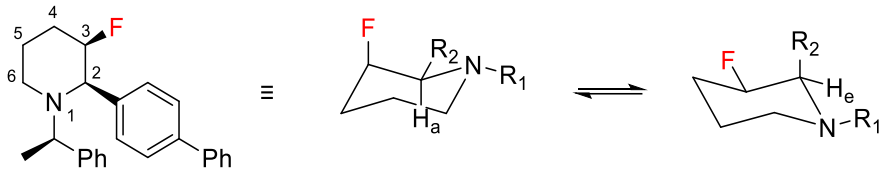
4-((2*R*,3*R*)-3-Fluoro-1-((*R*)-1-phenylethyl)piperidin-2-yl)phenol (17k):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (146.6 mg, 98%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 15:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H_a).

[**^{3}J(3-F, 2-H_a) = 30.1 Hz**]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.48 (d, *J* = 7.7 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.35-7.25 (m, 2H), 7.23-7.15 (m, 1H), 6.79 (d, *J* = 8.1 Hz, 2H), 4.57 (d, *J* = 47.4 Hz, 1H), 3.91 (q, *J* = 6.9 Hz, 1H), 3.57 (d, *J* = 30.1 Hz, 1H), 2.67-2.56 (m,

1H), 2.33-2.20 (m, 1H), 2.20-2.09 (m, 1H), 1.99-1.80 (m, 1H), 1.68-1.49 (m, 1H), 1.47-1.39 (m, 1H), 1.13 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ (ppm):** -194.74; **^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm):** 155.12, 144.25, 131.87, 130.36 (d, *J* = 2.4 Hz), 127.92, 127.50, 126.23, 115.21, 90.88 (d, *J* = 179.6 Hz), 67.50 (d, *J* = 16.3 Hz), 54.61, 44.79, 30.40 (d, *J* = 22.3 Hz), 20.37, 7.82; **HRMS for C$_{19}$H$_{23}$FNO [M+H]$^+$:** m/z calcd 300.1758, found 300.1760.



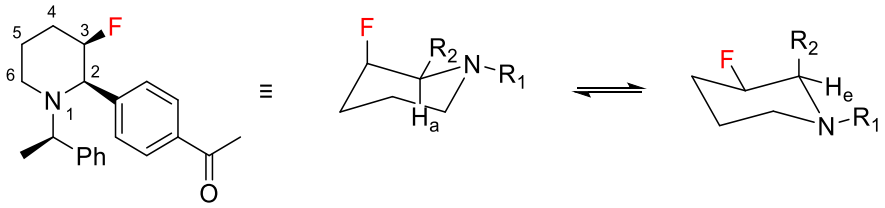
(2*R*,3*R*)-2-([1,1'-Biphenyl]-4-yl)-3-fluoro-1-((*R*)-1-phenylethyl)piperidine (17l):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (136.5 mg, 76%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 40:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H$_a$).

[**^{3}J(3-F, 2-H$_a$) = 29.7 Hz**]

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.65 (d, *J* = 8.2 Hz, 2H), 7.62-7.56 (m, 4H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.47-7.40 (m, 2H), 7.36-7.31 (m, 3H), 7.25-7.20 (m, 1H), 4.66 (d, *J* = 47.5 Hz, 1H), 3.99 (d, *J* = 6.8 Hz, 1H), 3.72 (d, *J* = 29.7 Hz, 1H), 2.74-

2.59 (m, 1H), 2.37-2.27 (m, 1H), 2.25-2.14 (m, 1H), 1.95 (dm, *J* = 12.8 Hz, 1H), 1.79-1.54 (m, 1H), 1.53-1.42 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -194.72; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 144.15, 140.95, 140.51, 138.91, 129.55 (d, *J* = 2.3 Hz), 128.71, 127.94, 127.48, 127.16, 127.08, 127.04, 126.26, 90.52 (d, *J* = 180.5 Hz), 67.97 (d, *J* = 16.4 Hz), 54.82, 44.74, 30.40 (d, *J* = 22.3 Hz), 20.34, 7.87; **HRMS for $C_{25}H_{27}FN$ $[M+H]^+$:** m/z calcd 360.2122, found 360.2129.

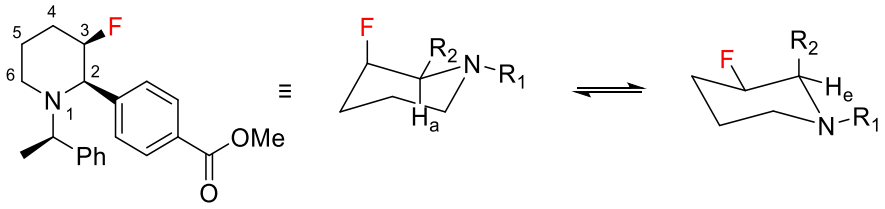


1-(4-((2*R*,3*R*)-3-Fluoro-1-((*R*)-1-phenylethyl)piperidin-2-yl)phenyl)ethan-1-one (17m):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (56.9 mg, 35%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 25:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H_a).

[**^{3}J(3-F, 2-H_a) = 29.2 Hz**]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.95 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 7.9 Hz, 2H), 7.49 (d, *J* = 7.7 Hz, 2H), 7.36-7.29 (m, 2H), 7.25-7.17 (m, 1H), 4.59 (d, *J* = 47.4 Hz, 1H), 3.84 (q, *J* = 6.9 Hz, 1H), 3.75 (d, *J* = 29.2 Hz, 1H), 2.71-2.61 (m, 1H), 2.59 (s, 3H), 2.36-2.25 (m, 1H), 2.24-2.12 (m, 1H), 1.99-1.85 (m, 1H), 1.77-1.55 (m, 1H), 1.54-1.40 (m, 1H), 1.17 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -194.76; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 197.84, 145.41, 143.65, 136.60, 129.36 (d, *J* = 2.4 Hz), 128.40, 128.01, 127.36, 126.42, 90.01 (d, *J* = 181.5 Hz), 67.99 (d, *J* = 16.3 Hz), 55.04, 44.52, 30.21 (d, *J* = 22.2 Hz), 26.64, 20.14, 7.90; **HRMS for $C_{21}H_{25}FNO$ $[M+H]^+$:** m/z calcd 326.1915, found 326.1922.

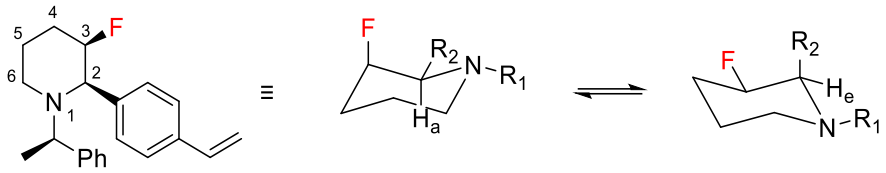


Methyl 4-((2*R*,3*R*)-3-fluoro-1-((*R*)-1-phenylethyl)piperidin-2-yl)benzoate (17n):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a brown oil (68.2 mg, 40%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 15:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H_a).

[^3J(3-F, 2-H$_a$) = 29.3 Hz]

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 8.03 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 7.9 Hz, 2H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.37-7.29 (m, 2H), 7.24-7.17 (m, 1H), 4.59 (d, *J* = 47.5 Hz, 1H), 3.90 (s, 3H), 3.83 (q, *J* = 6.9 Hz, 1H), 3.73 (d, *J* = 29.3 Hz, 1H), 2.71-2.58 (m, 1H), 2.36-2.24 (m, 1H), 2.24-2.09 (m, 1H), 1.92 (dm, *J* = 12.8 Hz, 1H), 1.75-1.56 (m, 1H), 1.54-1.40 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ (ppm):** -194.82; **^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm):** 166.97, 145.16, 143.67, 129.61, 129.54, 129.18 (d, *J* = 2.4 Hz), 127.98, 127.39, 126.39, 90.00 (d, *J* = 181.2 Hz), 68.04 (d, *J* = 16.5 Hz), 55.01, 52.05, 44.52, 30.23 (d, *J* = 22.2 Hz), 20.16, 7.85; **HRMS for C$_{21}$H$_{25}$FNO$_2$ [M+H]$^+$:** m/z calcd 342.1864, found 342.1879.

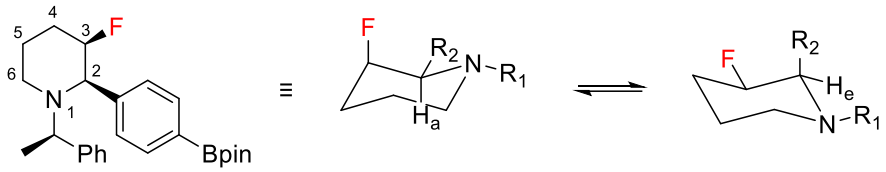


(2*R*,3*R*)-3-Fluoro-1-((*R*)-1-phenylethyl)-2-(4-vinylphenyl)piperidine (17o):

The titled compound was synthesised according to modified general procedure at 0.5 mmol scale, the reaction was performed for 12 h. The product was isolated as a brown oil (115.9 mg, 75%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 35:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^3J(F, H$_a$).

[^3J(3-F, 2-H$_a$) = 29.8 Hz]

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.59-7.47 (m, 4H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.36-7.29 (m, 2H), 7.24-7.15 (m, 1H), 6.72 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.75 (d, *J* = 17.6 Hz, 1H), 5.23 (d, *J* = 10.9 Hz, 1H), 4.61 (d, *J* = 47.8 Hz, 1H), 3.93 (q, *J* = 6.9 Hz, 1H), 3.66 (d, *J* = 29.8 Hz, 1H), 2.73-2.57 (m, 1H), 2.35-2.24 (m, 1H), 2.23-2.09 (m, 1H), 1.92 (dm, *J* = 12.8 Hz, 1H), 1.74-1.55 (m, 1H), 1.51-1.39 (m, 1H), 1.17 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ (ppm):** -194.83; **^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm):** 144.10, 139.51, 136.99, 136.59, 129.33 (d, *J* = 2.3 Hz), 127.92, 127.45, 126.25, 126.16, 113.66, 90.45 (d, *J* = 180.6 Hz), 67.99 (d, *J* = 16.5 Hz), 54.79, 44.69, 30.37 (d, *J* = 22.3 Hz), 20.32, 7.83; **HRMS for C$_{21}$H$_{25}$FN [M+H]$^+$:** m/z calcd 310.1966, found 310.1972.



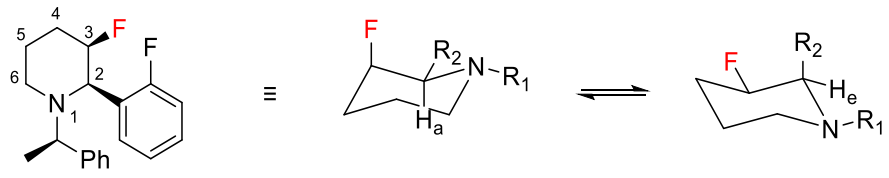
(2*R*,3*R*)-3-Fluoro-1-((*R*)-1-phenylethyl)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2 yl)phenyl) piperidine (17p):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (104.4 mg, 51%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 30:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The

orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H_a).

[^{3}J**(3-F, 2-H$_a$) = 30.0 Hz**]

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.83 (d, *J* = 7.9 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 7.7 Hz, 2H), 7.36-7.28 (m, 2H), 7.24-7.15 (m, 1H), 4.61 (d, *J* = 47.6 Hz, 1H), 3.89 (q, *J* = 6.8 Hz, 1H), 3.68 (d, *J* = 30.0 Hz, 1H)), 2.69-2.60 (m, 1H), 2.35-2.23 (m, 1H), 2.23-2.10 (m, 1H), 1.92 (dm, *J* = 12.7 Hz, 1H), 1.74-1.54 (m, 1H), 1.52-1.43 (m, 1H), 1.34 (s, 12H), 1.15 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ (ppm):** -194.77; **^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm):** 144.08, 143.22, 134.88, 128.78, 128.76, 128.00, 127.60, 126.36, 90.34 (d, *J* = 180.8 Hz), 83.84, 68.51 (d, *J* = 16.4 Hz), 55.00, 44.71, 30.47 (d, *J* = 22.2 Hz), 24.99 (d, *J* = 3.3 Hz), 20.42, 7.87; **HRMS for C$_{25}$H$_{34}$[^{10}B]FNO$_2$ [M+H]$^{+}$:** m/z calcd 409.2697, found 409.2704.



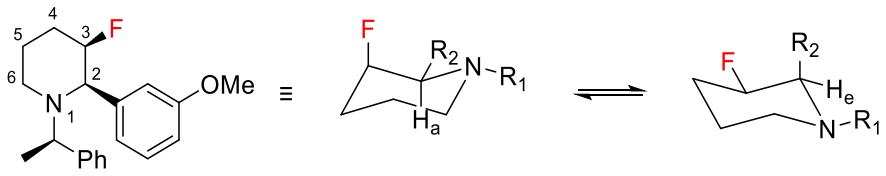
(2*R*,3*R*)-3-Fluoro-2-(2-fluorophenyl)-1-((*R*)-1-phenylethyl)piperidine (17q):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (93.4 mg, 62%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 35:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The

orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H_a).

[^{3}J**(3-F, 2-H_a) = 29.8 Hz**]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.97-7.84 (m, 1H), 7.52 (d, *J* = 7.7 Hz, 2H), 7.38-7.13 (m, 5H), 7.13-7.01 (m, 1H), 4.65 (d, *J* = 47.6 Hz, 1H), 4.22 (d, *J* = 29.8 Hz, 1H), 3.91 (q, *J* = 6.9 Hz, 1H), 2.74-2.58 (m, 1H), 2.40-2.26 (m, 1H), 2.25-2.13 (m, 1H), 2.02-1.84 (m, 1H), 1.78-1.57 (m, 1H), 1.55-1.42 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -120.00, -194.82; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 160.50 (d, *J* = 244.2 Hz), 143.92, 131.74 (t, *J* = 4.4 Hz), 128.70 (d, *J* = 8.4 Hz), 127.96, 127.91, 127.43, 126.31, 123.98 (d, *J* = 3.4 Hz), 115.27 (d, *J* = 22.9 Hz), 89.54 (d, *J* = 180.4 Hz), 54.97, 58.34 (d, *J* = 16.0 Hz), 44.77, 30.28 (d, *J* = 22.3 Hz), 20.22, 8.12; **HRMS for $C_{19}H_{22}F_2N$ $[M+H]^+$:** m/z calcd 302.1715, found 302.1724.



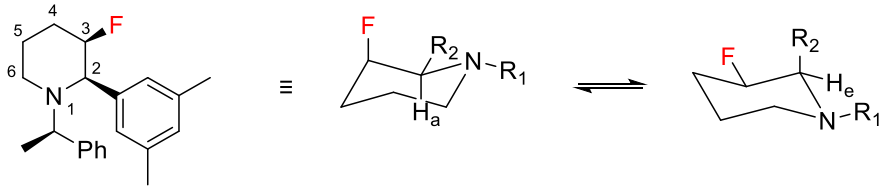
(2*R*,3*R*)-3-Fluoro-2-(3-methoxyphenyl)-1-((*R*)-1-phenylethyl)piperidine (17r):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a brown solid (142.5 mg, 91%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 40:1 to 30:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The

orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H_a).

[^{3}J**(3-F, 2-H$_a$) = 29.6 Hz**]

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.43 (d, *J* = 7.6 Hz, 2H), 7.29-7.00 (m, 6H), 6.78-6.70 (m, 1H), 4.53 (d, *J* = 47.6 Hz, 1H), 3.87 (q, *J* = 6.8 Hz, 1H), 3.72 (s, 3H), 3.55 (d, *J* = 29.6 Hz, 1H), 2.62-2.46 (m, 1H), 2.27-2.15 (m, 1H), 2.14-2.02 (m, 1H), 1.84 (dm, *J* = 12.7 Hz, 1H), 1.66-1.29 (m, 2H), 1.09 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ (ppm):** -194.36; **^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm):** 159.52, 144.20, 141.46, 129.15, 127.91, 127.41, 126.22, 121.47 (d, *J* = 2.1 Hz), 114.62 (d, *J* = 2.8 Hz), 113.23, 90.38 (d, *J* = 180.7 Hz), 68.22 (d, *J* = 16.4 Hz), 55.19, 54.76, 44.69, 30.38 (d, *J* = 22.2 Hz), 20.29, 7.94; **HRMS for C$_{20}$H$_{25}$FNO [M+H]$^{+}$:** m/z calcd 314.1915, found 314.1915.



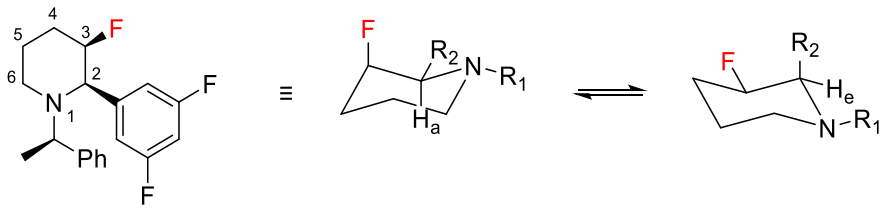
(2*R*,3*R*)-2-(3,5-Dimethylphenyl)-3-fluoro-1-((*R*)-1-phenylethyl)piperidine (17s):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (129.1 mg, 83%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 35:1). The compound exists

as two conformational isomers, as indicated by the $^{19}F\{^{1}H\}$ spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of $^{3}J(F, H_a)$.

[^{3}J(3-F, 2-H$_a$) = 30.1 Hz]

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.53 (d, *J* = 7.7 Hz, 2H), 7.40-7.31 (m, 2H), 7.30-7.17 (m, 3H), 6.95 (s, 1H), 4.61 (d, *J* = 47.6 Hz, 1H), 3.99 (q, *J* = 6.9 Hz, 1H), 3.60 (d, *J* = 30.1 Hz, 1H), 2.70-2.59 (m, 1H), 2.35 (s, 6H), 2.33-2.24 (m, 1H), 2.22-2.10 (m, 1H), 1.92 (dm, *J* = 12.7 Hz, 1H), 1.75-1.41 (m, 2H), 1.18 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ (ppm):** -194.43; **^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm):** 144.34, 139.70, 137.60, 129.30, 127.89, 127.55, 126.97 (d, *J* = 2.1 Hz), 126.18, 90.57 (d, *J* = 180.5 Hz), 68.31 (d, *J* = 16.4 Hz), 54.73, 44.73, 30.47 (d, *J* = 22.4 Hz), 21.44, 20.39, 7.76; **HRMS for C$_{21}$H$_{27}$FN [M+H]$^{+}$:** m/z calcd 312.2122, found 312.2134.



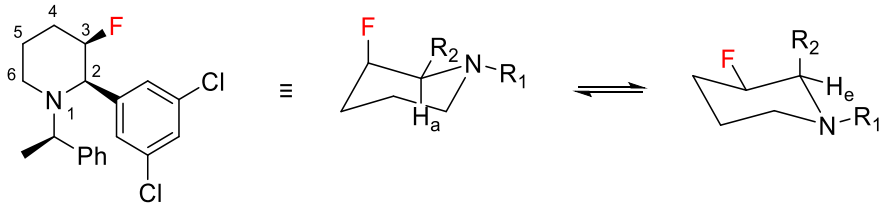
(2*R*,3*R*)-2-(3,5-Difluorophenyl)-3-fluoro-1-((*R*)-1-phenylethyl)piperidine (17):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (81.4 mg, 51%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 35:1). The compound exists

as two conformational isomers, as indicated by the $^{19}F\{^{1}H\}$ spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of $^{3}J(F, H_a)$.

[^{3}J(3-F, 2-H$_a$) = 28.5 Hz]

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.48 (d, *J* = 7.7 Hz, 2H), 7.39-7.29 (m, 2H), 7.27-7.20 (m, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.80-6.70 (m, 1H), 4.59 (d, *J* = 47.3 Hz, 1H), 3.87 (q, *J* = 6.9 Hz, 1H), 3.65 (d, *J* = 28.5 Hz, 1H), 2.70-2.58 (m, 1H), 2.35-2.12 (m, 2H), 1.90 (dm, *J* = 12.6 Hz, 1H), 1.73-1.39 (m, 2H), 1.19 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ (ppm):** -110.12, -194.52; **^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm):** 162.89 (dd, *J* = 247.9, 12.6 Hz), 143.84 (t, *J* = 8.9 Hz), 143.47, 128.07, 127.37, 126.50, 111.95 (d, *J* = 22.3 Hz), 103.13 (t, *J* = 25.4 Hz), 89.75 (d, *J* = 181.6 Hz), 67.62 (d, *J* = 16.3 Hz), 55.03, 44.43, 30.11 (d, *J* = 22.1 Hz), 20.03, 7.94; **HRMS for C$_{19}$H$_{21}$F$_3$N [M+H]$^+$:** m/z calcd 320.1621, found 320.1612.

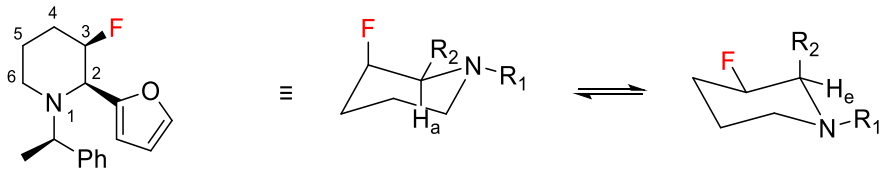


(2*R*,3*R*)-2-(3,5-Dichlorophenyl)-3-fluoro-1-((*R*)-1-phenylethyl)piperidine (17u):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (56.2 mg, 32%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 30:1). The compound exists as two conformational isomers, as indicated by the $^{19}F\{^{1}H\}$ spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of $^{3}J(F, H_a)$.

[^{3}J(3-F, 2-H$_a$) = 28.6 Hz]

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.50-7.27 (m, 7H), 7.25-7.20 (m, 1H), 4.57 (d, *J* = 47.5 Hz, 1H), 3.84 (q, *J* = 6.9 Hz, 1H), 3.62 (d, *J* = 28.6 Hz, 1H), 2.68-2.58 (m, 1H), 2.34-2.11 (m, 2H), 1.96-1.82 (m, 1H), 1.72-1.40 (m, 2H), 1.18 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ (ppm):** -194.63; **^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm):** 143.33, 134.79, 128.08, 127.94, 127.91, 127.61 (d, *J* = 2.6 Hz), 127.42, 126.54, 89.73 (d, *J* = 181.7 Hz), 67.44 (d, *J* = 16.6 Hz), 55.11, 44.38, 30.07 (d, *J* = 22.1 Hz), 20.00, 7.87; **HRMS for C$_{19}$H$_{21}$^{35}Cl$_2$FN [M+H]$^+$:** m/z calcd 352.1030, found 352.1043.



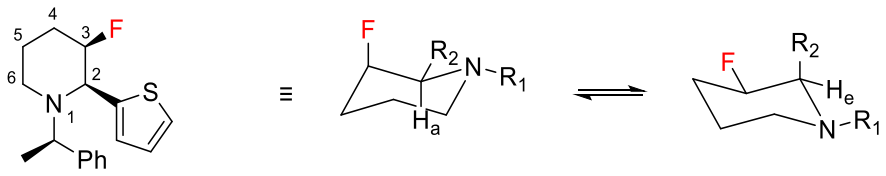
(2*R*,3*R*)-3-Fluoro-2-(furan-2-yl)-1-((*R*)-1-phenylethyl)piperidine (17v):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (91.5 mg, 67%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 40:1).

The compound exists as two conformational isomers, as indicated by the $^{19}F\{^{1}H\}$ spectrum. The orientation of the fluorine atom in the major isomer (right) is assigned as equatorial due to the small value of $^{3}J(F, H_a)$.

[^{3}J**(3-F, 2-H$_a$) = 14.3 Hz**]

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.36 (s, 1H), 7.28 (d, *J* = 7.6 Hz, 2H), 7.24-7.18 (m, 2H), 7.16-7.08 (m, 1H), 6.40-6.26 (m, 2H), 4.74 (d, *J* = 48.1 Hz, 1H), 4.32 (d, *J* = 14.3 Hz, 1H), 3.47 (q, *J* = 6.7 Hz, 1H), 2.53-2.37 (m, 1H), 2.31-2.17 (m, 1H), 2.03-1.86 (m, 1H), 1.81-1.58 (m, 2H), 1.49-1.33 (m, 1H), 1.22 (d, *J* = 6.7 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ (ppm):** -176.59, -183.58; **^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm):** 152.49, 145.38, 141.78, 128.13, 127.26, 126.57, 110.17, 109.85 (d, *J* = 2.5 Hz), 90.15 (d, *J* = 178.7 Hz), 59.29, 57.80 (d, *J* = 20.8 Hz), 44.74, 27.93 (d, *J* = 19.4 Hz), 22.04 (d, *J* = 7.0 Hz), 16.34; **HRMS for C$_{17}$H$_{21}$FNO [M+H]$^{+}$:** m/z calcd 274.1602, found 274.1609.

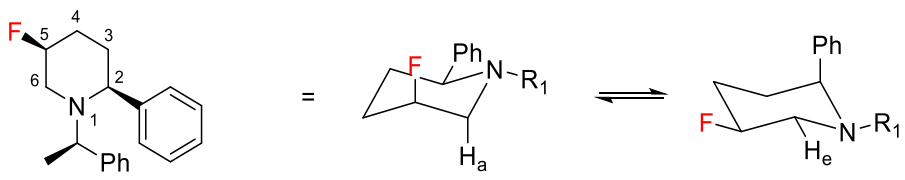


(2*S*,3*R*)-3-Fluoro-1-((*R*)-1-phenylethyl)-2-(thiophen-2-yl)piperidine (17w):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a brown solid (109.8 mg, 76%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 40:1). The compound exists as two conformational isomers, as indicated by the $^{19}F\{^{1}H\}$ spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of $^{3}J(F, H_a)$.

[^{3}J**(3-F, 2-H$_a$) = 24.2 Hz**]

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.47 (d, *J* = 7.6 Hz, 2H), 7.35-7.27 (m, 3H), 7.24-7.17 (m, 1H), 7.15-7.08 (m, 1H), 7.03-6.96 (m, 1H), 4.71 (d, *J* = 47.7 Hz, 1H), 4.22 (d, *J* = 24.2 Hz, 1H), 3.85 (q, *J* = 6.8 Hz, 1H), 2.68-2.55 (m, 1H), 2.38-2.25 (m, 1H), 2.22-2.09 (m, 1H), 1.93-1.55 (m, 2H), 1.53-1.42 (m, 1H), 1.23 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ (ppm):** -189.13; **^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm):** 144.37, 141.69, 127.93, 127.45, 126.82, 126.37, 125.88, 125.75, 90.16 (d, *J* = 180.3 Hz), 62.29 (d, *J* = 18.1 Hz), 55.85, 44.57, 29.37 (d, *J* = 21.5 Hz), 20.67 (d, *J* = 2.6 Hz), 10.29; **HRMS for C$_{17}$H$_{21}$FNS [M+H]$^+$:** m/z calcd 290.1373, found 290.1378.

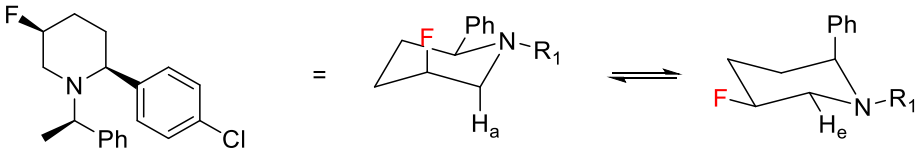


(2*S*,5*S*)-5-fluoro-2-phenyl-1-((*R*)-1-phenylethyl)piperidine (17x):

Following the modified procedure, 1 equiv. of $Mg(OMe)_2$ was added as an additive. The reaction was conducted at 0.5 mmol scale, giving a mixture of diastereomers (d.r. 4:2.2:1). The major *cis* product was isolated as a yellow solid (53.8 mg, 38%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 35:1). The orientation of the fluorine atom is assigned as axial due to the large value of ^3J(F, H_a).

[^3J**(5-F, 6-H$_a$) = 39.4 Hz**]

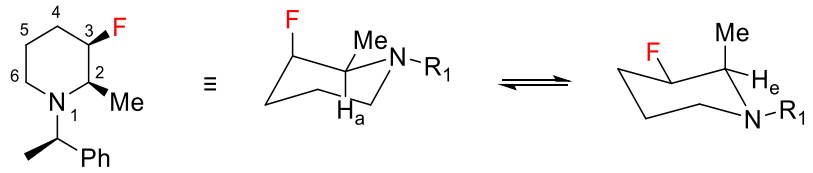
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.50 (d, *J* = 7.7 Hz, 4H), 7.37-7.15 (m, 6H), 4.73 (d, *J* = 48.1 Hz, 1H), 3.91 (q, *J* = 6.8 Hz, 1H), 3.59 (d, *J* = 10.7 Hz, 1H), 2.96-2.82 (m, 1H), 2.41 (dd, *J* = 39.4, 13.1 Hz, 1H), 2.20-2.03 (m, 2H), 1.76-1.49 (m, 2H), 1.18 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -188.05; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 144.09, 143.71, 128.63, 127.92, 127.53, 127.39, 127.21, 126.24, 87.06 (d, *J* = 173.9 Hz), 64.65, 54.30, 48.18 (d, *J* = 19.0 Hz), 30.97, 29.66 (d, *J* = 21.5 Hz), 8.17; **HRMS for $C_{19}H_{23}FN$ $[M+H]^+$:** m/z calcd 284.1809, found 284.1815.



(2*S*,5*S*)-2-(4-chlorophenyl)-5-fluoro-1-((*R*)-1-phenylethyl)piperidine (17y):

Following the modified procedure, 1 equiv. of $Mg(OMe)_2$ was added as an additive. The reaction was conducted at 0.5 mmol scale, giving a mixture of diastereomers (d.r. 4:2:1). The major *cis* product was isolated as a yellow solid (66.5 mg, 42%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 35:1). Due to the peak overlapping in the NMR spectrum we could not determine the orientation of the fluorine atom via ^3J(F,H) values.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35-7.09 (m, 9H), 4.44 (dm, *J* = 49.4 Hz, 1H), 3.70 (q, *J* = 6.8 Hz, 1H), 3.39 (dm, *J* = 10.5 Hz, 1H), 2.90-2.73 (m, 1H), 2.23-2.05 (m, 2H), 1.89-1.70 (m, 1H), 1.67-1.43 (m, 2H), 1.13 (d, *J* = 6.8 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -178.43; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 143.29, 141.86, 132.93, 128.93, 128.88, 128.01, 127.33, 126.59, 89.04 (d, *J* = 171.8 Hz), 63.56, 55.08, 49.35 (d, *J* = 26.9 Hz), 33.71 (d, *J* = 11.5 Hz), 31.87 (d, *J* = 18.5 Hz), 8.24; **HRMS for $C_{19}H_{22}{}^{35}ClFN$ $[M+H]^+$:** m/z calcd 318.1419, found 318.1423.



(2*R*,3*R*)-3-Fluoro-2-methyl-1-((*R*)-1-phenylethyl)piperidine (17z):

Following the general procedure, the reaction was conducted at 0.5 mmol scale, giving the titled compound in 64% yield (70.7 mg).

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (70.7 mg, 64%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 30:1). Due to the peak overlapping in the NMR spectrum we could not determine the orientation of the fluorine atom via ^{3}J(F,H) values.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.29 (d, *J* = 7.6 Hz, 2H), 7.25-7.18 (m, 2H), 7.17-7.09 (m, 1H), 4.60 (dm, *J* = 48.5 Hz, 1H), 3.67 (q, *J* = 6.7 Hz, 1H), 3.36 (dm, *J* = 11.5 Hz, 1H), 2.23-2.06 (m, 2H), 1.72-1.58 (m, 2H), 1.56-1.42 (m, 1H), 1.36-1.22 (m, 1H), 1.19 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -176.65; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 146.26, 128.22, 127.20, 126.58, 91.95 (d, *J* = 176.2 Hz), 59.00, 52.85 (d, *J* = 21.8 Hz), 43.19, 26.66 (d, *J* = 19.1 Hz), 22.74 (d, *J* = 8.3 Hz), 18.07, 6.79; **HRMS for $C_{14}H_{21}FN$ $[M+H]^+$:** m/z calcd 222.1653, found 222.1647.

2.6 References

[1] D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435–446.

[2] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.

[3] C. Wang, A. Pettman, J. Bacsa, J. Xiao, *Angew. Chem. Int. Ed.* **2010**, *49*, 7548–7552.

[4] D. Zhao, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 9616–9618.

[5] Z. Wu, M. Perez, M. Scalone, T. Ayad, V. Ratovelomanana-Vidal, *Angew. Chem. Int. Ed.* **2013**, *52*, 4925–4928.

[6] A. Iimuro, K. Yamaji, S. Kandula, T. Nagano, Y. Kita, K. Mashima, *Angew. Chem. Int. Ed.* **2013**, *52*, 2046–2050.

[7] Z.-S. Ye, R.-N. Guo, X.-F. Cai, M.-W. Chen, L. Shi, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2013**, *52*, 3685–3689.

[8] T. Wang, F. Chen, J. Qin, Y.-M. He, Q.-H. Fan, *Angew. Chem. Int. Ed.* **2013**, *52*, 7172–7176.

[9] N. Ortega, D.-T. D. Tang, S. Urban, D. Zhao, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 9500–9503.

[10] D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557–2590.

[11] M. P. Wiesenfeldt, Z. Nairoukh, T. Dalton, F. Glorius, *Angew. Chem. Int. Ed.* **2019**, *58*, 10460–10476.

[12] X.-B. Wang, W. Zeng, Y.-G. Zhou, *Tetrahedron Lett.* **2008**, *49*, 4922–4924.

[13] M. Chang, Y. Huang, S. Liu, Y. Chen, S. W. Krska, I. W. Davies, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 12761–12764.

[14] B. Balakrishna, J. L. Núñez-Rico, A. Vidal-Ferran, *Eur. J. Org. Chem.* **2015**, *2015*, 5293–5303.

[15] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.

[16] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.

[17] M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640.

[18] D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319.

[19] C. Thiehoff, Y. P. Rey, R. Gilmour, *Isr. J. Chem.* **2017**, *57*, 92–100.

[20] K. M. Dawood, *Tetrahedron* **2004**, *60*, 1435–1451.

[21] C. Hollingworth, V. Gouverneur, *Chem. Commun.* **2012**, *48*, 2929–2942.

[22] J. Wu, *Tetrahedron Lett.* **2014**, *55*, 4289–4294.

[23] Z. Nairoukh, M. Wollenburg, C. Schlepphorst, K. Bergander, F. Glorius, *Nat. Chem.* **2019**, *11*, 264–270.

[24] T. Wagener, A. Heusler, Z. Nairoukh, K. Bergander, C. G. Daniliuc, F. Glorius, *ACS Catal.* **2020**, *10*, 12052–12057.

[25] J. Wu, Z. Chen, J. H. Barnard, C. Pu, X. Wu, S. Zhang, R. Gunasekar, J. Ruan, J. Xiao, *Nat. Catal.* **2021**, under review.

[26] A. Grozavu, H. B. Hepburn, P. J. Smith, H. K. Potukuchi, P. J. Lindsay-

Scott, T. J. Donohoe, *Nat. Chem.* **2019**, *11*, 242–247.

[27] K. Holen, R. DiPaola, G. Liu, A. R. Tan, G. Wilding, K. Hsu, N. Agrawal, C. Chen, L. Xue, E. Rosenberg, M. Stein, *Invest. New Drugs* **2012**, *30*, 1088–1095.

[28] M. G. Bock, J. Longmore, *Curr. Opin. Chem. Biol.* **2000**, *4*, 401–406.

[29] M. Munoz, M. R. and R. Covenas, *Curr. Med. Chem.* **2010**, *17*, 504–516.

[30] T. D. Penning, et al., *J. Med. Chem.* **2010**, *53*, 3142–3153.

[31] J. Wu, W. Tang, A. Pettman, J. Xiao, *Adv. Synth. Catal.* **2013**, *355*, 35–40.

[32] B. Qu, H. P. R. Mangunuru, S. Tcyrulnikov, D. Rivalti, O. V Zatolochnaya, D. Kurouski, S. Radomkit, S. Biswas, S. Karyakarte, K. R. Fandrick, J. D. Sieber, S. Rodriguez, J.-N. Desrosiers, N. Haddad, K. McKellop, S. Pennino, H. Lee, N. K. Yee, J. J. Song, M. C. Kozlowski, C. H. Senanayake, *Org. Lett.* **2018**, *20*, 1333–1337.

[33] Y. Huang, S. Liu, Y. Liu, Y. Chen, M. Weisel, R. T. Williamson, I. W. Davies, X. Zhang, *Tetrahedron* **2018**, *74*, 2182–2190.

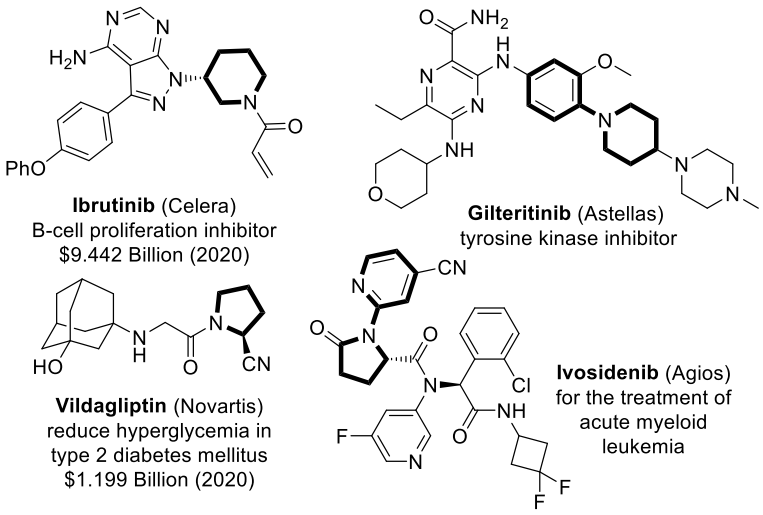
[34] Z. Nairoukh, F. Strieth-Kalthoff, K. Bergander, F. Glorius, *Chem. Eur. J.* **2020**, *26*, 6141–6146.

[35] R. Mondal, M. Agbaria, Z. Nairoukh, *Chem. Eur. J.* **2021**, *27*, 7193–7213.

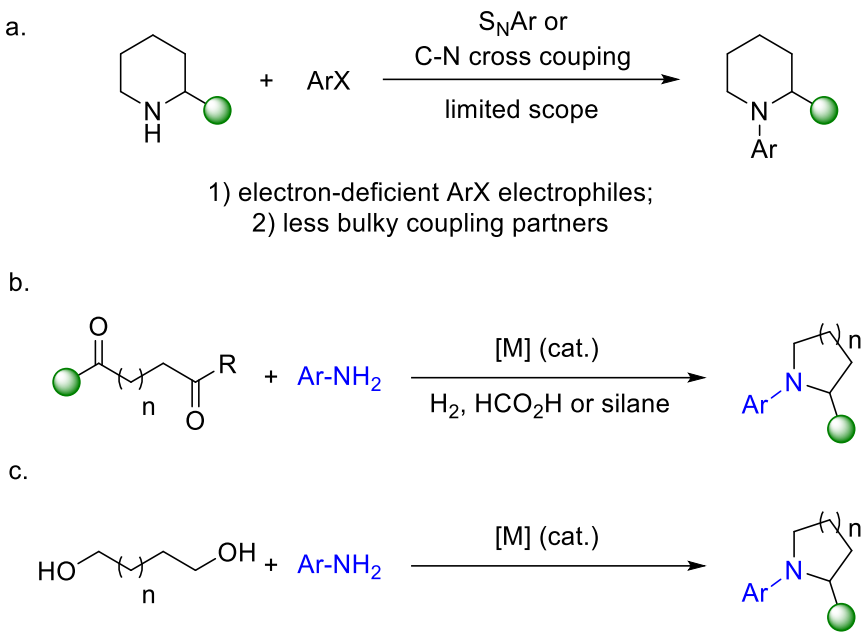
Chapter 3: Reductive Transamination to Access *N*-Aryl Piperidines and Pyrrolidines

3.1 Introduction

Saturated nitrogen heterocycles, such as piperidines and pyrrolidines, and their *N*-arylated derivatives, are significant structural motifs in natural products and pharmaceuticals (Scheme 3.1).[1–5] Modern synthetic methods for the Csp^2-N bond construction are based on two major strategies: (1) base-promoted nucleophilic aromatic substitution (S_NAr) reactions that depend on electron deficiency of aromatics electrophiles like fluoroarenes[6–8] and bromoarenes[9] and (2) transition metal-catalysed C-N cross-coupling reactions using palladium or copper catalysts developed by Hartwig, Buchwald and other groups.[10–15] Although these strategies have achieved great success, they are limited in substrate scope due to the necessary electron deficiency of electrophiles in general, resulting in a lack of electron-rich aromatics. Furthermore, the reaction could be hindered by the introduction of bulky substituents on either coupling partners (Scheme 3.2a).[16]



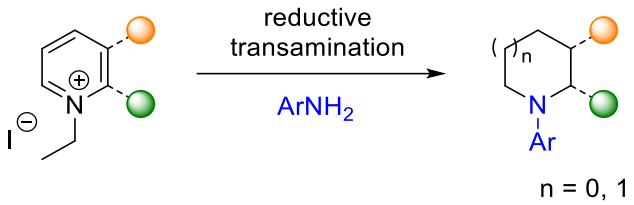
Scheme 3.1: Examples of piperidine and pyrrolidine containing FDA approved drugs



Scheme 3.2: Synthetic approaches to *N*-aryl piperidines through a) S_NAr or C-N cross coupling, b) reductive amination/cyclisation, and c) borrowing hydrogen

In 2011, the Fu group reported the first example of conversion of levulinic acid to pyrrolidines *via* reductive amination.[17] Later, the reductive amination/cyclisation sequence has been applied for the preparation of *N*-aryl pyrrolidines and piperidines from 1,4- or 1,5-dicarbonyl compounds with aryl amines in the presence of reducing agents (Scheme 3.2b).[18–24] The production of cyclic amines also can be achieved by the alkylation of amines with diols through the process known as "borrowing hydrogen" (Scheme 3.2c).[25–28] However, the main drawback of using dicarbonyl compounds and diols as starting materials is their scarce variety in terms of functionality, which restricts their applications in complicated heterocycle synthesis.

In Chapter 2, we reported a novel reaction, dubbed asymmetric reductive transamination (ART), for the synthesis of chiral piperidines from pyridinium salts. In this chapter, we present a synthetic approach for the efficient preparation of functionalised *N*-aryl piperidines and pyrrolidines from easily available pyridines *via* reductive transamination (Scheme 3.3).



Scheme 3.3: A new approach for the preparation of *N*-aryl heterocycles

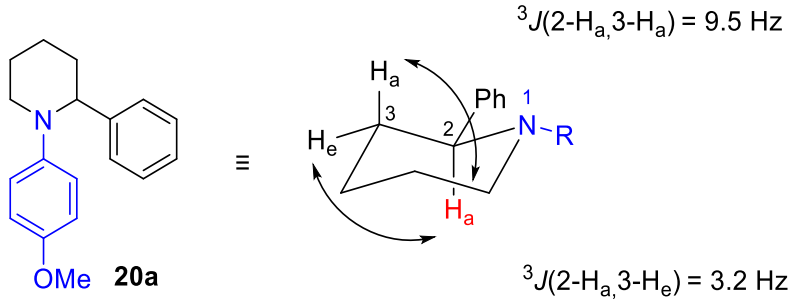
3.2 Results and discussion

3.2.1 Optimisation of reaction conditions

In the previous study, we obtained chiral piperidines using a mixture of a aliphatic amine (10 eq.)/formic acid (24 eq.) as the hydrogen source, and a catalyst *in situ* generated from $[Cp^*RhCl_2]_2$. However, this condition only gives a low yield for the target *N*-aryl piperidines when using aryl amines. Therefore, an optimisation was necessary. The reaction started with the same conditions except using *p*-anisidine as the arylamine source for the model reaction (Table 3.1). The formation of the desired *N*-aryl piperidine **20a** was observed under the standard reaction conditions, but in a poor yield (entry 1). We next investigated the effects of solvent

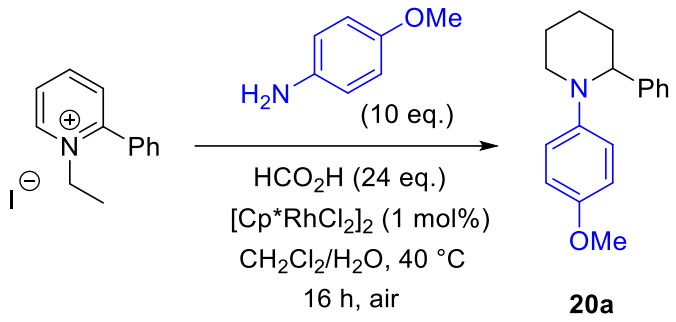
and temperature on the efficiency of the reductive transamination reaction. Heating the reaction mixture at 40 °C in polar protic solvents significantly increased the yields comparing with CH_2Cl_2. The highest yield (86 %) was obtained when the reaction was performed in a mixture of MeOH/H_2O (15:1) as solvent (entry 4). The yield plunged to 30 % when stirring at room temperature, whilst almost no changes were noted when the temperature was increased to 60 °C (entry 7-8). All the reagents, including the Rh(III) catalyst, are stable to air and moisture in solution, leading to reproducible results under both air and N_2 atmospheres (entry 9). Finally, an addition of 5 equiv. of trimethylamine (NEt_3) could be used to maintain the basicity of the reaction system when cutting the amount of aryl amine by half, and no deterioration in yield was observed (entry 10).

The conformation of the desired piperidine **20a** was characterised by ^{1}H NMR spectrum. The axial position of the C2 proton was determined based on the $^3J_{HH}$ coupling constant, 9.5 Hz, between *H*C2 and *Ha*C3.



Scheme 3.4: Conformation of *N*-aryl piperidine **20a**

Table 3.1: Optimisation of reaction conditions[a]



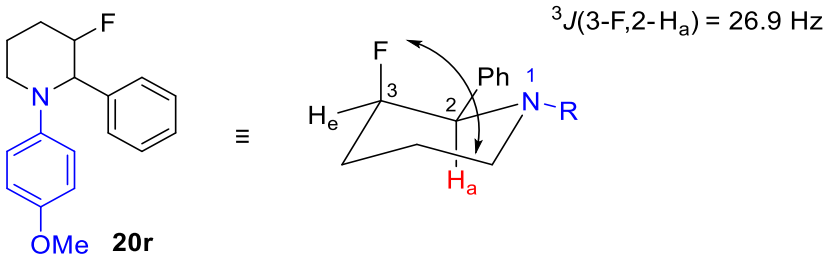
Entry	Variation from standard conditions	Yield (%)[b]
1	None	11
2	THF/H_2O	38
3	MeCN/H_2O	74
4	MeOH/H_2O	**86**
5	EtOH/H_2O	71
6	*i*PrOH/H_2O	59
7	MeOH/H_2O, 25 °C	30
8	MeOH/H_2O, 60 °C	82
9	MeOH/H_2O, N_2	85
10	*p*-anisidine (5 eq.) + NEt_3 (5 eq.)	**84**

[a] Reaction conditions: 0.5 mmol pyridinium salt, 10 eq. of *p*-anisidine, 24 eq. of HCO_2H, CH_2Cl_2/H_2O = 15 : 1 (4.0 mL), 1 mol% $[Cp^*RhCl_2]_2$, 40 °C, 16 h, in air. [b] Isolated yields.

3.2.2 Substrate scope for *N*-arylated piperidines

With the optimised reaction conditions in hand, we next explored the scope of functionalised pyridinium salts in the reaction with *p*-anisidine (Table 3.2). The

substrates were readily prepared from bromopyridines *via* Suzuki coupling followed by quaternisation, which makes pyridines more easily attacked by a metal hydride.[29–31] The reduction of pyridine rings along with the exchange of the imido groups underwent smoothly in the presence of other potentially reducible functional groups, like halides (**20b**, **c**, **o**, **s**), nitro (**20e**) and ketone (**20k**). Substrates bearing electron-withdrawing groups afforded slightly lower yields, compared with those bearing electron-donating ones, e.g. **20d-f** vs **20g-j**. In order to avoid the nucleophilic addition of excessive amine to the nitrile group in product **20f**, the amount of *p*-anisidine was reduced to 1.2 equiv., albeit with lower product yield being observed. Of particular note is that multi-functionalised pyridinium salts were well tolerated under the same conditions (**20r-v**).

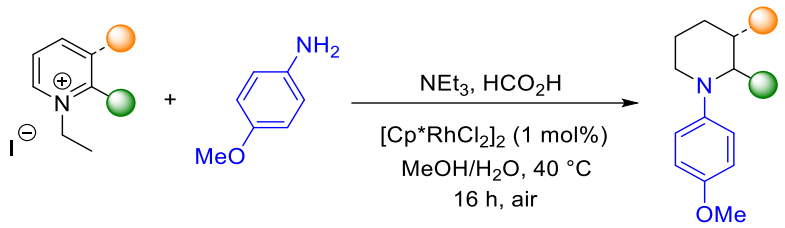


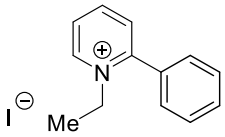
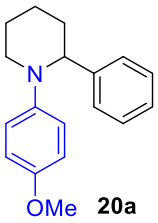
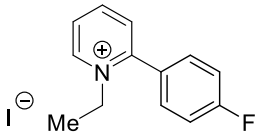
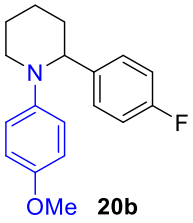
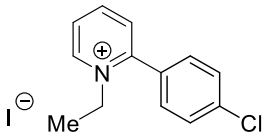
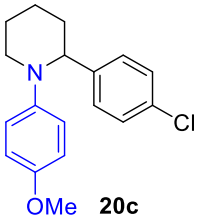
Scheme 3.5: Conformation of *N*-aryl piperidine **20r**

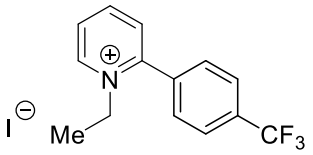
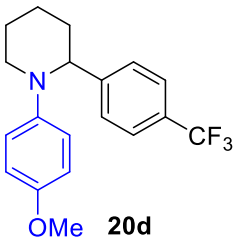
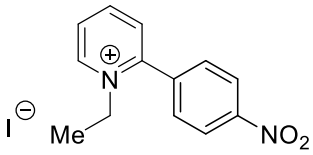
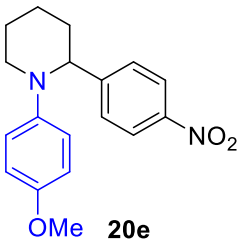
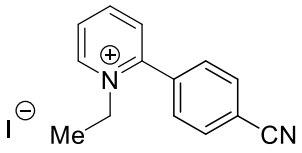
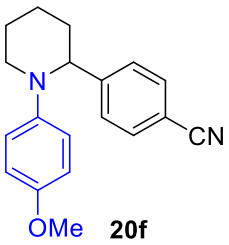
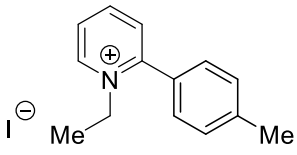
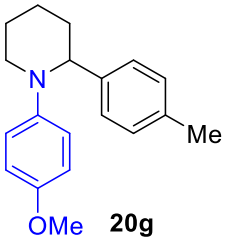
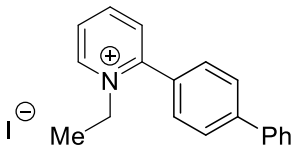
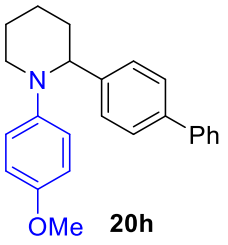
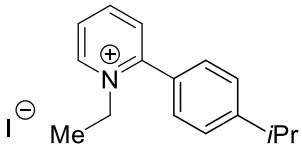
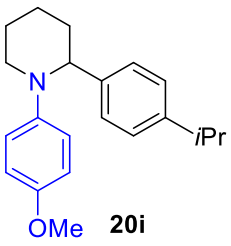
As mentioned in Chapter 2, around 20% of all approved medicines contain fluorine atoms;[32,33] however, the direct synthetic methods *via* hydrogenation of fluoropyridine precursors remain rare due to the possible hydrodefluorination side reaction.[34] Our new method thus provides an effective transfer hydrogenation approach to access *N*-aryl fluorinated piperidines (**20r-u**). These compounds are

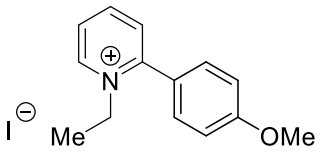
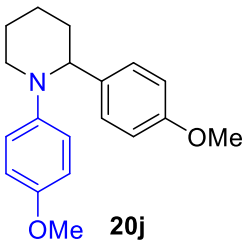
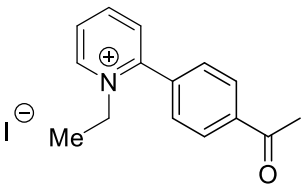
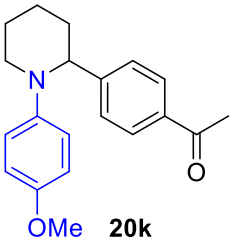
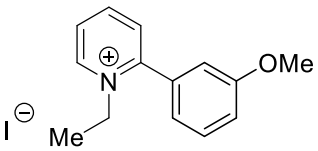
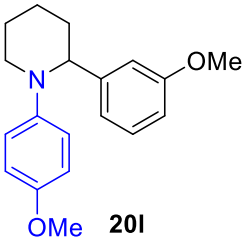
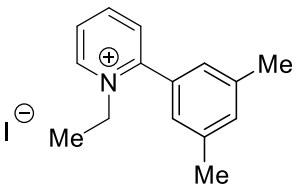
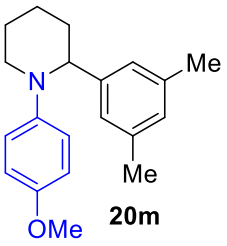
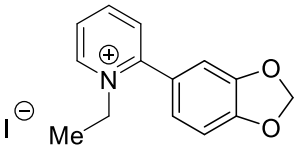
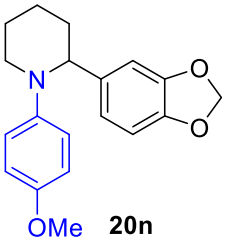
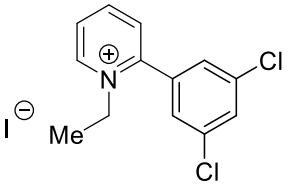
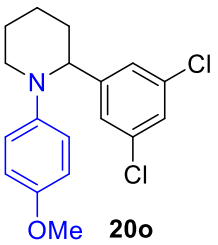
isolated in a mixture of diastereomers, with the *cis* configuration as the major products. It has been shown that the vicinal ^{3}J(F,H) coupling constant provide a useful method to determine conformational orientation, as large values indicate axial orientation and small values indicate equatorial orientation.[35,36] For product **20r**, the orientation of the fluorine atom was assigned as axial due to the large value of ^{3}J(3-F,2-H$_a$ = 26.9 Hz) (Scheme 3.5).

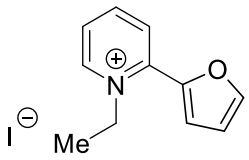
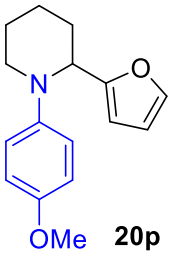
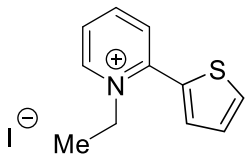
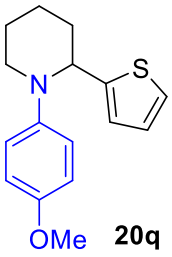
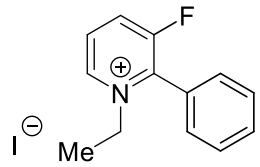
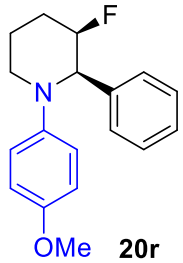
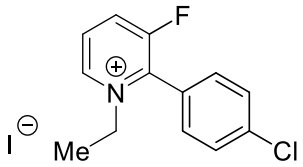
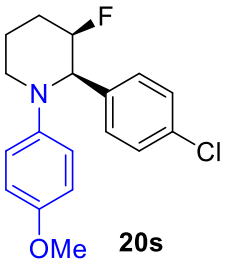
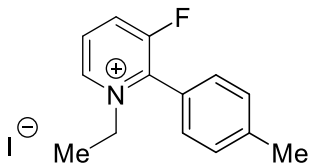
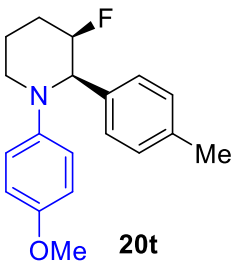
Table 3.2: Scope of the substituted pyridinium salts[a]

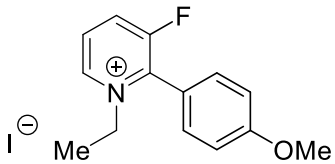
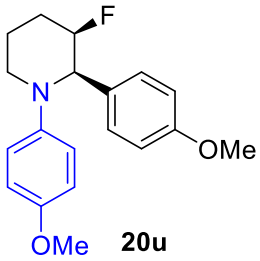
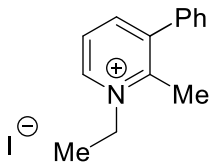
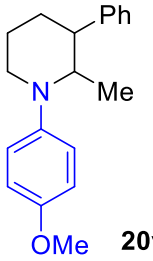


Entry	Substrate	Product	Yield (%)[b]
1		 **20a**	84
2		 **20b**	76
3		 **20c**	81

Entry	Substrate	Product	Yield (%)[b]
4		 **20d**	75
5		 **20e**	78
6		 **20f**	58[c]
7		 **20g**	85
8		 **20h**	88
9		 **20i**	85

Entry	Substrate	Product	Yield (%)[b]
10		 **20j**	86
11		 **20k**	38
12		 **20l**	82
13		 **20m**	76
14		 **20n**	88
15		 **20o**	68

Entry	Substrate	Product	Yield (%)[b]
16		 **20p**	71
17		 **20q**	70
18		 **20r**	72 d.r. 5:1 (*cis*/*trans*)
19		 **20s**	74 d.r. 6:1 (*cis*/*trans*)
20		 **20t**	60 d.r. 6:1 (*cis*/*trans*)

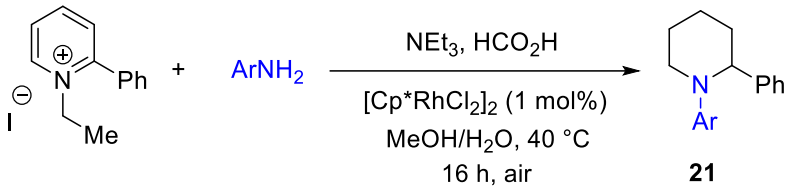
Entry	Substrate	Product	Yield (%)[b]
21		 **20u**	65 d.r. 6:1 (*cis*/*trans*)
22		 **20v**	31 d.r. 5:1

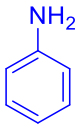
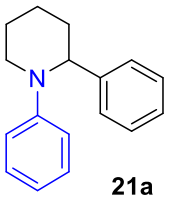
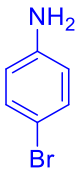
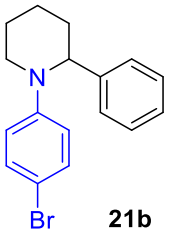
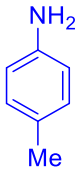
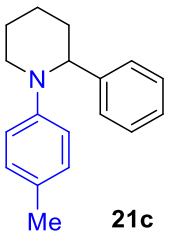
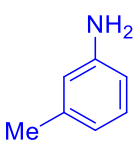
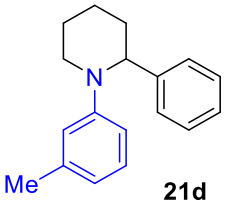
[a] Reaction conditions: 0.5 mmol pyridinium salt, 5 equiv. of *p*-anisidine, 5 equiv. of NEt_3, 24 equiv. of HCO_2H, MeOH/H_2O = 15 : 1 (4.0 mL), 1 mol% $[Cp^*RhCl_2]_2$, 40 °C, 16 h, in air. Analysis by ^1H NMR spectroscopy was conducted to determine the d.r. (*cis*/*trans*). [b] Isolated yield. [c] 1.2 eq. of *p*-anisidine was used.

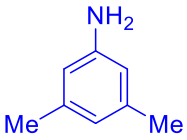
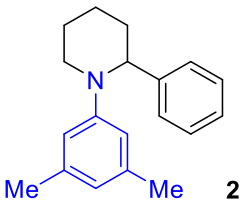
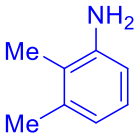
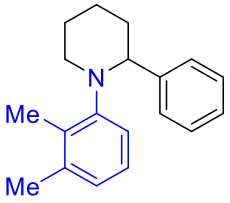
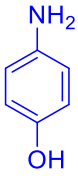
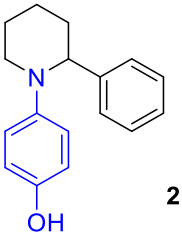
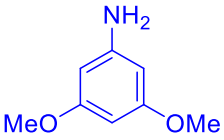
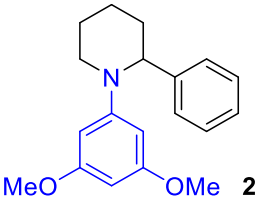
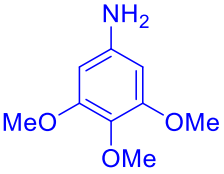
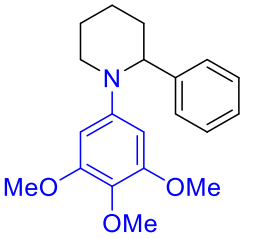
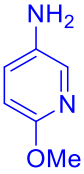
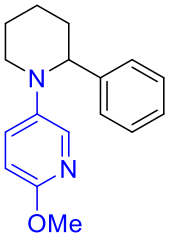
We also extended this approach to aniline derivatives for the synthesis of other *N*-aryl piperidines from their pyridinium precursors (Table 3.3). Methods for obtaining similar products *via* C-N couplings are largely limited to electron-deficient aryl halides coupling partners. Aryl halides without electron-withdrawing groups are usually inactive or give low yields.[37–39] Various electron-rich amines can be applied in the reductive transamination approach to access *N*-aryl piperidines in good yields. The low yield of product **21b**, which bears a *p*-bromine substituent, may be due to the lower nucleophilicity of the aniline. The good yield of product **21f** shows the steric tolerance of transamination in the reaction systems.

The heterocyclic amine (**21j**) was obtained only in 18% yield under the standard conditions (24 equiv. of formic acid), the yield was then increased to 45% when 12 equiv. of formic acid was used, although other heterocyclic amines are not well-tolerated in the reaction system.

Table 3.3: Scope of the aryl amines for *N*-aryl piperidines[a]



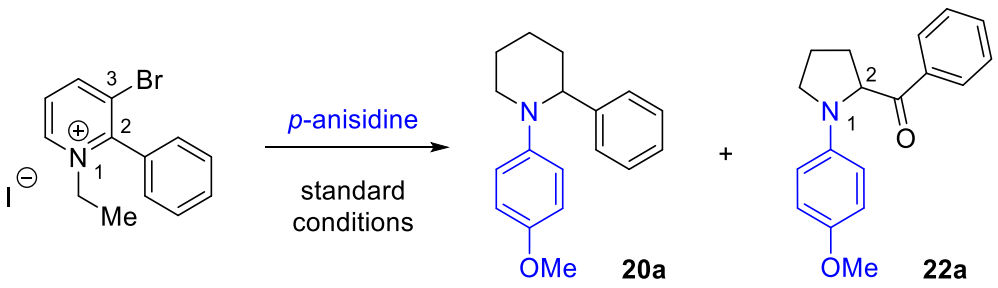
Entry	Amine	Product	Yield (%)[b]
1		 **21a**	48
2		 **21b**	37
3		 **21c**	64
4		 **21d**	57

Entry	Amine	Product	Yield (%)[b]
5		 **21e**	51
6		 **21f**	55
7		 **21g**	77
8		 **21h**	50
9		 **21i**	64
10		 **21j**	45[c]

[a] Reaction conditions were the same as the Table 3.2. [b] Isolated yields. [c] 12 equiv. of HCO_2H was used.

3.2.3 Substrate scope for *N*-arylated pyrrolidines

We next planned to extend the substrate scope of multi-functionalised pyridinium salts beyond the fluorine substituent. An experiment was conducted using 3-bromo-1-ethyl-2-phenylpyridinium iodide as substrate under the same conditions (Scheme 3.4). Product **21a** was isolated from the reaction mixture, presumably due to a hydrodebromination process. Surprisingly, the second product **22a** was identified as an *N*-aryl pyrrolidine, most likely as a result of amine attacking the C3-Br position during the ring-closing step and bromide acting as a leaving group. The product **22a** was characterised by NMR spectra, which are consistent with the structure previously reported in the literature.[40] A peak with the chemical shift at δ 200.39 ppm in the ^{13}C NMR spectrum confirmed the carbonyl group in **22a.** A distinct dd peak at δ 5.12 ppm in the ^{1}H NMR spectrum was observed and assigned to the proton attached to C2, which is adjacent to the nitrogen and carbonyl.



Scheme 3.4: Reductive transamination leads to an *N*-aryl pyrrolidine

Saturated pyrrolidines are widely found in biologically active natural products and are one of the most common ring systems in small molecule drugs.[1-

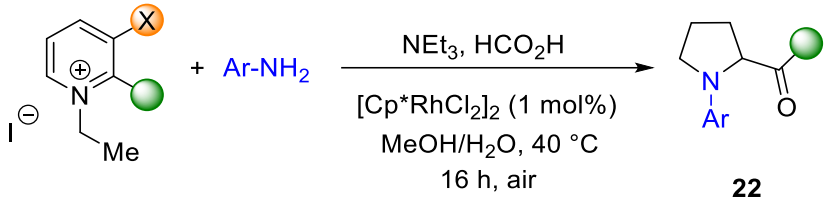
[5] Compound **22a** is also classified as α-amino aryl ketone, a type of structural motif widely available in natural products, pharmaceuticals and clinical drugs.[41–44] However, the reports on the synthesis of cyclic α-amino aryl ketone remain rare, which impedes the biological research on such structures.[40,45]

The yield of the *N*-aryl pyrrolidine is largely affected by the choice of leaving groups at the C3 position on the pyridinium salt. A similar yield (48%) was recorded when bromine was replaced with chlorine, whilst a higher yield (65%) was obtained with the substrate bearing the tosylate group (-OTs). Considering the convenience of the substrate synthesis and the yield of the desired product, we chose 3-tosylate as an optimising leaving group on pyridinium salts to test the functional group and arylamine tolerance. The reactions performed smoothly under the same conditions as for piperidines synthesis. Various pyridinium salts were transformed to the saturated and ring-contracted products, pyrrolidines, in good yields (Table 3.4).

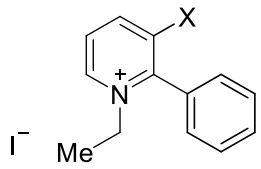
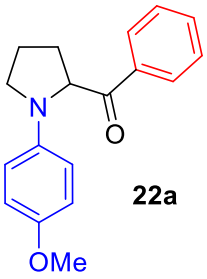
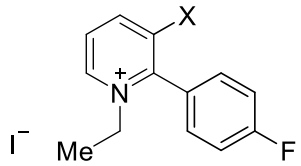
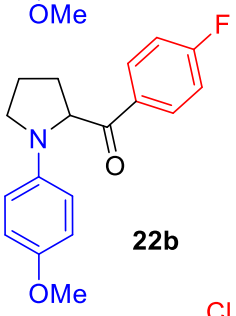
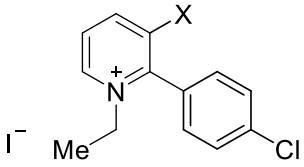
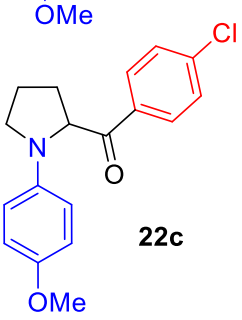
Following our investigation of functional groups on pyridinium salts (**22a-h**), we next explored the scope of a wide range of arylamines in the same reaction system. Taking 3-tosylate-1-ethyl-2-phenylpyridinium iodide as standard substrate, various arylamines were successfully incorporated into the pyrrolidine structures (**22i-s**). In the presence of a lower amount of formic acid (12 equiv.), we observed the incopration of several heteroaryl amines into the pyrrolidine rings (**22p-s**). Hindered five-membered heterocyclic amine gave a low yield of pyrrolidine (**22r**).

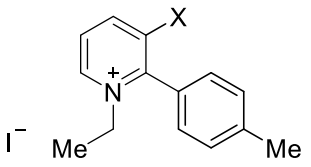
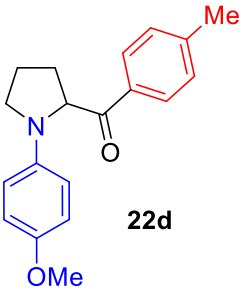
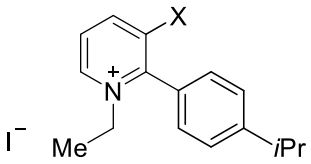
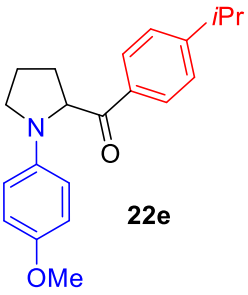
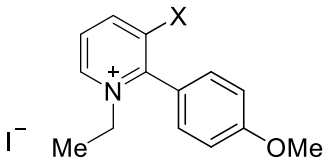
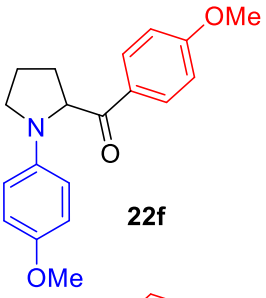
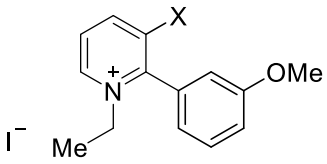
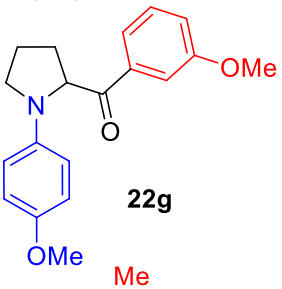
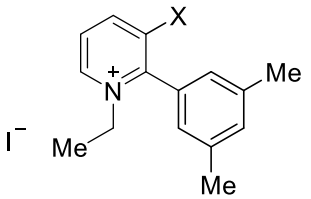
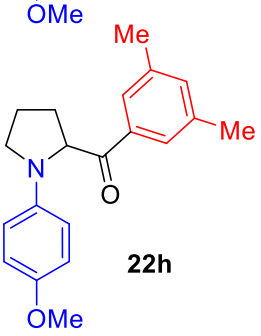
The coupling of pyrrolidines with heteroaromatics remains extremely challenging for current C-N coupling methodologies,[46] and the drawbacks are exacerbated when either coupling partner contains steric bulky functionalities.[47–49]

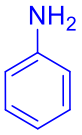
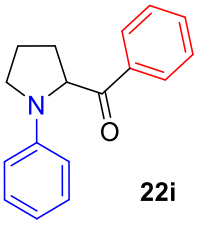
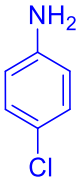
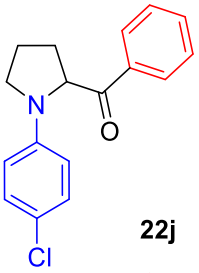
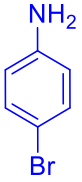
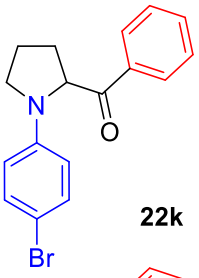
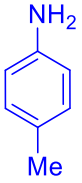
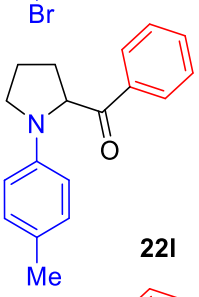
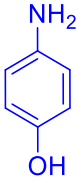
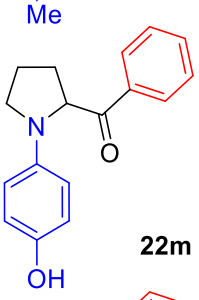
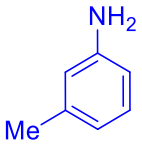
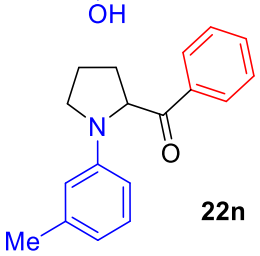
Table 3.4: Scope for synthesis of *N*-aryl pyrrolidines[a]

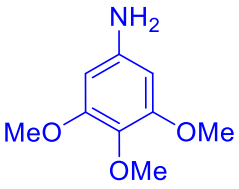
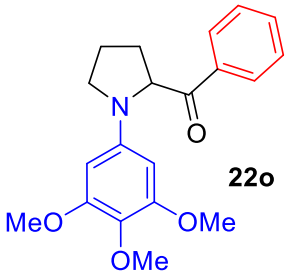
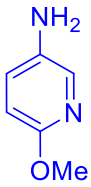
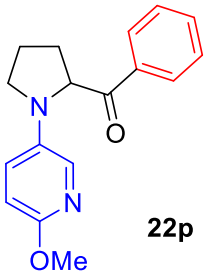
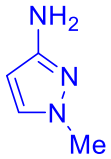
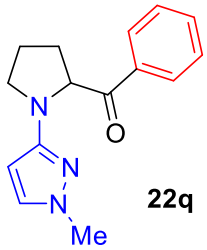
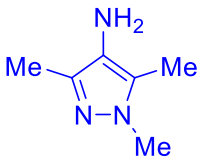
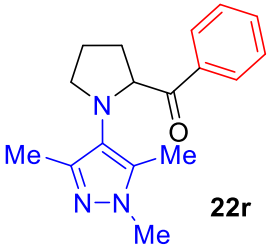
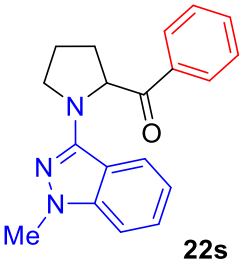


22

Entry	Substrate	Product	Yield (%)[b]
1		 **22a**	65, X = OTs 45, X = Br 48, X = Cl
2		 **22b**	52, X = OTs 24, X = Br
3		 **22c**	58, X = OTs 37, X = Br

Entry	Substrate	Product	Yield (%)[b]
4		 **22d**	70, X = OTs
5		 **22e**	73, X = OTs
6		 **22f**	75, X = OTs 26, X = Br
7		 **22g**	62, X = OTs 25, X = Br
8		 **22h**	72, X = OTs

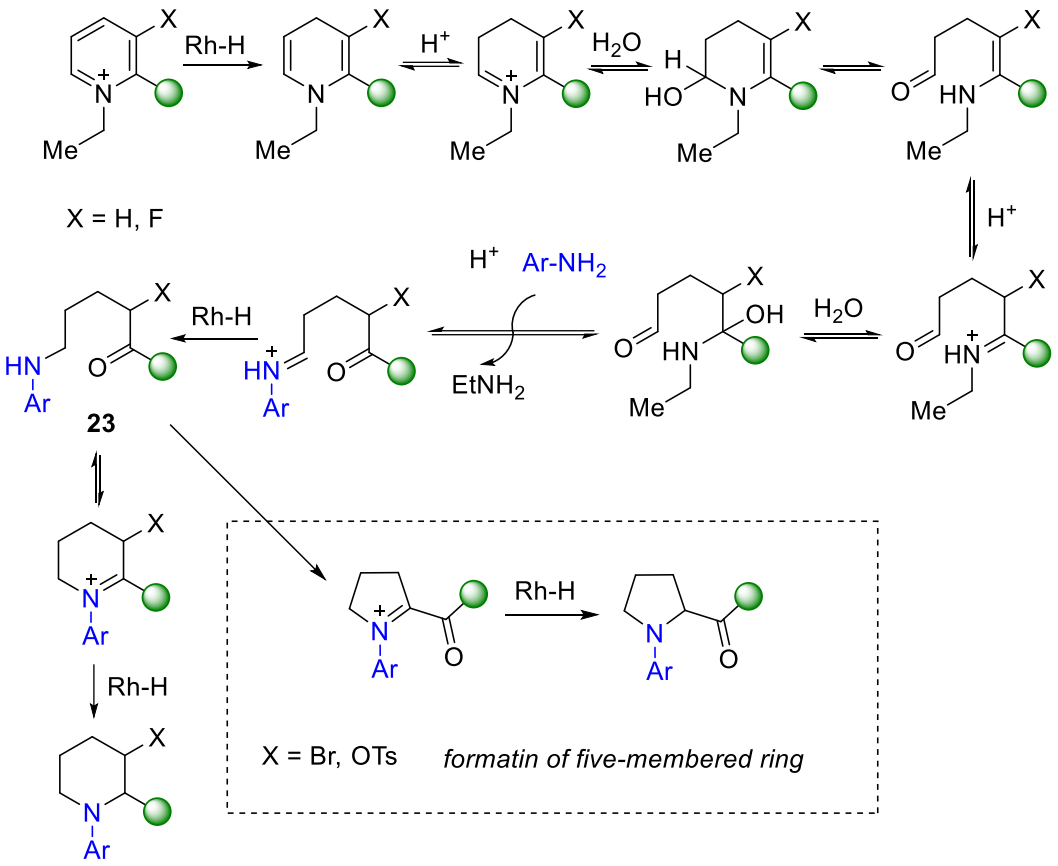
Entry	Amine	Product	Yield (%)[b]
9		 **22i**	53, X = OTs
10		 **22j**	49, X = OTs
11		 **22k**	50, X = OTs
12		 **22l**	63, X = OTs
13		 **22m**	51, X = OTs
14		 **22n**	55, X = OTs

Entry	Amine	Product	Yield (%)[b]
15		 **22o**	57, X = OTs
16		 **22p**	65[c], X = OTs
17		 **22q**	31[c], X = OTs
18		 **22r**	23[c], X = OTs
19		 **22s**	55[c], X = OTs

[a] Reaction conditions were the same as Table 3.2. [b] Isolated yields. [c] 12 equiv. of HCO_2H was used.

3.2.4 Proposed mechanism

Based on previous mechanistic studies on asymmetric hydrogenation of pyridinium salts[50–52] and our research on ART, a plausible mechanism is proposed. The formation of *N*-aryl piperidines would follow the same mechanism as explained in Chapter 2, which is shown in Scheme 3.5. As suggested before, in the presence of water, the interception of dihydropyridinium by water leads to the ring opening of the dihydropyridine, which is followed by the exchange of amino groups *via* hydrolysis at acidic conditions. After condensation of the arylamine with the ring-opened compound, the ring closes and reduction of the tetrahydropyridinium ion gives the *N*-aryl piperidine. For substrates bearing a good leaving group, like tosylate, at the C3 position, the intermediate **23** undergoes a S_N2 nucleophilic substitution reaction, preferentially affording a five-membered pyrrolidine.



Scheme 3.5: Proposed mechanism for the formation of *N*-aryl piperidines and pyrrolidines *via* reductive transamination

3.3 Conclusion

In conclusion, we have developed an efficient catalytic approach for the preparation of *N*-aryl piperidines from easily available pyridinium salts and arylamines *via* reductive transamination using formic acid as reducing agent. This methodology tolerates a wide range of substrates, even those bearing reducible

functional groups, and operates under a mild reaction condition. Notably, introduction of a leaving group on pyridinium salts leads to a ring contracted product, *N*-aryl pyrrolidine. This work thus provides an efficient methodology to access valuable *N*-aryl heterocyclic amines, alternative to the traditional C-N cross couplings. Further applications of chiral rhodium complexes for the ART of pyridinium salts for the synthesis of chiral *N*-aryl heterocyclic amines are under investigation.

3.4 Experimental

3.4.1 General information

Unless otherwise specified, the chemicals were purchased from commercial suppliers (Sigma-Aldrich, Alfa Aesar, Fluorochem, Apollo Scientific and TCI) and used without further purification. DCM was used as purchased and water was distilled. Silica gel plates (GF_{254}) were used for TLC monitoring and silica gel (230-400 mesh) was used for running column chromatography. NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer with TMS as the internal standard. The mass spectra were obtained by chemical ionization (CI). The mass spectra were obtained using a Thermo Finnigan Trio-1000 Mass spectrometer.

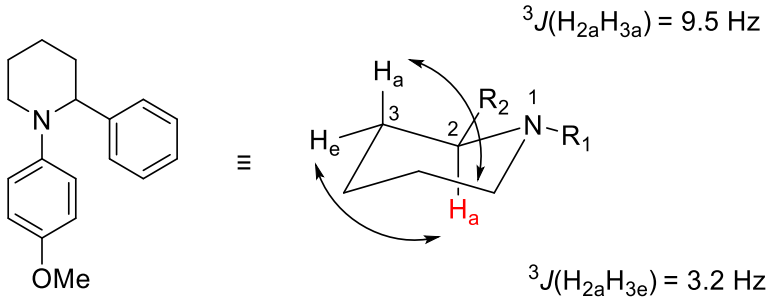
3.4.2 Preparation of pyridinium salts

The pyridinium salts were prepared using the same method as described in Chapter 2.

3.4.3 General procedure for synthesis of *N*-arylated heterocycles

To a carousel reaction tube containing a magnetic stirring bar and *p*-anisidine (308 mg, 2.5 mmol) was added formic acid (564 mg, 12 mmol) and NEt_3 (253 mg, 2.5 mmol) dropwise at room temperature. After stirring the amine/acid mixture for 10 min, a pyridinium salt, *N*-ethyl-2-phenylpyridinium iodide (156 mg, 0.5 mmol), $[Cp^*RhCl_2]_2$ (3.1 mg, 5 μmol), 3.75 mL of MeOH and 0.25 mL of distilled H_2O were introduced into the mixture. The reaction system was placed in a carousel reactor. The mixture was stirred at 40 °C for 16 h, cooled to room temperature and then basified with an aqueous solution of KOH. The resulting mixture was extracted with ethyl acetate (3×10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane) to give the desired product.

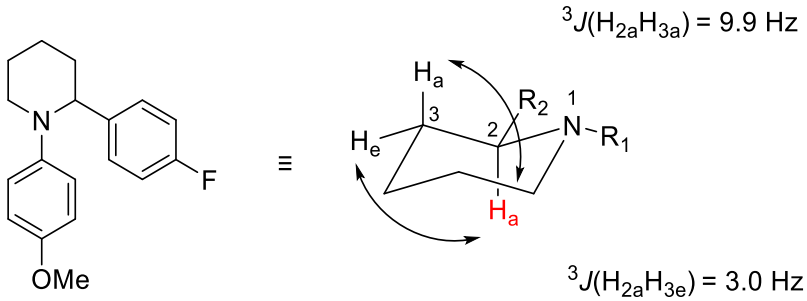
3.5 Analytic data of isolated products



1-(4-Methoxyphenyl)-2-phenylpiperidine (20a):[53]

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a colourless oil (112.2 mg, 84%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 15:1).

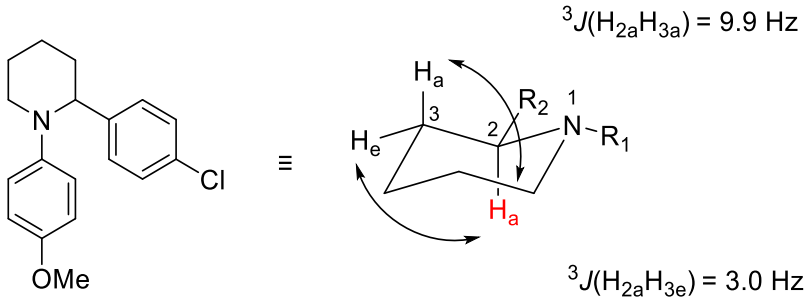
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.30 (d, *J* = 8.0 Hz, 2H), 7.26 – 7.17 (m, 2H), 7.16 – 7.04 (m, 1H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), 4.08 (dd, *J* = 9.5, 3.2 Hz, 1H), 3.71 (s, 3H), 3.48 – 3.36 (m, 1H), 2.93 (ddd, *J* = 11.6, 11.2, 3.2 Hz, 1H), 2.03 – 1.71 (m, 5H), 1.64 – 1.47 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 154.73, 146.40, 144.80, 128.14, 127.55, 126.28, 123.89, 113.89, 64.58, 56.54, 55.36, 36.29, 26.61, 24.29; **HRMS for $C_{18}H_{22}NO$ $[M+H]^+$:** m/z calcd 268.1696, found 268.1700.



2-(4-Fluorophenyl)-1-(4-methoxyphenyl)piperidine (20b):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a pale yellow oil (108.3 mg, 76%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 9:1).

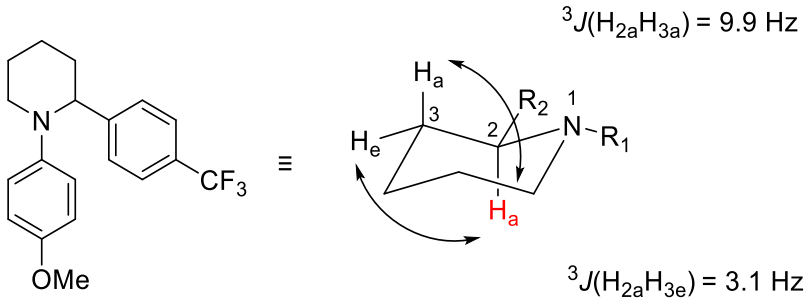
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.20 (dd, *J* = 8.3, 5.6 Hz, 2H), 6.96 – 6.77 (m, 4H), 6.67 (d, *J* = 8.5 Hz, 2H), 3.98 (dd, *J* = 9.9, 3.0 Hz, 1H), 3.69 (s, 3H), 3.42 – 3.28 (m, 1H), 2.91 – 2.77 (m, 1H), 1.97 – 1.61 (m, 5H), 1.59 – 1.40 (m, 1H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -116.92; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 161.30 (d, *J* = 243.8 Hz), 155.04, 146.22, 140.54 (d, *J* = 3.1 Hz), 128.94 (d, *J* = 7.8 Hz), 124.40, 114.92 (d, *J* = 21.0 Hz), 113.91, 64.19, 56.96, 55.37, 36.56, 26.64, 24.43; **HRMS for $C_{18}H_{21}FNO$ $[M+H]^+$:** m/z calcd 286.1602, found 286.1613.



2-(4-Chlorophenyl)-1-(4-methoxyphenyl)piperidine (20c):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a pale yellow oil (121.9 mg, 81%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.18 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 3.97 (dd, *J* = 9.9, 3.0 Hz, 1H), 3.69 (s, 3H), 3.40 – 3.28 (m, 1H), 2.89 – 2.76 (m, 1H), 1.94 – 1.39 (m, 6H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 155.07, 146.13, 143.50, 131.71, 128.90, 128.33, 124.32, 113.97, 64.19, 57.01, 55.39, 36.52, 26.61, 24.39; **HRMS for $C_{18}H_{21}{}^{35}ClNO$ $[M+H]^+$:** m/z calcd 302.1306, found 302.1296.

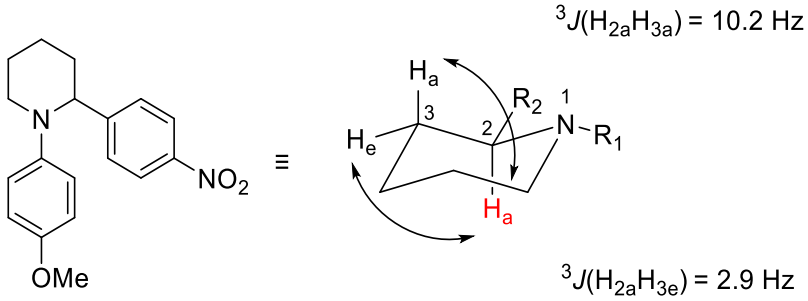


1-(4-Methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)piperidine (20d):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (125.7 mg, 75%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49 – 7.30 (m, 4H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 4.07 (dd, *J* = 9.9, 3.1 Hz, 1H), 3.69 (t, *J* = 1.4 Hz,

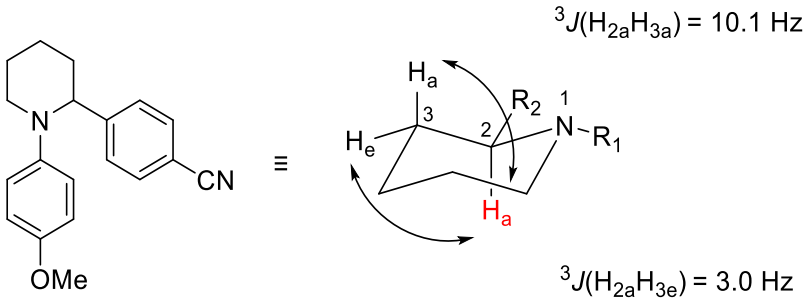
3H), 3.44 – 3.30 (m, 1H), 2.94 – 2.75 (m, 1H), 2.00 – 1.42 (m, 6H); **^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ (ppm):** -62.30; **^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm):** 155.15, 149.19, 146.02, 128.50 (q, *J* = 32.0 Hz), 127.79, 125.19 (q, *J* = 3.8 Hz), 124.40 (q, *J* = 273.7 Hz), 124.24, 114.06, 64.42, 57.09, 55.39, 36.55, 26.56, 24.35; **HRMS for C$_{19}$H$_{21}$F$_3$NO [M+H]$^+$:** m/z calcd 336.1570, found 336.1571.



1-(4-Methoxyphenyl)-2-(4-nitrophenyl)piperidine (20e):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (121.7 mg, 78%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 8:1).

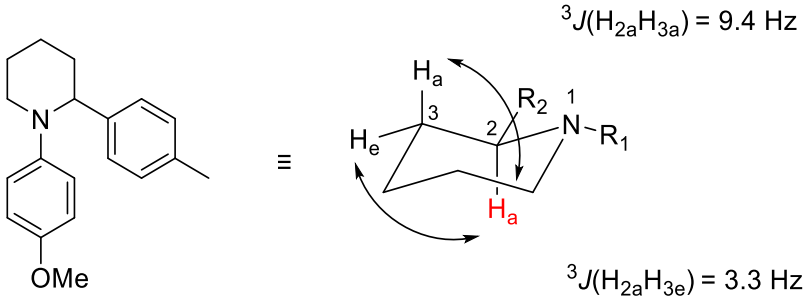
^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 8.01 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 6.65 (d, *J* = 9.0 Hz, 2H), 4.09 (dd, *J* = 10.2, 2.9 Hz, 1H), 3.67 (s, 3H), 3.42 – 3.30 (m, 1H), 2.80 (ddd, *J* = 12.0, 10.4, 3.8 Hz, 1H), 1.97 – 1.73 (m, 4H), 1.71 – 1.39 (m, 2H); **^{13}C NMR (101 MHz, CDCl$_3$) δ (ppm):** 155.47, 153.00, 146.53, 145.73, 128.28, 124.64, 123.60, 114.10, 64.56, 57.49, 55.36, 36.62, 26.53, 24.44; **HRMS for C$_{18}$H$_{21}$N$_2$O$_3$ [M+H]$^+$:** m/z calcd 313.1547, found 313.1542.



4-(1-(4-Methoxyphenyl)piperidin-2-yl)benzonitrile (20f):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (84.7 mg, 58%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 10:1).

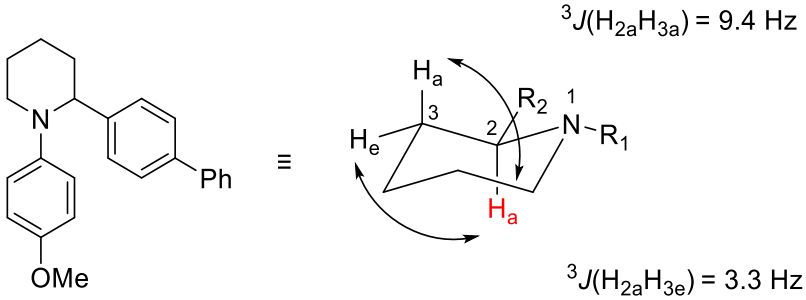
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.65 (d, *J* = 8.9 Hz, 2H), 4.03 (dd, *J* = 10.1, 3.0 Hz, 1H), 3.68 (s, 3H), 3.40 – 3.29 (m, 1H), 2.80 (ddd, *J* = 12.0, 10.1, 3.9 Hz, 1H), 1.95 – 1.72 (m, 4H), 1.70 – 1.41 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 155.36, 150.76, 145.77, 132.14, 128.27, 124.49, 119.17, 114.07, 110.10, 64.68, 57.27, 55.38, 36.49, 26.51, 24.38; **HRMS for $C_{19}H_{21}N_2O$ $[M+H]^+$:** m/z calcd 293.1648, found 293.1640.



1-(4-Methoxyphenyl)-2-(*p*-tolyl)piperidine (20g):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (119.5 mg, 85%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 10:1).

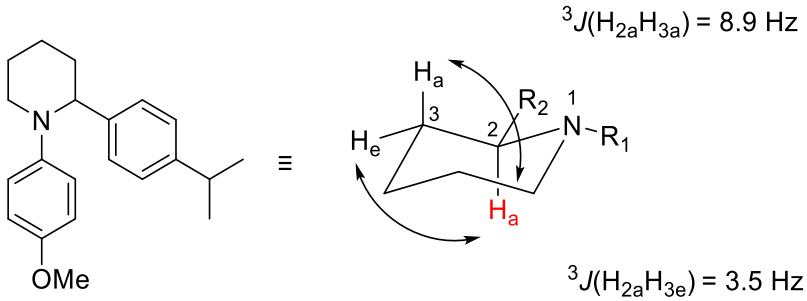
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.14 (d, *J* = 7.8 Hz, 2H), 6.99 (d, *J* = 7.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.9 Hz, 2H), 4.02 (dd, *J* = 9.4, 3.3 Hz, 1H), 3.69 (s, 3H), 3.44 – 3.32 (m, 1H), 2.88 (ddd, *J* = 12.2, 10.1, 3.2 Hz, 1H), 2.25 (s, 3H), 1.98 – 1.68 (m, 5H), 1.61 – 1.42 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 154.65, 146.51, 141.76, 135.66, 128.88, 127.41, 123.78, 113.89, 64.18, 56.46, 55.38, 36.30, 26.62, 24.26, 21.14; **HRMS for $C_{19}H_{24}NO$ $[M+H]^+$:** m/z calcd 282.1852, found 282.1850.



2-([1,1'-Biphenyl]-4-yl)-1-(4-methoxyphenyl)piperidine (20h):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (151.0 mg, 88%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 15:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.58 – 7.49 (m, 2H), 7.45 – 7.34 (m, 4H), 7.34 – 7.27 (m, 3H), 6.96 – 6.89 (m, 2H), 6.71 – 6.64 (m, 2H), 4.09 (dd, *J* = 9.4, 3.3 Hz, 1H), 3.68 (s, 3H), 3.43 – 3.33 (m, 1H), 2.96 – 2.83 (m, 1H), 2.03 – 1.69 (m, 5H), 1.62 – 1.46 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 154.61, 146.29, 143.84, 140.95, 138.87, 128.61, 127.82, 126.92, 126.90, 126.74, 123.67, 113.85, 64.06, 56.29, 55.29, 36.09, 26.47, 24.11; **HRMS for $C_{24}H_{26}NO$ $[M+H]^+$:** m/z calcd 344.2009, found 344.2006.

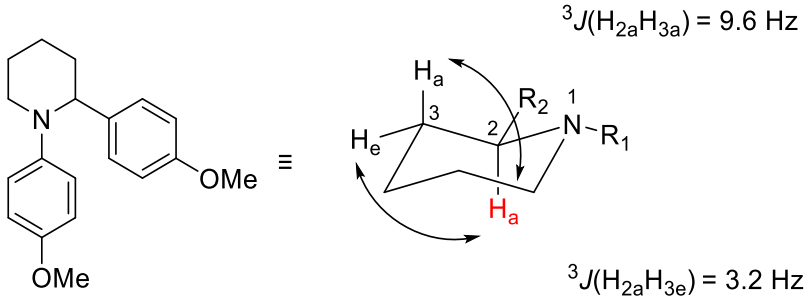


2-(4-Isopropylphenyl)-1-(4-methoxyphenyl)piperidine (20i):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (131.4 mg, 85%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.16 (d, *J* = 8.1 Hz, 2H), 7.07 – 7.00 (m, 2H), 6.94 – 6.87 (m, 2H), 6.73 – 6.64 (m, 2H), 4.08 (dd, *J* = 8.9, 3.5 Hz, 1H), 3.69 (s, 3H), 3.45 – 3.30 (m, 1H), 2.93 (ddd, *J* = 12.5, 9.4, 3.4 Hz, 1H), 2.82 (hept, *J* = 6.9 Hz, 1H), 2.01 – 1.88 (m, 1H), 1.88 – 1.67 (m, 4H), 1.60 – 1.43 (m, 1H), 1.20 (d, *J* = 7.2 Hz, 6H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 154.42, 146.57, 146.50,

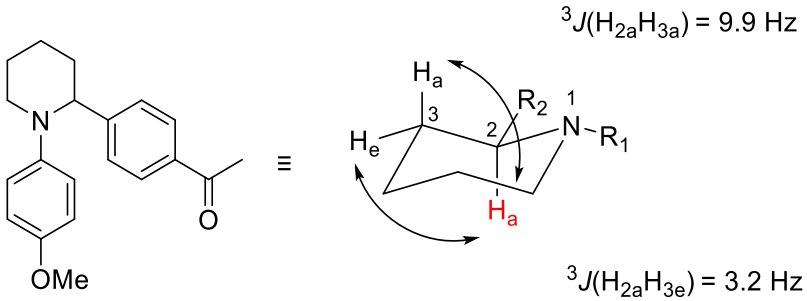
141.83, 127.35, 126.17, 123.26, 113.93, 63.89, 55.74, 55.42, 35.88, 33.67, 26.52, 24.09, 24.03; **HRMS for $C_{21}H_{28}NO$ [M+H]$^+$:** m/z calcd 310.2165, found 310.2172.



1,2-Bis(4-methoxyphenyl)piperidine (20j):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (127.7 mg, 86%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 10:1).

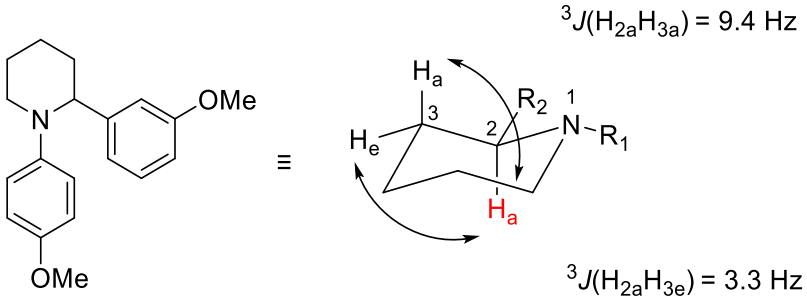
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.16 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.76 – 6.61 (m, 4H), 3.99 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.42 – 3.28 (m, 1H), 2.96 – 2.79 (m, 1H), 2.00 – 1.65 (m, 5H), 1.61 – 1.41 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 157.92, 154.75, 146.45, 136.86, 128.51, 124.02, 113.86, 113.50, 64.02, 56.55, 55.36, 55.15, 36.30, 26.62, 24.33; **HRMS for $C_{19}H_{24}NO_2$ [M+H]$^+$:** m/z calcd 298.1802, found 298.1799.



1-(4-(1-(4-Methoxyphenyl)piperidin-2-yl)phenyl)ethan-1-one (20k):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (58.7 mg, 38%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 15:1).

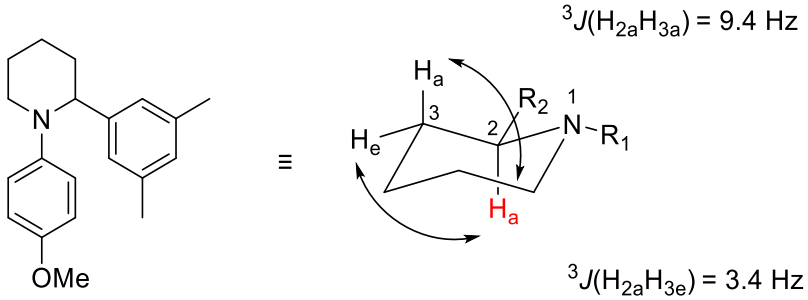
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 6.65 (d, *J* = 8.9 Hz, 2H), 4.06 (dd, *J* = 9.9, 3.2 Hz, 1H), 3.67 (s, 3H), 3.43 – 3.29 (m, 1H), 2.82 (ddd, *J* = 11.9, 10.5, 3.5 Hz, 1H), 2.50 (s, 3H), 1.96 – 1.38 (m, 6H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 197.97, 155.11, 150.82, 146.09, 135.49, 128.46, 127.69, 124.28, 114.00, 64.62, 57.16, 55.37, 36.43, 26.63, 26.58, 24.39; **HRMS for $C_{20}H_{24}NO_2$ $[M+H]^+$:** m/z calcd 310.1802, found 310.1796.



2-(3-Methoxyphenyl)-1-(4-methoxyphenyl)piperidine (20l):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (121.8 mg, 82%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 10:1).

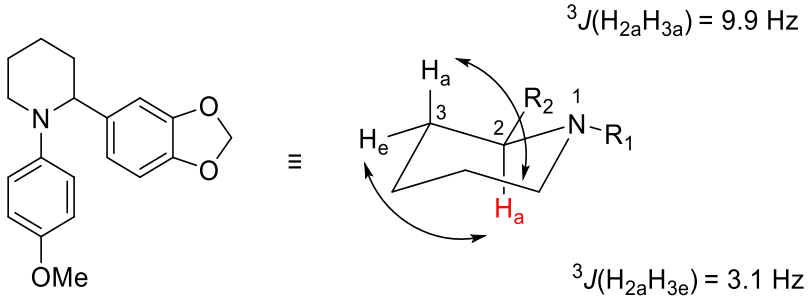
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.08 (t, *J* = 8.0 Hz, 1H), 6.94 – 6.87 (m, 2H), 6.86 – 6.79 (m, 2H), 6.70 – 6.63 (m, 2H), 6.63 – 6.56 (m, 1H), 4.01 (dd, *J* = 9.4, 3.3 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.40 – 3.30 (m, 1H), 2.85 (ddd, *J* = 12.0, 10.1, 3.5 Hz, 1H), 1.97 – 1.65 (m, 5H), 1.55 – 1.41 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 159.53, 154.75, 146.62, 146.47, 129.05, 123.77, 120.06, 113.96, 113.20, 111.72, 64.47, 56.51, 55.43, 55.23, 36.20, 26.58, 24.25; **HRMS for $C_{19}H_{24}NO_2$ $[M+H]^+$:** m/z calcd 298.1802, found 298.1795.



2-(3,5-Dimethylphenyl)-1-(4-methoxyphenyl)piperidine (20m):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (112.1 mg, 76%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.95 – 6.88 (m, 2H), 6.86 (s, 2H), 6.72 (s, 1H), 6.71 – 6.63 (m, 2H), 3.98 (dd, *J* = 9.4, 3.4 Hz, 1H), 3.69 (s, 3H), 3.43 – 3.30 (m, 1H), 2.87 (ddd, *J* = 12.4, 9.8, 3.4 Hz, 1H), 2.21 (s, 6H), 1.97 – 1.63 (m, 5H), 1.57 – 1.40 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 154.58, 146.56, 144.69, 137.42, 127.99, 125.34, 123.52, 113.94, 64.38, 56.27, 55.42, 36.11, 26.53, 24.18, 21.46; **HRMS for $C_{20}H_{26}NO$ $[M+H]^+$:** m/z calcd 296.2009, found 296.2022.

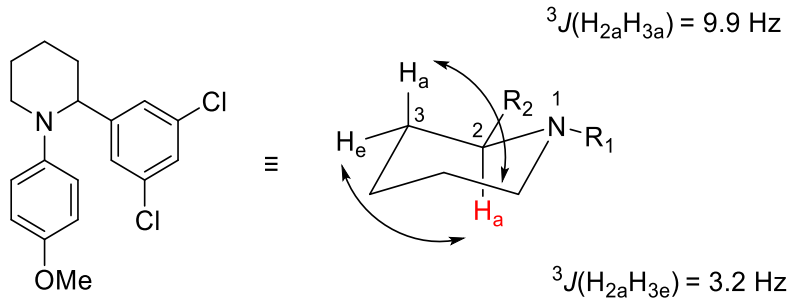


2-(Benzo[d][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)piperidine (20n):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (136.9 mg, 88%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 15:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.96 – 6.84 (m, 2H), 6.78 (s, 1H), 6.72 – 6.63 (m, 3H), 6.64 – 6.55 (m, 1H), 5.84 (s, 2H), 3.91 (dd, *J* = 9.9, 3.1 Hz, 1H), 3.70 (s, 3H), 3.40 – 3.25 (m, 1H), 2.88 – 2.72 (m, 1H), 1.96 – 1.55 (m, 5H), 1.55 – 1.36 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 154.93, 147.45, 146.41, 145.79, 139.07, 124.26, 120.61, 113.91, 107.97, 107.87, 100.75, 64.45, 56.95, 55.40, 36.60,

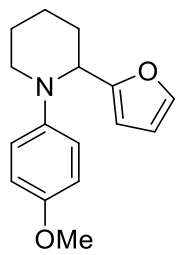
26.63, 24.40; **HRMS for $C_{19}H_{22}NO_3$ [M+H]$^+$:** m/z calcd 312.1594, found 312.1585.



2-(3,5-Dichlorophenyl)-1-(4-methoxyphenyl)piperidine (20o):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (113.9 mg, 68%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 10:1).

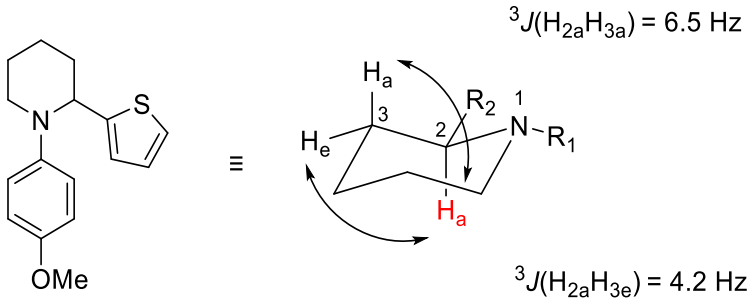
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.18 – 7.11 (m, 2H), 7.09 – 7.02 (m, 1H), 6.94 – 6.84 (m, 2H), 6.73 – 6.66 (m, 2H), 3.95 (dd, *J* = 9.9, 3.2 Hz, 1H), 3.70 (s, 3H), 3.38 – 3.27 (m, 1H), 2.80 (ddd, *J* = 12.1, 9.7, 4.0 Hz, 1H), 1.97 – 1.55 (m, 5H), 1.55 – 1.39 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 155.34, 148.70, 145.71, 134.58, 126.61, 126.09, 124.31, 114.18, 64.08, 56.92, 55.41, 36.35, 26.41, 24.21; **HRMS for $C_{18}H_{20}{}^{35}Cl_2NO$ [M+H]$^+$:** m/z calcd 336.0916, found 336.0904.



2-(Furan-2-yl)-1-(4-methoxyphenyl)piperidine (20p):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (91.3 mg, 71%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 15:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32 – 7.20 (m, 1H), 6.95 – 6.86 (m, 2H), 6.82 – 6.72 (m, 2H), 6.24 – 6.15 (m, 1H), 5.95 – 5.86 (m, 1H), 4.62 – 4.54 (m, 1H), 3.75 (s, 3H), 3.24 – 3.12 (m, 2H), 2.22 – 2.09 (m, 1H), 2.06 – 1.93 (m, 1H), 1.88 – 1.51 (m, 4H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 155.41, 153.92, 145.66, 140.89, 120.17, 114.23, 109.96, 107.26, 56.94, 55.57, 49.14, 30.58, 26.04, 21.70; **HRMS for $C_{16}H_{20}NO_2$ $[M+H]^+$:** m/z calcd 258.1489, found 258.1495.

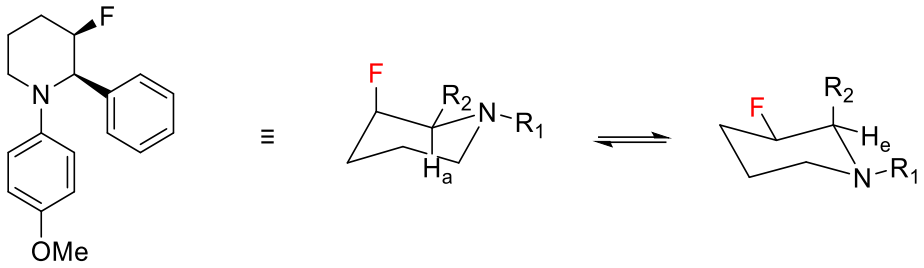


1-(4-Methoxyphenyl)-2-(thiophen-2-yl)piperidine (20q):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (95.5 mg, 70%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 15:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.11 – 7.04 (m, 1H), 6.98 – 6.90 (m, 2H), 6.84 – 6.78 (m, 1H), 6.79 – 6.71 (m, 3H), 4.71 (dd, *J* = 6.5, 4.2 Hz, 1H), 3.73 (s,

3H), 3.25 (ddd, *J* = 11.4, 7.2, 3.9 Hz, 1H), 3.10 (ddd, *J* = 12.2, 6.8, 3.9 Hz, 1H), 2.17 – 1.91 (m, 2H), 1.89 – 1.68 (m, 3H), 1.68 – 1.50 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 154.26, 147.35, 145.69, 126.12, 124.76, 123.79, 121.49, 114.20, 59.10, 55.52, 51.11, 34.44, 25.96, 22.31; **HRMS for $C_{16}H_{20}NOS$ $[M+H]^+$:** m/z calcd 274.1260, found 274.1269.

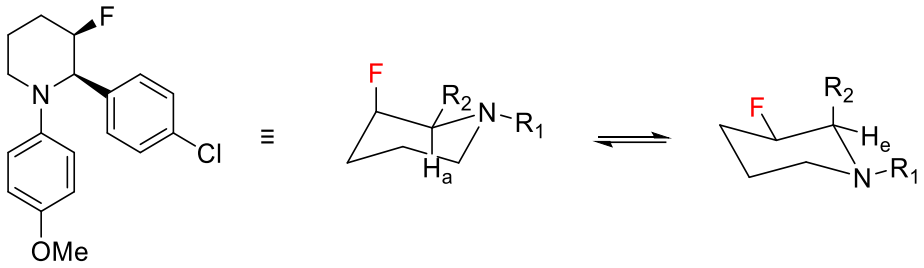


3-Fluoro-1-(4-methoxyphenyl)-2-phenylpiperidine (20r):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated in a mixture of diastereomers (d.r. 5:1 *cis*/*trans*) as a yellow oil (102.6 mg, 72%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1). The compound exists as two conformational isomers, as indicated by the $^{19}F\{^1H\}$ spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of $^3J(F, H_a)$.[35,36] [^3J(3-F, 2-H_a) = 26.9 Hz]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 – 7.26 (m, 2H), 7.23 – 7.06 (m, 3H), 6.98 – 6.85 (m, 2H), 6.72 – 6.59 (m, 2H), 4.77 (dm, *J* = 47.4 Hz, 1H), 4.16 (dm, *J* = 26.9 Hz, 1H), 3.68 (s, 3H), 3.48 – 3.37 (m, 1H), 2.91 – 2.77 (m, 1H), 2.32 – 2.13

(m, 2H), 1.98 – 1.60 (m, 2H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -193.78; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 155.25, 145.53, 139.81, 128.98, 127.98, 127.03, 124.43, 114.00, 90.65 (d, *J* = 181.0 Hz), 67.19 (d, *J* = 17.6 Hz), 56.87, 55.38, 29.39 (d, *J* = 21.7 Hz), 21.20; **HRMS for $C_{18}H_{21}FNO$ $[M+H]^+$:** m/z calcd 286.1602, found 286.1602.

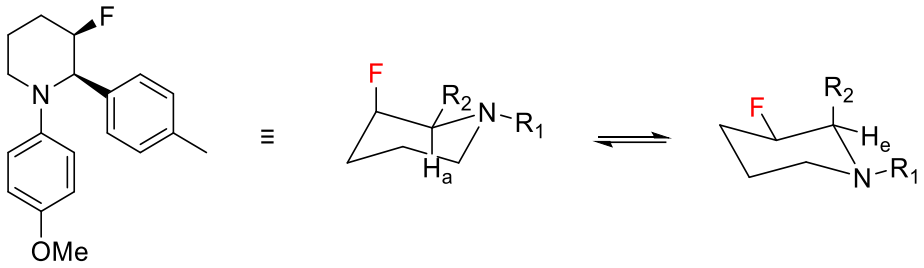


2-(4-Chlorophenyl)-3-fluoro-1-(4-methoxyphenyl)piperidine (20s):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated in a mixture of diastereomers (d.r. 6:1 *cis*/*trans*) as a yellow oil (118.1 mg, 74%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H_a).[35,36] [^{3}J(3-F, 2-H_a) = 26.9 Hz]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32 – 7.23 (m, 2H), 7.22 – 7.12 (m, 2H), 6.96 – 6.88 (m, 2H), 6.73 – 6.64 (m, 2H), 4.74 (dm, *J* = 47.3 Hz, 1H), 4.14 (dm, *J* = 26.9 Hz, 1H), 3.71 (s, 3H), 3.48 – 3.36 (m, 1H), 2.91 – 2.77 (m, 1H), 2.32 – 2.16

(m, 2H), 1.90 – 1.63 (m, 2H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -194.36; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 155.52, 145.20, 138.42, 132.63, 130.32, 128.19, 124.69, 114.09, 90.40 (d, *J* = 181.0 Hz), 66.67 (d, *J* = 17.4 Hz), 57.07, 55.39, 29.36 (d, *J* = 21.7 Hz), 21.09 (d, *J* = 2.0 Hz); **HRMS for $C_{18}H_{20}{}^{35}ClFNO$ [M+H]$^+$:** m/z calcd 320.1212, found 320.1204.

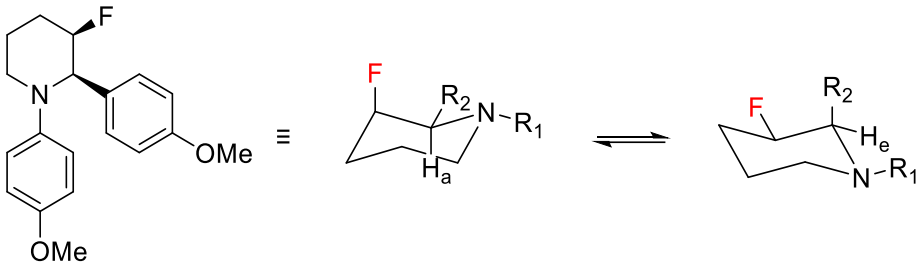


3-Fluoro-1-(4-methoxyphenyl)-2-(p-tolyl)piperidine (20t):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated in a mixture of diastereomers (d.r. 6:1 *cis*/*trans*) as a yellow solid (89.7 mg, 60%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H_a).[35,36] [^{3}J(3-F, 2-H_a) = 26.8 Hz]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.23 – 7.17 (m, 2H), 7.03 – 6.97 (m, 2H), 6.96 – 6.90 (m, 2H), 6.71 – 6.63 (m, 2H), 4.75 (dm, *J* = 47.2 Hz, 1H), 4.14 (dm, *J* = 26.8 Hz, 1H), 3.68 (s, 3H), 3.49 – 3.37 (m, 1H), 2.89 – 2.78 (m, 1H), 2.24 (s, 3H),

2.28 – 2.18 (m, 2H), 1.97 – 1.62 (m, 2H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -193.53; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 155.17, 145.63, 136.74, 136.47, 128.77 (d, *J* = 1.6 Hz), 128.73, 124.34, 113.97, 90.80 (d, *J* = 180.6 Hz), 66.81 (d, *J* = 17.6 Hz), 56.81, 55.36, 29.35 (d, *J* = 21.7 Hz), 21.24 (d, *J* = 2.1 Hz), 21.19; **HRMS for $C_{19}H_{23}FNO$ $[M+H]^+$:** m/z calcd 300.1758, found 300.1752.

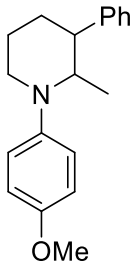


3-Fluoro-1,2-bis(4-methoxyphenyl)piperidine (20u):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated in a mixture of diastereomers (d.r. 6:1 *cis*/*trans*) as a yellow solid (102.4 mg, 65%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1). The compound exists as two conformational isomers, as indicated by the ^{19}F{^{1}H} spectrum. The orientation of the fluorine atom in the major isomer (left) is assigned as axial due to the large value of ^{3}J(F, H_a).[35,36] [^{3}J(3-F, 2-H_a) = 26.7 Hz]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.25 – 7.19 (m, 2H), 6.96 – 6.88 (m, 2H), 6.76 – 6.70 (m, 2H), 6.70 – 6.63 (m, 2H), 4.74 (dm, *J* = 48.7 Hz, 1H), 4.11 (dm, *J* = 26.7 Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.47 – 3.36 (m, 1H), 2.91 – 2.77 (m, 1H),

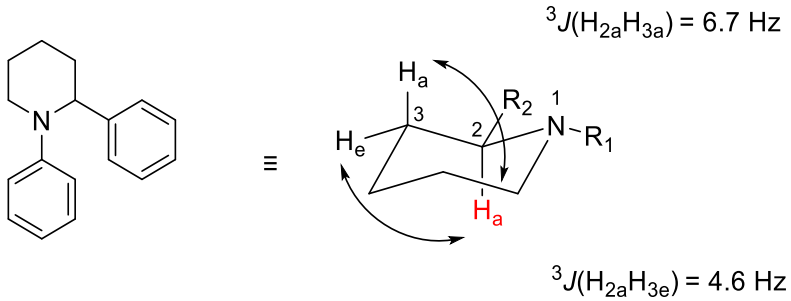
2.30 – 2.12 (m, 2H), 1.96 – 1.58 (m, 2H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -193.72; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 158.33, 155.11, 145.47, 131.74, 129.83, 124.40, 113.84, 113.27, 90.73 (d, *J* = 180.3 Hz), 66.41 (d, *J* = 17.5 Hz), 56.71, 55.25, 55.05, 29.26 (d, *J* = 21.7 Hz), 21.13 (d, *J* = 2.1 Hz); **HRMS for $C_{19}H_{23}FNO_2$ [M+H]$^+$:** m/z calcd 316.1707, found 316.1704.



1-(4-Methoxyphenyl)-2-methyl-3-phenylpiperidine (20v):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated in a mixture of diastereomers (d.r. 5:1) as a yellow oil (43.6 mg, 31%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 15:1).

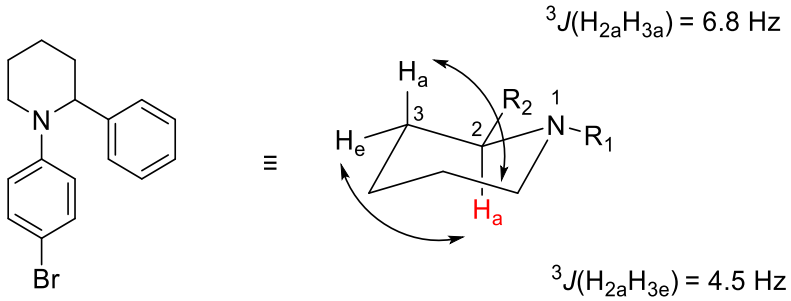
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 – 7.20 (m, 5H), 6.97 – 6.89 (m, 2H), 6.88 – 6.81 (m, 2H), 4.17 – 4.02 (m, 1H), 3.79 (s, 3H), 3.38 – 3.20 (m, 2H), 3.07 – 2.93 (m, 1H), 2.11 – 1.92 (m, 2H), 1.90 – 1.75 (m, 2H), 0.68 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 153.00, 145.32, 143.98, 128.40, 127.89, 126.33, 118.48, 114.57, 58.62, 55.72, 45.99, 42.19, 26.03, 22.61, 6.53; **HRMS for $C_{19}H_{24}NO$ [M+H]$^+$:** m/z calcd 282.1852, found 282.1843.



1,2-Diphenylpiperidine (21a):[21]

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (56.9 mg, 48%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 10:1).

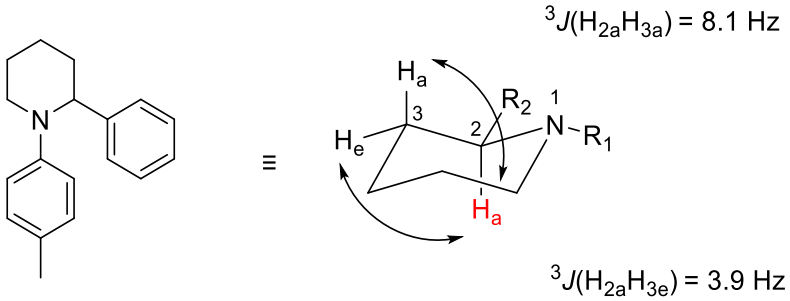
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 – 7.22 (m, 4H), 7.23 – 7.11 (m, 3H), 6.94 (d, *J* = 8.1 Hz, 2H), 6.80 (t, *J* = 7.3 Hz, 1H), 4.55 (dd, *J* = 6.7, 4.6 Hz, 1H), 3.54 – 3.38 (m, 1H), 3.37 – 3.21 (m, 1H), 2.11 – 1.92 (m, 2H), 1.89 – 1.66 (m, 3H), 1.66 – 1.53 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 151.94, 143.70, 128.90, 128.36, 127.33, 126.32, 119.67, 118.86, 61.13, 50.63, 33.57, 25.75, 22.15; **HRMS for $C_{17}H_{20}N$ $[M+H]^+$:** m/z calcd 238.1590, found 238.1593.



1-(4-Bromophenyl)-2-phenylpiperidine (21b):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (58.2 mg, 37%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 8:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.25 – 7.18 (m, 6H), 7.18 – 7.10 (m, 1H), 6.75 (d, *J* = 8.9 Hz, 2H), 4.44 (dd, *J* = 6.8, 4.5 Hz, 1H), 3.46 – 3.30 (m, 1H), 3.28 – 3.14 (m, 1H), 2.10 – 1.85 (m, 2H), 1.83 – 1.61 (m, 3H), 1.61 – 1.43 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 150.97, 143.26, 131.72, 128.50, 127.24, 126.53, 120.48, 111.89, 61.12, 50.66, 33.64, 25.65, 21.94; **HRMS for $C_{17}H_{19}BrN$ $[M+H]^+$:** m/z calcd 316.0695 and 318.0675, found 316.0694 and 318.0681.

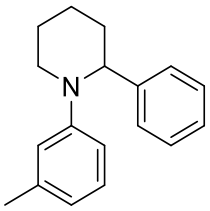


2-Phenyl-1-(*p*-tolyl)piperidine (21c):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (80.3 mg, 64%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32 (d, *J* = 7.7 Hz, 2H), 7.29 – 7.21 (m, 2H), 7.21 – 7.12 (m, 1H), 6.99 (d, *J* = 8.1 Hz, 2H), 6.88 (d, *J* = 8.1 Hz, 2H), 4.36 (dd, *J* = 8.1, 3.9 Hz, 1H), 3.52 – 3.39 (m, 1H), 3.20 – 3.07 (m, 1H), 2.24 (s, 3H),

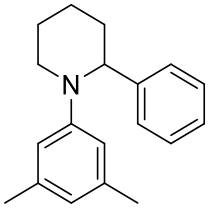
2.09 – 1.97 (m, 1H), 1.97 – 1.71 (m, 4H), 1.67 – 1.49 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 150.02, 144.35, 129.82, 129.38, 128.27, 127.39, 126.25, 120.44, 62.42, 53.24, 34.80, 26.14, 23.10, 20.65; **HRMS for $C_{18}H_{22}N$ $[M+H]^+$:** m/z calcd 252.1747, found 252.1742.



2-Phenyl-1-(m-tolyl)piperidine (21d):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (71.5 mg, 57%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 10:1).

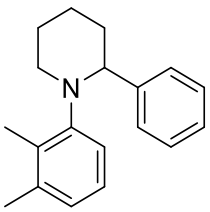
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 – 7.24 (m, 4H), 7.24 – 7.13 (m, 1H), 7.12 – 7.01 (m, 1H), 6.79 (s, 1H), 6.77 – 6.70 (m, 1H), 6.67 – 6.59 (m, 1H), 4.64 – 4.51 (m, 1H), 3.51 – 3.38 (m, 1H), 3.38 – 3.25 (m, 1H), 2.29 (s, 3H), 2.11 – 1.94 (m, 2H), 1.91 – 1.52 (m, 4H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 151.93, 143.67, 138.51, 128.72, 128.36, 127.32, 126.28, 120.43, 119.45, 115.55, 60.94, 50.22, 33.25, 25.72, 22.07, 21.83; **HRMS for $C_{18}H_{22}N$ $[M+H]^+$:** m/z calcd 252.1747, found 252.1749.



1-(3,5-Dimethylphenyl)-2-phenylpiperidine (21e):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (67.6 mg, 51%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 10:1).

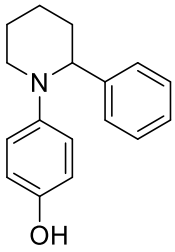
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36 – 7.27 (m, 4H), 7.22 – 7.12 (m, 1H), 6.56 (s, 2H), 6.45 (s, 1H), 4.65 – 4.54 (m, 1H), 3.45 – 3.26 (m, 2H), 2.23 (s, 6H), 2.09 – 1.95 (m, 2H), 1.85 – 1.48 (m, 4H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 151.91, 143.59, 138.36, 128.37, 127.32, 126.25, 121.27, 116.06, 60.67, 49.62, 32.80, 25.66, 21.93, 21.73; **HRMS for $C_{19}H_{24}N$ $[M+H]^+$:** m/z calcd 266.1903, found 266.1905.



1-(2,3-Dimethylphenyl)-2-phenylpiperidine (21f):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow solid (72.9 mg, 55%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 10:1).

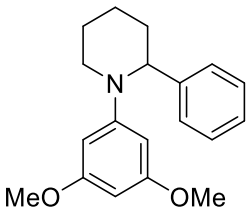
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.22 – 7.14 (m, 2H), 7.14 – 7.06 (m, 2H), 7.04 – 6.95 (m, 1H), 6.84 – 6.76 (m, 2H), 6.76 – 6.64 (m, 1H), 4.09 – 3.96 (m, 1H), 3.14 – 2.99 (m, 1H), 2.58 – 2.44 (m, 1H), 2.33 (s, 3H), 2.19 (s, 3H), 2.00 – 1.47 (m, 6H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 150.97, 145.33, 137.30, 133.07, 127.91, 127.12, 126.10, 125.01, 124.92, 120.02, 65.41, 56.88, 37.82, 26.67, 25.38, 20.62, 13.37; **HRMS for $C_{19}H_{24}N$ $[M+H]^+$:** m/z calcd 266.1903, found 266.1902.



4-(2-Phenylpiperidin-1-yl)phenol (21g):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a white solid (97.4 mg, 77%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 15:1).

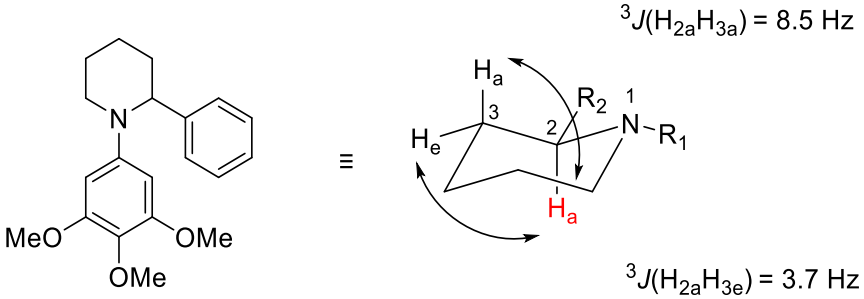
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28 – 7.20 (m, 2H), 7.20 – 7.12 (m, 2H), 7.11 – 7.02 (m, 1H), 6.94 – 6.72 (m, 2H), 6.67 – 6.40 (m, 2H), 4.86 (brs, 1H), 4.11 – 3.80 (m, 1H), 3.49 – 3.18 (m, 1H), 3.06 – 2.64 (m, 1H), 2.01 – 1.65 (m, 5H), 1.61 – 1.38 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 150.76, 146.38, 144.65, 128.14, 127.65, 126.35, 124.36, 115.48, 65.07, 56.72, 36.18, 26.53, 24.37; **HRMS for $C_{17}H_{20}NO$ $[M+H]^+$:** m/z calcd 254.1539, found 254.1532.



1-(3,5-Dimethoxyphenyl)-2-phenylpiperidine (21h):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (74.3 mg, 50%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 15:1).

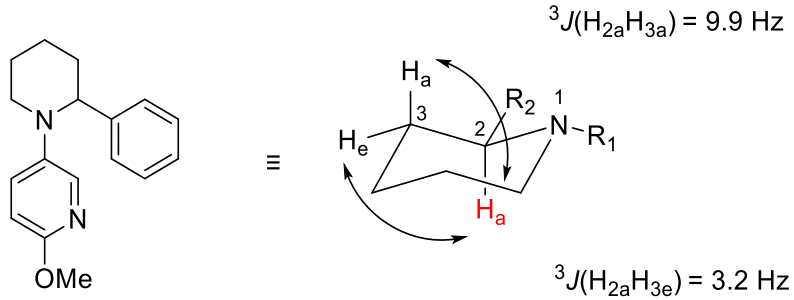
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34 – 7.24 (m, 4H), 7.23 – 7.11 (m, 1H), 6.09 (d, *J* = 2.2 Hz, 2H), 5.95 (t, *J* = 2.2 Hz, 1H), 4.68 – 4.55 (m, 1H), 3.71 (s, 6H), 3.42 – 3.33 (m, 2H), 2.07 – 1.99 (m, 2H), 1.83 – 1.72 (m, 2H), 1.71 – 1.52 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 161.34, 153.64, 143.30, 128.46, 127.18, 126.36, 96.62, 91.31, 60.53, 55.26, 48.84, 32.50, 25.45, 21.43; **HRMS for $C_{19}H_{24}NO_2$ $[M+H]^+$:** m/z calcd 298.1802, found 298.1804.



2-Phenyl-1-(3,4,5-trimethoxyphenyl)piperidine (21i):

The titled compound was synthesised according to general procedure at 0.5 mmol scale. The product was isolated as a yellow oil (104.7 mg, 64%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 15:1).

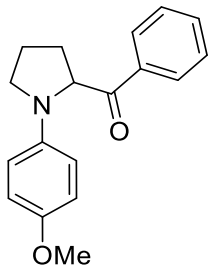
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32 – 7.18 (m, 4H), 7.18 – 7.06 (m, 1H), 6.16 (s, 2H), 4.20 (dd, *J* = 8.5, 3.7 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 6H), 3.52 – 3.41 (m, 1H), 3.13 – 3.00 (m, 1H), 2.04 – 1.94 (m, 1H), 1.92 – 1.72 (m, 4H), 1.63 – 1.45 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 153.08, 148.75, 144.34, 132.52, 128.34, 127.23, 126.43, 98.92, 63.54, 60.99, 56.02, 53.98, 34.99, 26.22, 23.33; **HRMS for $C_{20}H_{26}NO_3$ $[M+H]^+$:** m/z calcd 328.1907, found 328.1917.



2-Methoxy-5-(2-phenylpiperidin-1-yl)pyridine (21j):

The titled compound was synthesised according to modified general procedure at 0.5 mmol scale using 12 equiv. of formic acid. The product was isolated as a yellow oil (60.3 mg, 45%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 12:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.82 (d, *J* = 2.8 Hz, 1H), 7.31 – 7.23 (m, 3H), 7.21 – 7.14 (m, 2H), 7.13 – 7.05 (m, 1H), 6.52 (d, *J* = 8.8 Hz, 1H), 3.99 (dd, *J* = 9.9, 3.2 Hz, 1H), 3.82 (s, 3H), 3.42 – 3.28 (m, 1H), 2.94 – 2.79 (m, 1H), 2.00 – 1.67 (m, 5H), 1.62 – 1.43 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 159.73, 144.12, 143.04, 142.03, 134.43, 128.35, 127.60, 126.64, 110.27, 64.96, 57.15, 53.37, 36.47, 26.57, 24.42; **HRMS for $C_{17}H_{21}N_2O$ $[M+H]^+$:** m/z calcd 269.1648, found 269.1655.

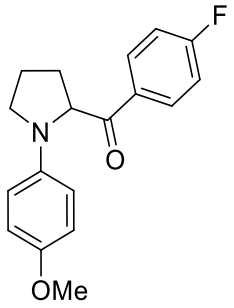


(1-(4-Methoxyphenyl)pyrrolidin-2-yl)(phenyl)methanone (22a):[40]

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a dark yellow oil (91.3 mg, 65%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.06 (d, *J* = 7.1 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 6.83 – 6.70 (m, 2H), 6.46 – 6.34 (m, 2H), 5.12 (dd, *J* = 9.5, 2.4 Hz, 1H), 3.71 (s, 3H), 3.70 – 3.67 (m, 1H), 3.42 (dd, *J* = 15.6, 7.6 Hz, 1H), 2.55 – 2.37 (m, 1H), 2.16 – 1.96 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 200.39, 151.35, 141.61, 135.22, 133.47, 128.93, 128.51, 115.17, 112.96,

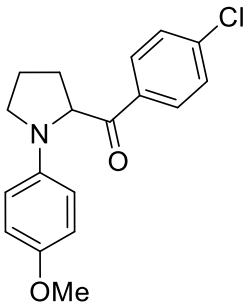
64.23, 56.02, 49.23, 31.12, 23.95; **HRMS for $C_{18}H_{20}NO_2$ $[M+H]^+$:** m/z calcd 282.1489, found 282.1493.



(4-Fluorophenyl)(1-(4-methoxyphenyl)pyrrolidin-2-yl)methanone (22b):

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a yellow solid (77.8 mg, 52%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1).

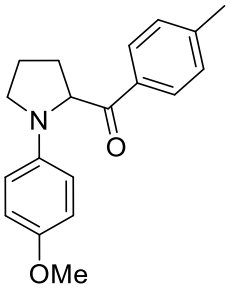
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.09 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.17 (t, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.39 (d, *J* = 9.0 Hz, 2H), 5.05 (dd, *J* = 9.5, 2.5 Hz, 1H), 3.71 (s, 3H), 3.70 – 3.67 (m, 1H), 3.47 – 3.38 (m, 1H), 2.53 – 2.37 (m, 1H), 2.17 – 2.00 (m, 3H); **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ (ppm):** -104.59; **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 199.02, 165.99 (d, *J* = 255.5 Hz), 151.45, 141.54, 131.61 (d, *J* = 3.1 Hz), 131.21 (d, *J* = 9.3 Hz), 116.07 (d, *J* = 21.9 Hz), 115.18, 113.00, 64.36, 56.00, 49.27, 31.15, 23.99; **HRMS for $C_{18}H_{19}FNO_2$ $[M+H]^+$:** m/z calcd 300.1394, found 300.1405.



(4-Chlorophenyl)(1-(4-methoxyphenyl)pyrrolidin-2-yl)methanone (22c):

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a dark yellow solid (91.4 mg, 58%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1).

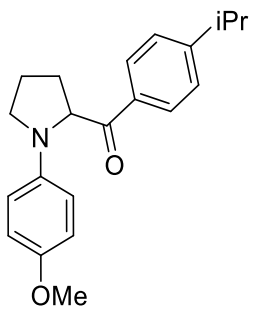
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.99 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.39 (d, *J* = 9.0 Hz, 2H), 5.04 (dd, *J* = 9.5, 2.6 Hz, 1H), 3.71 (s, 3H), 3.70 – 3.66 (m, 1H), 3.46 – 3.35 (m, 1H), 2.52 – 2.36 (m, 1H), 2.13 – 2.01 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 199.53, 151.48, 141.49, 139.97, 133.47, 129.96, 129.27, 115.18, 113.01, 64.44, 56.00, 49.28, 31.10, 23.98; **HRMS for $C_{18}H_{19}{}^{35}ClNO_2$ $[M+H]^+$:** m/z calcd 316.1099, found 316.1101.



(1-(4-Methoxyphenyl)pyrrolidin-2-yl)(p-tolyl)methanone (22d):

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a yellow solid (103.3 mg, 70%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.98 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.82 – 6.74 (m, 2H), 6.47 – 6.37 (m, 2H), 5.12 (dd, *J* = 9.4, 2.4 Hz, 1H), 3.73 (s, 3H), 3.72 – 3.68 (m, 1H), 3.51 – 3.36 (m, 1H), 2.49 – 2.41 (m, 1H), 2.46 (s, 3H), 2.18 – 2.02 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 200.01, 151.28, 144.34, 141.67, 132.67, 129.59, 128.62, 115.14, 112.94, 64.09, 56.00, 49.22, 31.20, 23.96, 21.82; **HRMS for $C_{19}H_{22}NO_2$ $[M+H]^+$:** m/z calcd 296.1645, found 296.1650.

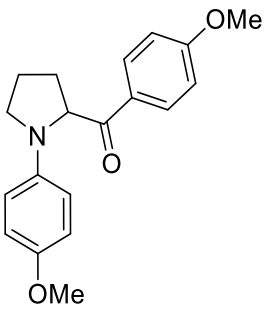


(4-Isopropylphenyl)(1-(4-methoxyphenyl)pyrrolidin-2-yl)methanone (22e):

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was

isolated as a yellow solid (117.9 mg, 73%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.01 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.41 (d, *J* = 9.0 Hz, 2H), 5.12 (dd, *J* = 9.4, 2.3 Hz, 1H), 3.71 (s, 3H), 3.70 – 3.67 (m, 1H), 3.48 – 3.36 (m, 1H), 3.00 (hept, *J* = 7.0 Hz, 1H), 2.53 – 2.36 (m, 1H), 2.18 – 2.00 (m, 3H), 1.30 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 199.89, 154.99, 151.25, 141.66, 132.98, 128.76, 126.99, 115.12, 112.93, 64.07, 55.99, 49.21, 34.42, 31.17, 23.94, 23.78; **HRMS for $C_{21}H_{26}NO_2$ $[M+H]^+$:** m/z calcd 324.1958, found 324.1953.

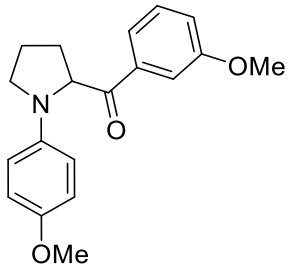


(4-Methoxyphenyl)(1-(4-methoxyphenyl)pyrrolidin-2-yl)methanone (22f):

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a yellow solid (116.6 mg, 75%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.05 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.40 (d, *J* = 9.0 Hz, 2H), 5.07 (dd, *J* = 9.4, 2.4

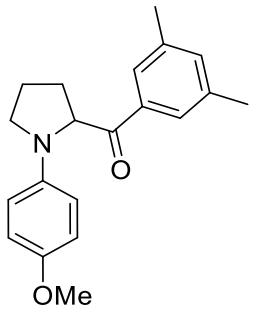
Hz, 1H), 3.89 (s, 3H), 3.71 (s, 3H), 3.70 – 3.67 (m, 1H), 3.46 – 3.35 (m, 1H), 2.51 – 2.35 (m, 1H), 2.18 – 1.97 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 198.94, 163.78, 151.27, 141.72, 130.81, 128.18, 115.14, 114.07, 112.94, 63.98, 56.02, 55.64, 49.25, 31.32, 24.00; **HRMS for $C_{19}H_{22}NO_3$ $[M+H]^+$:** m/z calcd 312.1594, found 312.1604.



(3-Methoxyphenyl)(1-(4-methoxyphenyl)pyrrolidin-2-yl)methanone (22g):

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a yellow solid (96.4 mg, 62%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1).

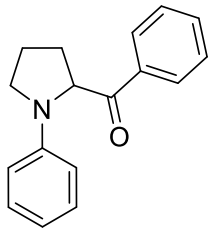
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65 (d, *J* = 7.7 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.19 – 7.12 (m, 1H), 6.80 – 6.73 (m, 2H), 6.43 – 6.37 (m, 2H), 5.11 (dd, *J* = 9.5, 2.4 Hz, 1H), 3.86 (s, 3H), 3.71 (s, 3H), 3.69 – 3.66 (m, 1H), 3.48 – 3.35 (m, 1H), 2.51 – 2.36 (m, 1H), 2.17 – 1.99 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 200.31, 160.09, 151.35, 141.60, 136.54, 129.89, 120.94, 119.95, 115.18, 112.96, 112.92, 64.27, 56.03, 55.60, 49.22, 31.18, 23.95; **HRMS for $C_{19}H_{22}NO_3$ $[M+H]^+$:** m/z calcd 312.1594, found 312.1592.



(3,5-Dimethylphenyl)(1-(4-methoxyphenyl)pyrrolidin-2-yl)methanone (22h):

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a yellow solid (111.3 mg, 72%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 15:1).

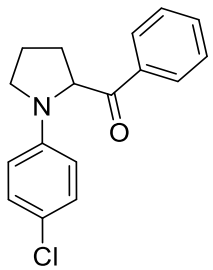
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68 (s, 2H), 7.27 (d, *J* = 2.6 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.42 (d, *J* = 9.0 Hz, 2H), 5.13 (dd, *J* = 9.4, 2.3 Hz, 1H), 3.73 (s, 3H), 3.72 – 3.68 (m, 1H), 3.50 – 3.34 (m, 1H), 2.52 – 2.43 (m, 1H), 2.42 (s, 6H), 2.15 – 1.95 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 200.63, 151.26, 141.66, 138.56, 135.30, 135.13, 126.24, 115.13, 112.94, 64.06, 56.01, 49.21, 31.19, 23.92, 21.44; **HRMS for $C_{20}H_{24}NO_2$ $[M+H]^+$:** m/z calcd 310.1802, found 310.1800.



Phenyl(1-phenylpyrrolidin-2-yl)methanone (22i):[40]

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a yellow solid (66.5 mg, 53%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 (d, *J* = 7.3 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.21 – 7.11 (m, 2H), 6.67 (t, *J* = 7.3 Hz, 1H), 6.46 (d, *J* = 8.1 Hz, 2H), 5.21 (dd, *J* = 9.6, 2.3 Hz, 1H), 3.78 – 3.67 (m, 1H), 3.54 – 3.42 (m, 1H), 2.56 – 2.37 (m, 1H), 2.22 – 2.00 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 199.91, 146.65, 135.10, 133.51, 129.30, 128.95, 128.49, 116.46, 112.15, 63.61, 48.68, 31.00, 23.78; **HRMS for $C_{17}H_{18}NO$ $[M+H]^+$:** m/z calcd 252.1383, found 252.1376.

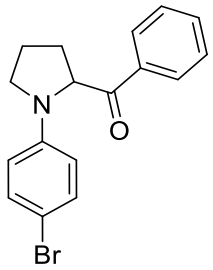


(1-(4-Chlorophenyl)pyrrolidin-2-yl)(phenyl)methanone (22j):[40]

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was

isolated as a yellow solid (69.8 mg, 49%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.05 (d, *J* = 6.7 Hz, 2H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 8.9 Hz, 2H), 6.35 (d, *J* = 8.8 Hz, 2H), 5.18 (dd, *J* = 9.5, 2.4 Hz, 1H), 3.73 – 3.59 (m, 1H), 3.53 – 3.35 (m, 1H), 2.57 – 2.37 (m, 1H), 2.24 – 1.98 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 199.41, 145.24, 134.88, 133.70, 129.07, 129.02, 128.48, 121.17, 113.19, 63.62, 48.82, 31.05, 23.75; **HRMS for $C_{17}H_{17}{}^{35}ClNO$ $[M+H]^+$:** m/z calcd 286.0993, found 286.1001.

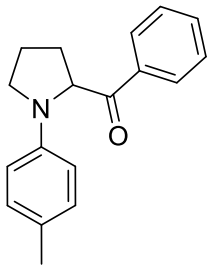


(1-(4-Bromophenyl)pyrrolidin-2-yl)(phenyl)methanone (22k):[40]

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a yellow solid (82.3 mg, 50%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.05 (d, *J* = 7.2 Hz, 2H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.30 (d, *J* = 8.9 Hz, 2H), 5.17 (dd, *J* = 9.5, 2.5 Hz, 1H), 3.65 (ddd, *J* = 8.7, 6.3, 4.6 Hz, 1H), 3.51 – 3.33 (m,

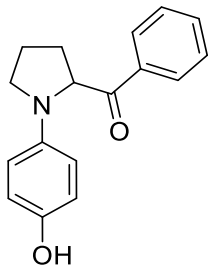
1H), 2.56 – 2.35 (m, 1H), 2.22 – 1.97 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 199.33, 145.61, 134.85, 133.71, 131.91, 129.03, 128.47, 113.74, 108.25, 63.54, 48.76, 31.03, 23.72; **HRMS for $C_{17}H_{17}BrNO$ $[M+H]^+$:** m/z calcd 330.0488 and 332.0468, found 330.0482 and 332.0472.



Phenyl(1-(p-tolyl)pyrrolidin-2-yl)methanone (22l):[40]

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a yellow solid (83.5 mg, 63%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1).

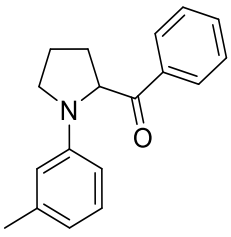
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.07 (d, *J* = 6.8 Hz, 2H), 7.67 – 7.58 (m, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 6.38 (d, *J* = 8.4 Hz, 2H), 5.16 (dd, *J* = 9.5, 2.4 Hz, 1H), 3.78 – 3.65 (m, 1H), 3.51 – 3.37 (m, 1H), 2.51 – 2.38 (m, 1H), 2.21 (s, 3H), 2.17 – 2.01 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 200.23, 144.65, 135.21, 133.43, 129.83, 128.92, 128.49, 125.48, 112.18, 63.86, 48.87, 31.03, 23.84, 20.38; **HRMS for $C_{18}H_{20}NO$ $[M+H]^+$:** m/z calcd 266.1539, found 266.1537.



(1-(4-Hydroxyphenyl)pyrrolidin-2-yl)(phenyl)methanone (22m):

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a yellow solid (68.1 mg, 51%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 10:1).

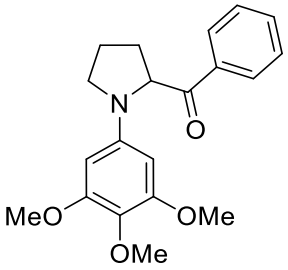
^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ (ppm): 8.42 (s, 1H), 8.08 (d, *J* = 7.0 Hz, 2H), 7.73 – 7.63 (m, 1H), 7.62 – 7.51 (m, 2H), 6.61 – 6.50 (m, 2H), 6.27 – 6.17 (m, 2H), 5.29 (dd, *J* = 9.5, 2.3 Hz, 1H), 3.47 (td, *J* = 8.1, 3.3 Hz, 1H), 3.33 – 3.27 (m, 1H), 2.48 – 2.34 (m, 1H), 2.07 – 1.94 (m, 1H), 1.94 – 1.77 (m, 2H); **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ (ppm):** 200.51, 147.98, 140.05, 134.72, 133.50, 128.96, 128.16, 115.76, 112.53, 62.93, 48.52, 30.36, 23.27; **HRMS for $C_{17}H_{18}NO_2$ [M+H]$^+$:** m/z calcd 268.1332, found 268.1336.



Phenyl(1-(m-tolyl)pyrrolidin-2-yl)methanone (22n):

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a yellow solid (72.9 mg, 55%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 20:1).

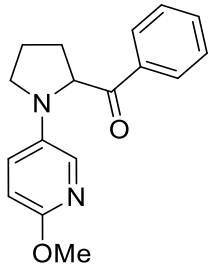
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):8.07 (d, *J* = 7.0 Hz, 2H), 7.67 – 7.59 (m, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.04 (t, *J* = 7.8 Hz, 1H), 6.50 (d, *J* = 7.4 Hz, 1H), 6.31 (s, 1H), 6.29 – 6.21 (m, 1H), 5.19 (dd, *J* = 9.6, 2.3 Hz, 1H), 3.77 – 3.66 (m, 1H), 3.54 – 3.40 (m, 1H), 2.52 – 2.36 (m, 1H), 2.25 (s, 3H), 2.18 – 2.01 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 200.08, 146.74, 138.98, 135.19, 133.45, 129.15, 128.93, 128.49, 117.51, 112.89, 109.41, 63.70, 48.72, 31.01, 23.77, 21.97; **HRMS for $C_{18}H_{20}NO$ $[M+H]^+$:** m/z calcd 266.1539, found 266.1532.



Phenyl(1-(3,4,5-trimethoxyphenyl)pyrrolidin-2-yl)methanone (22o):

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a yellow solid (97.2 mg, 57%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 25:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.05 (d, *J* = 7.3 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 5.64 (s, 2H), 5.17 (dd, *J* = 9.2, 2.5 Hz, 1H), 3.71 (s, 3H), 3.70 – 3.67 (m ,1H), 3.68 (s, 6H), 3.52 – 3.42 (m, 1H), 2.52 – 2.38 (m, 1H), 2.21 – 2.00 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 200.88, 153.90, 143.58, 135.31, 133.60, 129.65, 129.01, 128.20, 90.00, 63.76, 61.12, 55.88, 49.05, 31.05, 23.95; **HRMS for $C_{20}H_{24}NO_4$ $[M+H]^+$:** m/z calcd 342.1700, found 342.1700.

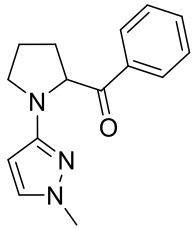


(1-(6-Methoxypyridin-3-yl)pyrrolidin-2-yl)(phenyl)methanone (22p):

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a yellow solid (91.7 mg, 65%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.03 (d, *J* = 7.0 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.37 (d, *J* = 3.1 Hz, 1H), 6.81 (dd, *J* = 8.9, 3.1 Hz, 1H), 6.59 (d, *J* = 8.9 Hz, 1H), 5.13 (dd, *J* = 9.6, 2.5 Hz, 1H), 3.81 (s, 3H), 3.71 – 3.62 (m, 1H), 3.47 – 3.35 (m, 1H), 2.53 – 2.38 (m, 1H), 2.17 – 1.99 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 199.60, 156.46, 138.34, 134.89, 133.67,

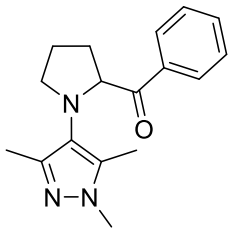
129.26, 128.96, 128.47, 124.04, 110.71, 63.71, 53.32, 48.97, 31.03, 23.76; **HRMS for $C_{17}H_{19}N_2O_2$ $[M+H]^+$:** m/z calcd 283.1441, found 283.1444.



(1-(1-Methyl-1*H*-pyrazol-3-yl)pyrrolidin-2-yl)(phenyl)methanone (22q):

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a yellow solid (39.5 mg, 31%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 2:1).

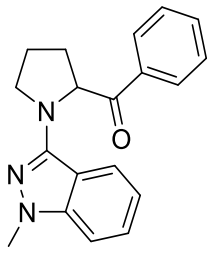
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.04 (d, *J* = 7.0 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.05 (d, *J* = 2.2 Hz, 1H), 5.36 (d, *J* = 2.2 Hz, 1H), 5.15 (dd, *J* = 9.3, 3.1 Hz, 1H), 3.75 – 3.68 (m, 1H), 3.64 (s, 3H), 3.50 – 3.42 (m, 1H), 2.46 – 2.34 (m, 1H), 2.14 – 1.96 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 200.80, 156.72, 135.78, 133.06, 131.06, 128.67, 128.61, 90.26, 64.44, 49.45, 38.63, 30.90, 24.11; **HRMS for $C_{15}H_{18}N_3O$ $[M+H]^+$:** m/z calcd 256.1444, found 256.1438.



Phenyl(1-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)pyrrolidin-2-yl)methanone (22r):

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a yellow solid (32.5 mg, 23%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.82 (d, *J* = 6.7 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 4.75 (dd, *J* = 8.9, 4.6 Hz, 1H), 3.58 (s, 3H), 3.43 – 3.34 (m, 1H), 3.22 – 3.10 (m, 1H), 2.39 – 2.26 (m, 1H), 2.23 – 2.16 (m, 1H), 2.20 (s, 3H), 2.12 – 2.00 (m, 2H), 1.97 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 200.35, 143.57, 136.88, 136.51, 132.72, 128.71, 128.33, 126.72, 67.10, 54.98, 36.22, 30.60, 25.84, 12.92, 9.12; **HRMS for $C_{17}H_{22}N_3O$ $[M+H]^+$:** m/z calcd 284.1757, found 284.1753.



(1-(1-Methyl-1*H*-indazol-3-yl)pyrrolidin-2-yl)(phenyl)methanone (22s):

The titled compound was synthesised according to general procedure at 0.5 mmol scale with the substrate bearing the tosylate group at C3 position. The product was isolated as a yellow solid (83.9 mg, 55%) after column chromatography (silica gel, eluent: n-hexane/EtOAc 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.10 (d, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.86 (t, *J* = 7.5 Hz, 1H), 5.60 (dd, *J* = 9.2, 3.3 Hz, 1H), 4.23 – 4.09 (m, 1H), 3.94 – 3.81 (m, 1H), 3.78 – 3.64 (m, 3H), 2.52 – 2.37 (m, 1H), 2.23 – 2.01 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm):** 200.55, 148.71, 142.24, 135.86, 133.06, 128.70, 128.58, 126.39, 121.76, 117.72, 114.31, 108.52, 64.44, 49.97, 34.86, 30.42, 24.25; **HRMS for $C_{19}H_{20}N_3O$ $[M+H]^+$:** m/z calcd 306.1601, found 306.1590.

3.6 References

[1] R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845–5859.

[2] P. Goel, O. Alam, M. J. Naim, F. Nawaz, M. Iqbal, M. I. Alam, *Eur. J. Med. Chem.* **2018**, *157*, 480–502.

[3] D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383–394.

[4] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.

[5] D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435–446.

[6] R. P. Trump, J.-B. E. Blanc, E. L. Stewart, P. J. Brown, M. Caivano, D. W. Gray, W. J. Hoekstra, T. M. Willson, B. Han, P. Turnbull, *J. Comb. Chem.* **2007**, *9*, 107–114.

[7] F. Diness, D. P. Fairlie, *Angew. Chem. Int. Ed.* **2012**, *51*, 8012–8016.

[8] C. Liu, H. Wang, X. Xing, Y. Xu, J.-A. Ma, B. Zhang, *Tetrahedron Lett.* **2013**, *54*, 4649–4652.

[9] S. Yang, C. Wu, M. Ruan, Y. Yang, Y. Zhao, J. Niu, W. Yang, J. Xu, *Tetrahedron Lett.* **2012**, *53*, 4288–4292.

[10] P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564–12649.

[11] I. P. Beletskaya, A. V Cheprakov, *Organometallics* **2012**, *31*, 7753–7808.

[12] D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27–50.

[13] J.-H. Chu, P.-S. Lin, Y.-M. Lee, W.-T. Shen, M.-J. Wu, *Chem. Eur. J.* **2011**, *17*, 13613–13620.

[14] T. Maejima, Y. Shimoda, K. Nozaki, S. Mori, Y. Sawama, Y. Monguchi, H. Sajiki, *Tetrahedron* **2012**, *68*, 1712–1722.

[15] J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534–1544.

[16] J. P. Wolfe, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1144–1157.

[17] Y.-B. Huang, J.-J. Dai, X.-J. Deng, Y.-C. Qu, Q.-X. Guo, Y. Fu, *ChemSusChem* **2011**, *4*, 1578–1581.

[18] Y. Ogiwara, T. Uchiyama, N. Sakai, *Angew. Chem. Int. Ed.* **2016**, *55*, 1864–1867.

[19] C. Wu, X. Luo, H. Zhang, X. Liu, G. Ji, Z. Liu, Z. Liu, *Green Chem.* **2017**, *19*, 3525–3529.

[20] T. Wang, H. Xu, J. He, Y. Zhang, *Tetrahedron* **2020**, *76*, 131394.

[21] D. Wei, C. Netkaew, C. Darcel, *Adv. Synth. Catal.* **2019**, *361*, 1781–1786.

[22] M. A. Larsen, E. T. Hennessy, M. C. Deem, Y. Lam, J. Saurí, A. C. Sather, *J. Am. Chem. Soc.* **2020**, *142*, 726–732.

[23] D. Wei, C. Netkaew, J. Wu, C. Darcel, *ChemCatChem* **2020**, *12*, 5449–5455.

[24] J. Wu, S. Tongdee, Y. Ammaiyappan, C. Darcel, *Adv. Synth. Catal.* **2021**, *363*, 3859–3865.

[25] K. Yuan, F. Jiang, Z. Sahli, M. Achard, T. Roisnel, C. Bruneau, *Angew. Chem. Int. Ed.* **2012**, *51*, 8876–8880.

[26] Q. Zou, C. Wang, J. Smith, D. Xue, J. Xiao, *Chem. A Eur. J.* **2015**, *21*, 9656–9661.

[27] S. P. Shan, X. Xiaoke, B. Gnanaprakasam, T. T. Dang, B. Ramalingam, H.

V. Huynh, A. M. Seayad, *RSC Adv.* **2015**, *5*, 4434–4442.

[28] P. Yang, C. Zhang, W.-C. Gao, Y. Ma, X. Wang, L. Zhang, J. Yue, B. Tang, *Chem. Commun.* **2019**, *55*, 7844–7847.

[29] C. Y. Legault, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 8966–8967.

[30] Z.-S. Ye, M.-W. Chen, Q.-A. Chen, L. Shi, Y. Duan, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2012**, *51*, 10181–10184.

[31] M. Chang, Y. Huang, S. Liu, Y. Chen, S. W. Krska, I. W. Davies, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 12761–12764.

[32] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.

[33] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.

[34] M. K. Whittlesey, E. Peris, *ACS Catal.* **2014**, *4*, 3152–3159.

[35] Z. Nairoukh, M. Wollenburg, C. Schlepphorst, K. Bergander, F. Glorius, *Nat. Chem.* **2019**, *11*, 264–270.

[36] T. Wagener, A. Heusler, Z. Nairoukh, K. Bergander, C. G. Daniliuc, F. Glorius, *ACS Catal.* **2020**, *10*, 12052–12057.

[37] Y. Kawamata, J. C. Vantourout, D. P. Hickey, P. Bai, L. Chen, Q. Hou, W. Qiao, K. Barman, M. A. Edwards, A. F. Garrido-Castro, J. N. deGruyter, H. Nakamura, K. Knouse, C. Qin, K. J. Clay, D. Bao, C. Li, J. T. Starr, C.

Garcia-Irizarry, N. Sach, H. S. White, M. Neurock, S. D. Minteer, P. S. Baran, *J. Am. Chem. Soc.* **2019**, *141*, 6392–6402.

[38] Y.-Y. Liu, D. Liang, L.-Q. Lu, W.-J. Xiao, *Chem. Commun.* **2019**, *55*, 4853–4856.

[39] S. Gisbertz, S. Reischauer, B. Pieber, *Nat. Catal.* **2020**, *3*, 611–620.

[40] G.-Q. Xu, T.-F. Xiao, G.-X. Feng, C. Liu, B. Zhang, P.-F. Xu, *Org. Lett.* **2021**, *23*, 2846–2852.

[41] C. Béguin, S. V Andurkar, A. Y. Jin, J. P. Stables, D. F. Weaver, H. Kohn, *Bioorg. Med. Chem.* **2003**, *11*, 4275–4285.

[42] M. C. Myers, Wang, J. A. Iera, J. Bang, T. Hara, S. Saito, G. P. Zambetti, D. H. Appella, *J. Am. Chem. Soc.* **2005**, *127*, 6152–6153.

[43] P. C. Meltzer, D. Butler, J. R. Deschamps, B. K. Madras, *J. Med. Chem.* **2006**, *49*, 1420–1432.

[44] F. I. Carroll, B. E. Blough, P. Abraham, A. C. Mills, J. A. Holleman, S. A. Wolckenhauer, A. M. Decker, A. Landavazo, K. T. McElroy, H. A. Navarro, M. B. Gatch, M. J. Forster, *J. Med. Chem.* **2009**, *52*, 6768–6781.

[45] C. L. Joe, A. G. Doyle, *Angew. Chem. Int. Ed.* **2016**, *55*, 4040–4043.

[46] A. C. Sather, T. A. Martinot, *Org. Process Res. Dev.* **2019**, *23*, 1725–1739.

[47] N. H. Park, E. V Vinogradova, D. S. Surry, S. L. Buchwald, *Angew. Chem.*

Int. Ed. **2015**, *54*, 8259–8262.

[48] P. Ruiz-Castillo, D. G. Blackmond, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 3085–3092.

[49] A. Khadra, S. Mayer, D. Mitchell, M. J. Rodriguez, M. G. Organ, *Organometallics* **2017**, *36*, 3573–3577.

[50] Y. Huang, S. Liu, Y. Liu, Y. Chen, M. Weisel, R. T. Williamson, I. W. Davies, X. Zhang, *Tetrahedron* **2018**, *74*, 2182–2190.

[51] B. Qu, H. P. R. Mangunuru, S. Tcyrulnikov, D. Rivalti, O. V Zatolochnaya, D. Kurouski, S. Radomkit, S. Biswas, S. Karyakarte, K. R. Fandrick, J. D. Sieber, S. Rodriguez, J.-N. Desrosiers, N. Haddad, K. McKellop, S. Pennino, H. Lee, N. K. Yee, J. J. Song, M. C. Kozlowski, C. H. Senanayake, *Org. Lett.* **2018**, *20*, 1333–1337.

[52] J. Wu, W. Tang, A. Pettman, J. Xiao, *Adv. Synth. Catal.* **2013**, *355*, 35–40.

[53] R. A. Watile, A. Bunrit, J. Margalef, S. Akkarasamiyo, R. Ayub, E. Lagerspets, S. Biswas, T. Repo, J. S. M. Samec, *Nat. Commun.* **2019**, *10*, 3826.

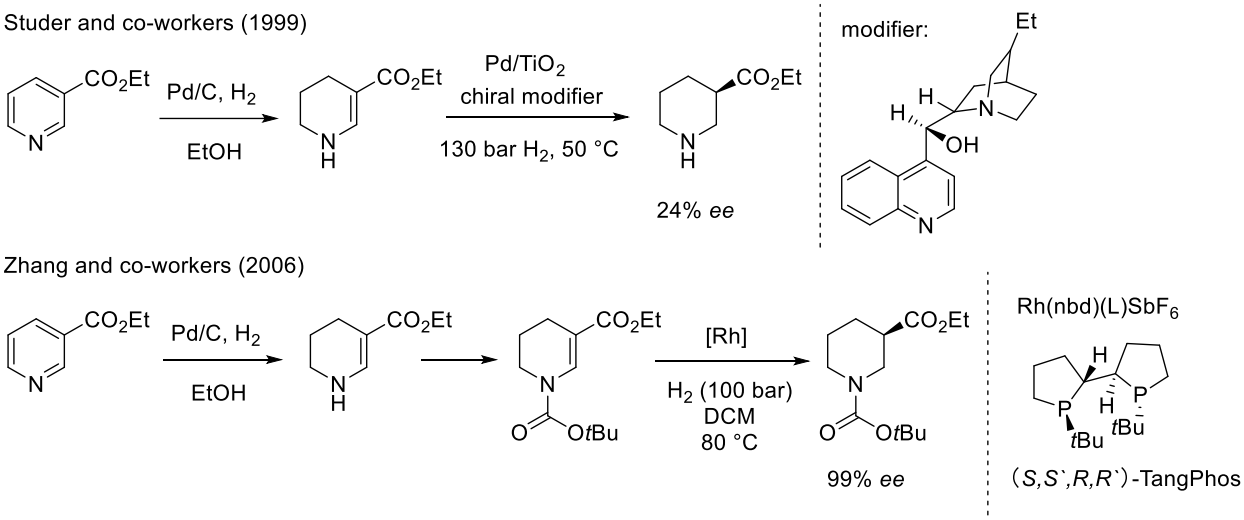
Chapter 4: Asymmetric Transamination of Pyridinium Salts with Achiral Amines

4.1 Introduction

As mentioned in the previous chapters, enantiometrically pure heterocyclic moieties are very common in nature products and pharmaceuticals. Catalytic asymmetric hydrogenation of *N*-heteroaromatics is one of the most direct and atom-economic methods to access chiral heterocyclic compounds.[1] The asymmetric hydrogenation of pyridines is of particular interest to industry because chiral piperidines are prevalent structural motifs in bioactive compounds.[2] The challenges to overcome the high aromatic resonance stability and the propensity to poison and/or deactivate the catalyst *via* coordination make the AH of pyridines more difficult to achieve good enantioselectivies. This chapter will briefly summarise the key achievements on AH of pyridines and present the preliminary studies in this area with our novel catalytic protocol.

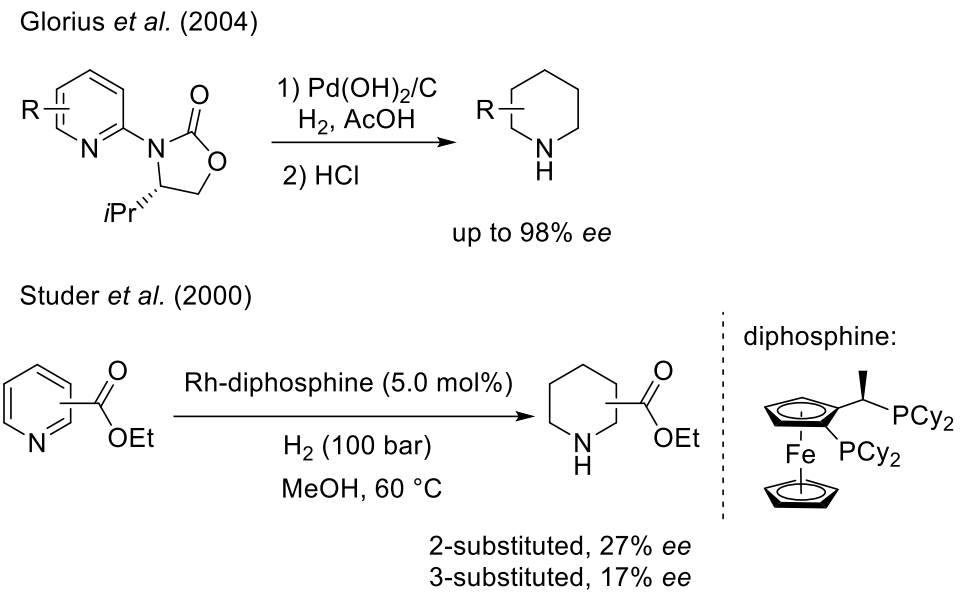
In 1999, Studer and co-workers reported the first approach for the synthesis of chiral piperidine in a two-steps reaction (Scheme 4.1).[3] In the first step, the starting material, ethyl nicotinate, was hydrogenated to 1,4,5,6-tetrahydropyridine with Pd/C. Then, under harsh conditions using Pd/TiO_2 as catalyst and 10,11-dihydrocinchonidine as chiral modifier, the intermediate was converted to chiral ethyl nipecotinate with 10% conversion and 24% *ee*. In 2006, Zhang and co-workers improved this method by using a chiral rhodium catalyst for the second step (Schme 4.1).[4] Until 2000, Johnson and co-workers reported the first example

for the synthesis of chiral ethyl nicotinate with 17% *ee via* AH in one step using a supported Pd-diphenylphosphino-ferrocene catalyst.[5]



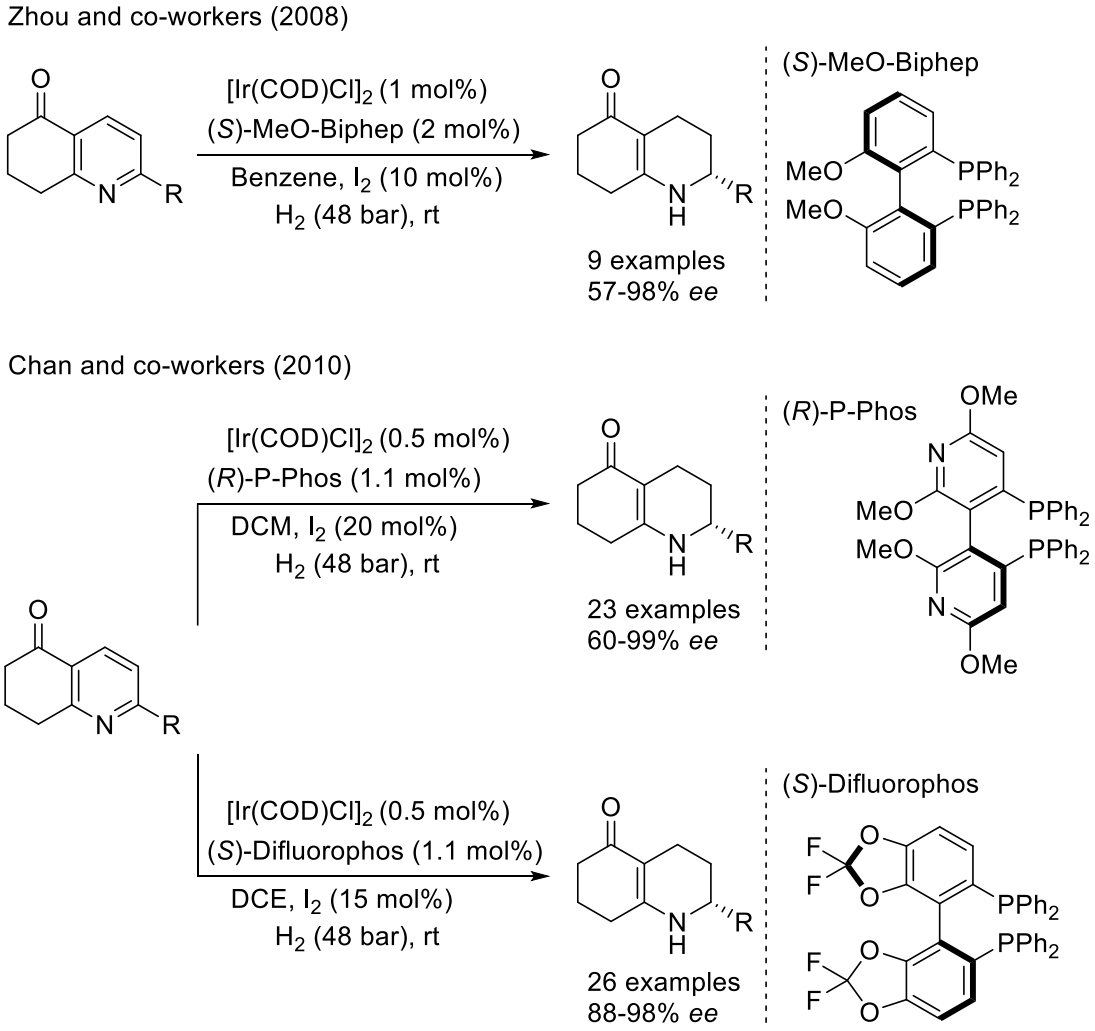
Scheme 4.1: AH of ethyl nicotinate with a two-step strategy

In 2004, the Glorius group reported a novel and efficient synthesis of chiral piperidines from oxazolidinone-substituted pyridines. With the chiral auxiliary installed, piperidines with multiple sterocentres can be obtained in good yields and excellent enantiometric excess (up to 98% *ee*).[6] Studer *et al.* presented the first case of homogeneous AH of monosubstituted pyridines using a Rh-diphosphine complex, although the best enantioselectivities achieved was 27% *ee* (Scheme 4.2).[7]



Scheme 4.2: Pioneering attempts on asymmetric heterogeneous and homogeneous hydrogenation of pyridines

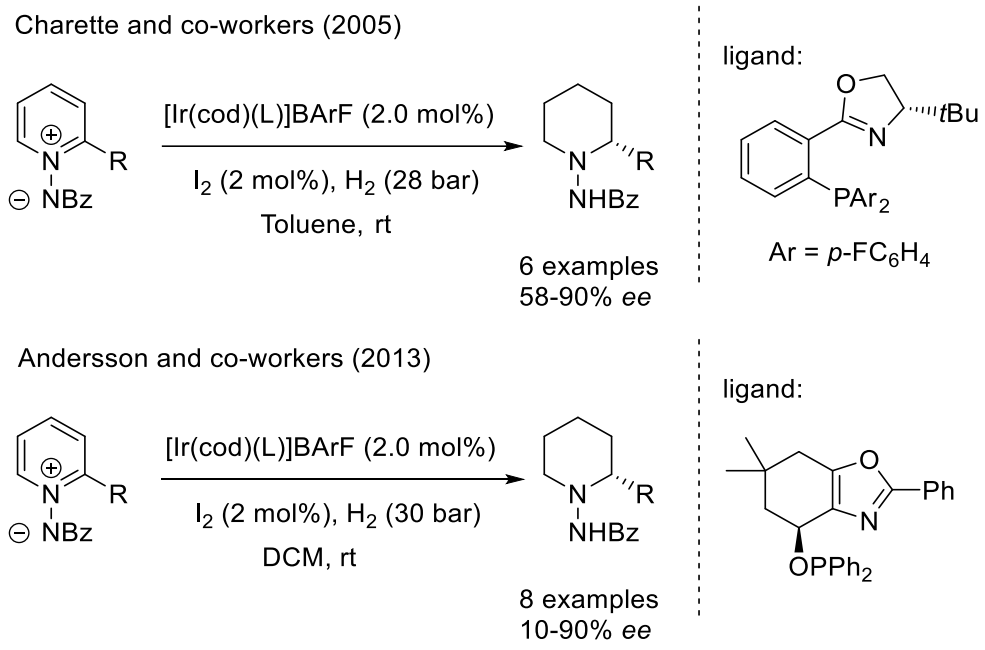
In 2008, Zhou and co-workers reported iridium-catalysed partial AH of pyridine derivatives 7,8-dihydro-quinolin-5(6*H*)-ones (Scheme 4.3). The $[Ir(COD)Cl]_2$/(*S*)-MeO-Biphep catalyst system has been successfully applied in the AH of the 2-substituted pyridine derivatives with *ee*`s up to 97%.[8] Later, similar results were obtained by the Chan group using the same reaction conditions, differing only in the phosphine ligands.[9,10]



Scheme 4.3: Partial AH of 7,8-dihydro-quinolin-5(6*H*)-ones

Since these early developments, almost all new methodologies have relied on the activation of the pyridines by quaternisation to generate corresponding pyridinium derivatives, including but not limited to acylation, alkoxycarbonylation and alkylation.[1,11,12] The alkylation of the nitrogen atom creates a positive charge in the nitrogen that increases the reactivity of pyridine towards hydrogenation. Additionally, the quaternisation also eliminates the possibility of coordination

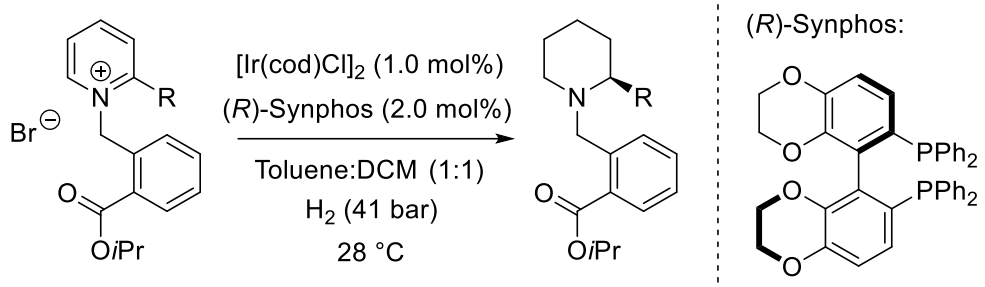
between nitrogen and metal centre from the catalyst. In 2005, Charette and co-workers developed an activation protocol for the enantioselective hydrogenation of pyridines with an Ir-phosphinooxazoline complex, in which the pyridines were converted to *N*-iminopyridinium ylides.[13] In 2013, Andersson and co-workers reported similar products with different phosphine ligand (Scheme 4.4).[14]



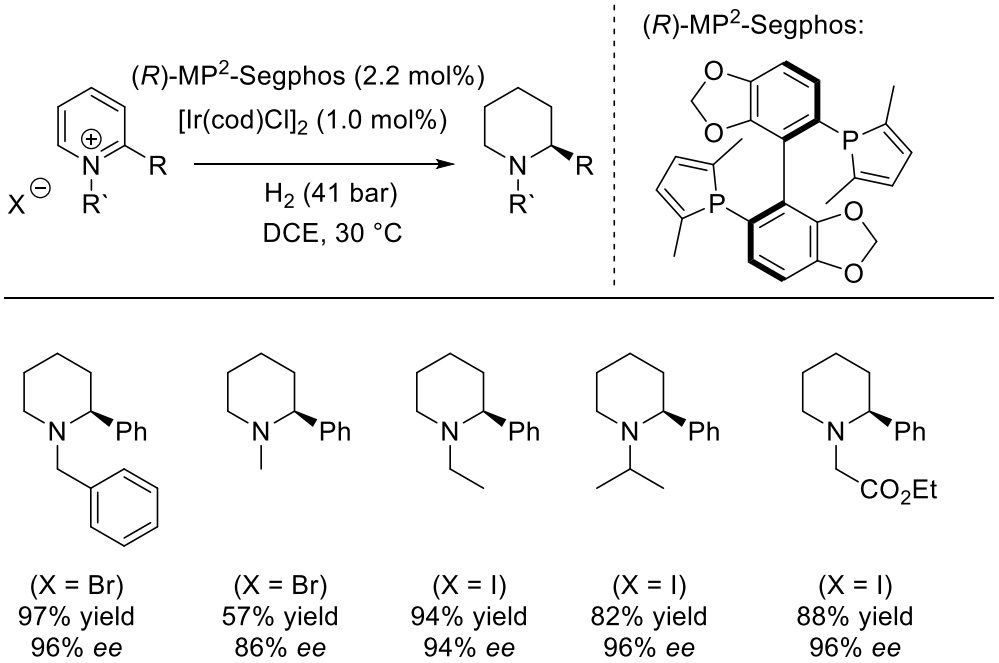
Scheme 4.4: AH of *N*-iminopyridinium ylides

In 2012, Zhou and co-workers reported the synthesis of chiral 2-substituted piperidines from *N*-benzyl-pyridinium salts with up to 93% *ee* (Scheme 4.5).[15] The simple benzyl substituent was used as activating group, and when a isopropyl ester was introduced to the 2-position of the benzyl, excellent *ee*'s were achieved due to the increased steric hindrance and possible directing effect caused by the coordinating group. Two years later, the Zhang group demonstrated the AH of *N*-

alkyl-2-arylpyridinium salts with excellent reactivity and enantioselectivity (Scheme 4.6).[15] With a chiral phosphole-based ligand, excellent *ee*'s were obtained without the need for a directing group in the *N*-benzyl substituent compared with the results from Zhou.



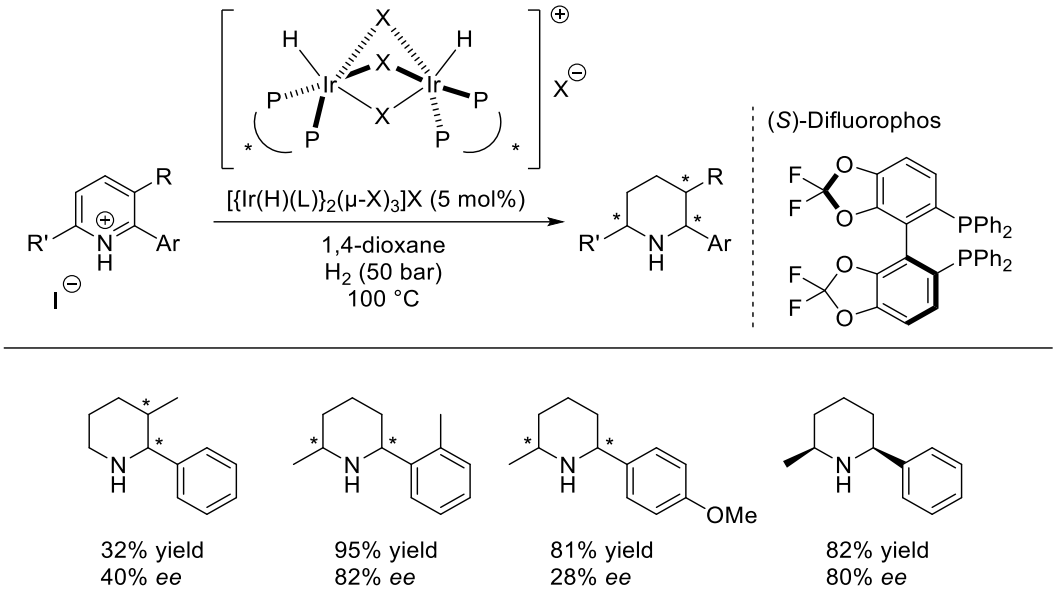
Scheme 4.5: AH of *N*-benzyl-pyridinium salts



Scheme 4.6: AH of *N*-substituted pyridinium salts

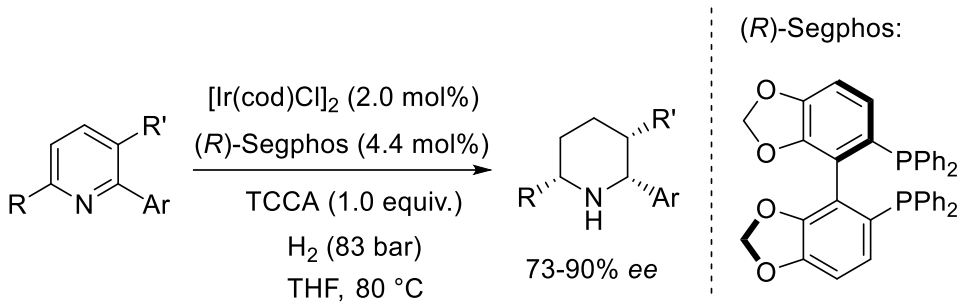
In 2014, Mashima and co-workers developed an AH of multisubstituted pyridinium salts to corresponding piperidines using iodide-bridged iridium

dinuclear complex.[16] Various 2,3- and 2,6-disubstituted pyridinium salts were converted to piperidines in good yields, high diasteroselectivites (*dr* > 95:5) and modest to good enantioselectivities (28-82% *ee*) (Scheme 4.7).



Scheme 4.7: AH of disubstituted pyridinium salts

The most recent study was published by Zhou and co-workers in 2017. They developed an efficient AH of trisubstituted pyridinium salts with excellent enantioselectivities.[17] The study showed that hydrogen halide generated *in situ* from TCCA (trichloroisocyanuric acid) acts as a traceless activator of pyridine during hydrogenation, avoiding the removal of the activating groups afterwards (Scheme 4.8).



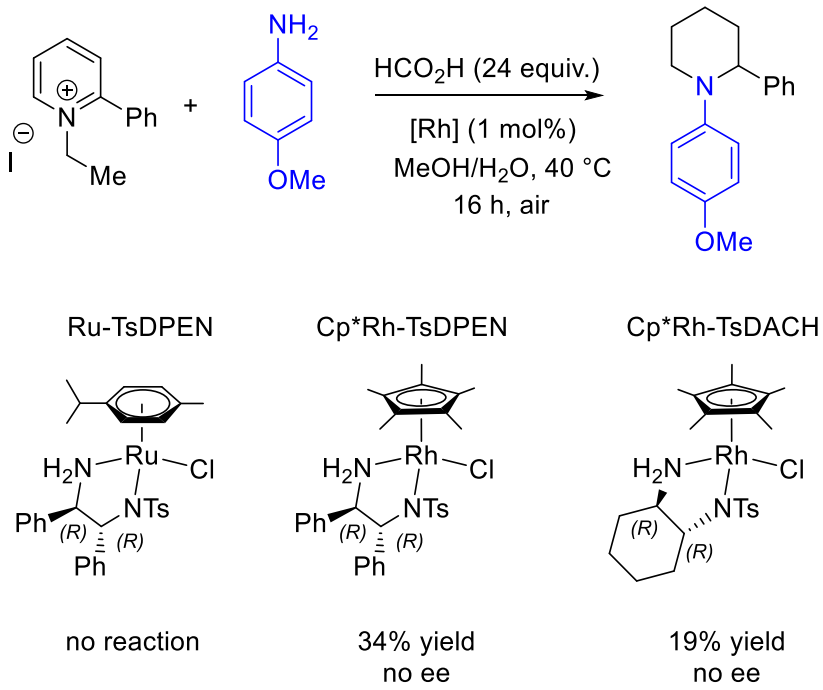
Scheme 4.8: AH of trisubstituted pyridines

As summarised above, transition metal catalysed AH is currently the most common strategy to reduce pyridines enantioselectively. However, other reduction methods, such as catalytic ATH, are yet to be well-developed. Chapter 2 reports a novel ART approach to effectively reduce pyridinium salts to chiral piperidines while inducing chirality on the ring from the chiral secondary amine. Chapter 3 shows the expansion of the protocol to non-enantioselective reduction of pyridines with aryl amines. The ART of pyridines with achiral amines could provide a new pathway to access chiral piperidines without using a chiral amine. This would greatly expand the utility of the ART. In this chapter, we present our attempts to find a chiral catalyst for ART with achiral amines.

4.2 Results and discussion

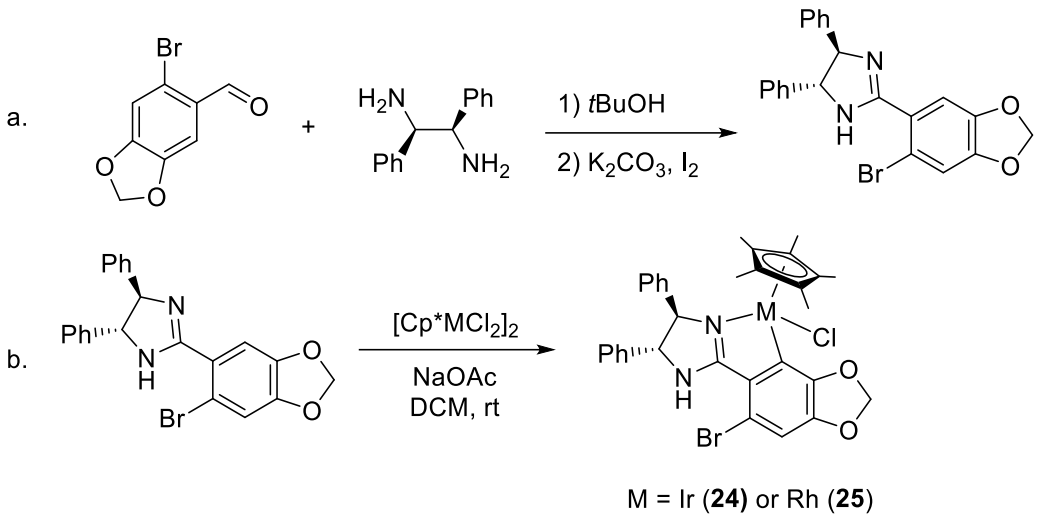
To enable ART reactions with achiral amines, we attempted the use of chiral catalysts to induce asymmetry during the reduction. Of the various chiral catalysts reported, the most attractive one is the Ru-TsDPEN (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) complex developed by Noyori,

Ikariya and co-workers.[18] Based on this complex and related variants, a number of reports on the asymmetric reduction of ketones and imines have appeared.[19–25] The analogous Rh-TsDPEN complex has also been shown to be highly effective in the reduction of such compounds.[26,27] Taking the model reaction from Chapter 3 as a starting point, we attempted the ART of *N*-ethyl-2-phenylpyridinium iodide with formic acid as hydrogen source (Scheme 4.9). The previously used $[Cp^*RhCl_2]_2$ was replaced with Ru-TsDPEN, other conditions being unchanged. However, the Noyori's catalyst was found unreactive for the transamination reaction. Using Cp*Rh-TsDPEN, then the reaction gave the desired piperidine product in 34% yield; however, no enantioselectivity was obtained. Similarly, by employing Cp*Rh-TsDACH (DACH = 1,2-diaminocyclohexane), a lower yield (19%) was recorded and no enantioselectivity was observed (Scheme 4.6). We also carried out the reactions using *in situ* formed catalyst from $[Cp^*RhCl_2]_2$ and the chiral ligand under the same conditions. In both cases, high and same yields (86%) were achieved; but no enantioselectivity was obtained with either (*R*,*R*)-TsDPEN or (*R*,*R*)-TsDACH ligands, indicating the high efficiency of $[Cp^*RhCl_2]_2$ in the reduction reaction, but no formation of the rhodium complexes.



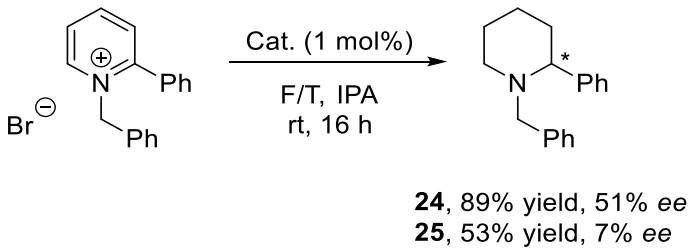
Scheme 4.9: Chiral Rh complexes catalysed ART of a pyridinium salt

Our group have reported iridium complexes bearing chiral oxazoline and imidazoline ligands for direct asymmetric reductive amination of ketones and ATH of pyridiniums.[28] Inspired by the previous works, we investigated the potential of cyclometalated iridium and rhodium complexes in ART of pyridinium salts. The imidazoline ligands and cyclometalated complexes were synthesised according to the literature (Scheme 4.10).[28]



Scheme 4.10: Synthesis of a) chiral imidazoline ligand, and b) cyclometalated complexes

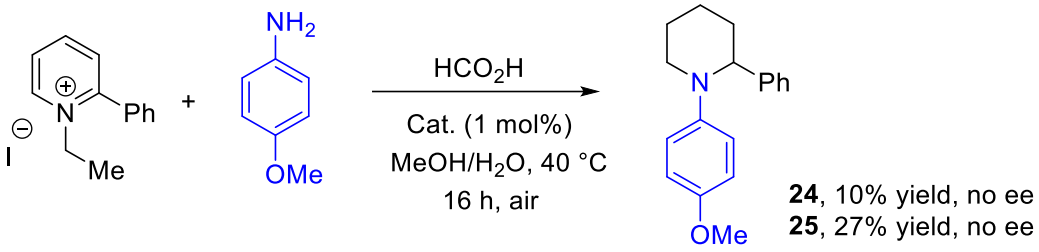
We first reproduced the ATH of *N*-benzyl-2-phenylpyridinium bromide salt using iridacycle **24**. The desired piperidine was isolated in 89% yield and 51% *ee*, which are similar to the literature report.[28] Under the same conditions, the rhodacycle **25** exhibited lower effectiveness in terms of both yields (53%) and enantioselectivity (7% *ee*) (Scheme 4.11).



Scheme 4.11: ATH of pyridinium salt with **24** and **25**

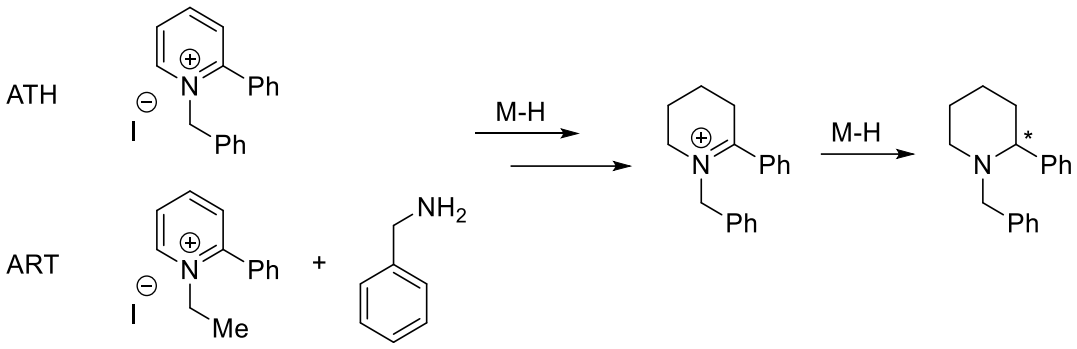
Then we examined the ART of the pyridine model substrate with both cyclometalated complexes. The results show that the rhodium complex **25** is more

active than the iridium analogue in terms of yield; however, still no enantioselectivity was achieved (Scheme 4.12).

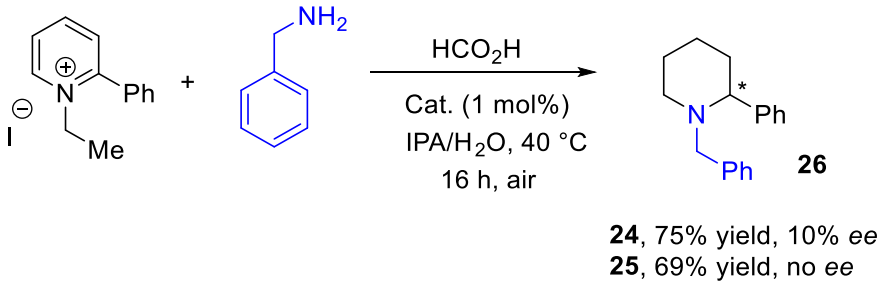


Scheme 4.12: ART of a pyridinium salt to access chiral *N*-aryl piperidines

Considering the differences of aryl amine and benzyl amine, we replaced aniline with benzyl amine and repeated the ART reactions using chiral imidazoline catalysts. According to our mechanistic investigation of ART in Chapter 2, the formation of the chiral *N*-benzyl piperidines involves the hydrogenation of iminium species in the final step of ART, which should be identical to the process in ATH of *N*-benzyl pyridinium salts (Scheme 4.13). The iridacycle **24** was shown to be active for the ART of pyridinium salt with benzyl amine, affording the corresponding piperidine in 75% yield and 10% *ee* (Scheme 4.14). However, the analogue rhodacycle **25**, while active, could not induce chirality into the piperidine ring. The difference in the enantioselectivity induced by **24** in the ART (Scheme 4.14) vs the ATH (Scheme 4.11) may be due to difference in reaction conditions and/or mechanism.



Scheme 4.13: Formation of piperidines *via* ATH and ART through a common intermediate



Scheme 4.14: ART of a pyridinium salt to access chiral *N*-benzyl piperidines

4.3 Conclusion

A few chiral metal catalysts were examined for the ART of pyridinium salts with achiral amines. An iridium imidazoline complex currently gave the highest enantioselectivity, 10% *ee*. This complex and analogues can be easily synthesised *via* cyclometalation reaction of $[Cp^*IrCl_2]_2$ with a chiral imidazoline ligand that undergoes C-H activation. The preliminary investigation demonstrates the potential of chiral metal catalysts for the ART of pyridines. A wider variety of

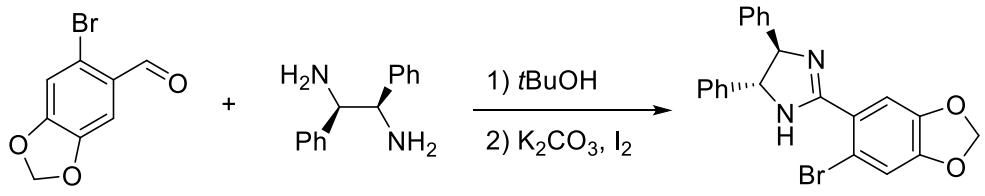
substituents can be introduced into the ligands synthesis, with the potential to afford a higher reactivity and enantioselectivity in the ART reactions.

4.4 Experimental

4.4.1 General information

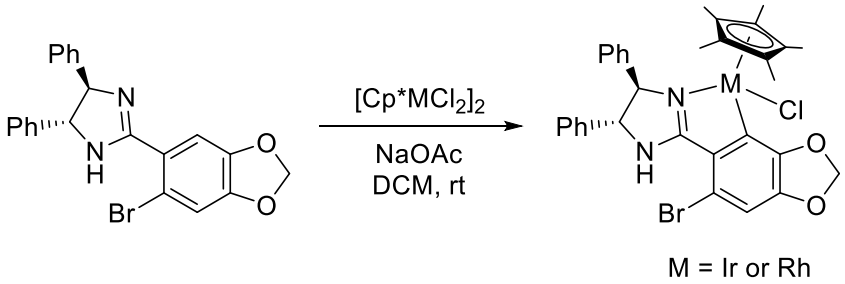
Unless otherwise specified, the chemicals were purchased from commercial suppliers (Sigma-Aldrich, Alfa Aesar, Fluorochem) and used without further purification. Silica gel plates (GF254) were used for TLC monitoring and silica gel (230-400 mesh) was used for running column chromatography. NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer with TMS as the internal standard. The mass spectra were obtained by chemical ionization (CI). The mass spectra were obtained using a Thermo Finnigan Trio-1000 Mass spectrometer. HPLC analysis was performed on Gilson UV/VIS-151 or Shimadzu LC-20A UV/VIS equipped with an OJ-H or AD-H or OX-H column purchased from Daicel Chemical Industries.

4.4.2 Preparation of chiral imidazoline ligand



A round botton flask was charged with (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (1 equiv.), aldehyde (1 equiv, 1 mmol) and a magnetic stirring bar. *t*BuOH (5 mL) was then added and the resulting mixture was stirred at room temperature for 16 h. Then, K_2CO_3 (3 equiv.) and I_2 (1.25 equiv.) were added and the resulting solution was heated to 70 °C for 3 h. After completion, the reaction was cooled to room temperature and quenched by addition of saturated $Na_2S_2O_4$ aqueous solution (10 mL). The organic layer was extracted with EtOAc and washed with water (10 mL x 3) and dried over $MgSO_4$. The solvent was then removed under reduced pressure and the residue purified by column chromatography (n-hexane/EtOAc). The NMR spectrum of the chiral imidazoline ligand can be found in the previous literature.[28]

4.4.3 Preparation of cyclometalated complexes



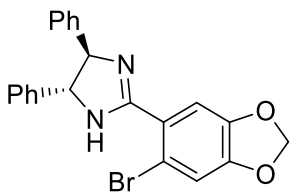
A reaction tube was charged with $[Cp^*MCl_2]_2$ (1 equiv.), imidazoline ligand (2 equiv.), NaOAc (10 equiv.) and a magnetic stirring bar. Dichloromethane was added and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was filtered through Celite and the solvent was removed under

reduced pressure. The complex was recrystallised from DCM/hexane to afford iridium and rhodium complexes. The ^{1}H NMR spectra of the chiral cyclometalated complexes can be found in the previous literature.[28]

4.4.4 General procedure for ATH of pyridinium salts

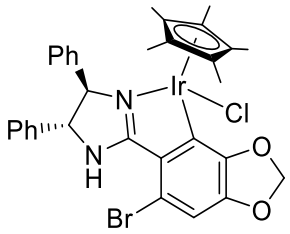
To a carousel reaction tube containing a magnetic stirring bar and *p*-anisidine (308 mg, 2.5 mmol) was added formic acid (564 mg, 12 mmol) dropwise at room temperature. After stirring the amine/acid mixture for 10 min, a pyridinium salt, *N*-ethyl-2-phenylpyridinium iodide (156 mg, 0.5 mmol), metal complex (1 mol%), 3.75 mL of MeOH and 0.25 mL of distilled H_2O were introduced into the mixture. The reaction system was placed in a carousel reactor. The mixture was stirred at 40 °C for 16 h, cooled to room temperature and then basified with an aqueous solution of KOH. The resulting mixture was extracted with ethyl acetate (3×10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane) to give the desired product.

4.5 Analytic data



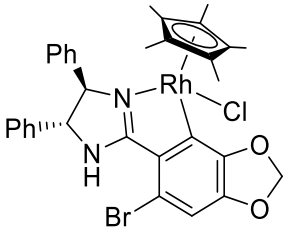
(4*R*,5*R*)-2-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-4,5-diphenyl-4,5-dihydro-1*H*-imidazole:[28]

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.38 – 7.27 (m, 11H), 7.08 (s, 1H), 6.04 (s, 2H), 5.61 (s, 1H), 5.01 (s, 1H), 4.81 (s, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 163.03, 150.19, 147.63, 142.81, 128.86, 127.80, 126.81, 124.95, 113.49, 112.63, 111.31, 102.53, 77.36; **HRMS for $C_{22}H_{18}BrN_2O_2$ $[M+H]^+$:** m/z calcd 421.0547 and 423.0526; found 421.0549 and 423.0532.



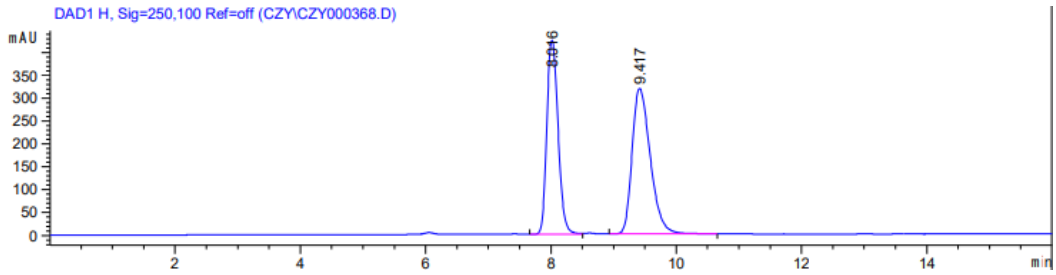
Complex 24: A mixture of two isomers (2:1 ratio); **^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm):** 7.50 – 7.37 (m, 7H), 7.36 – 7.27 (m, 6.5H), 7.11 (s, 1H), 6.88 (s, 0.5H), 6.79 (s, 0.5H), 6.76 (s, 1H), 6.12 (s, 1H), 6.01 (s, 1H), 5.98 (s, 1H), 5.02 (d, *J* = 5.6 Hz, 0.5H), 4.93-4.86 (m, 2H), 4.69 (d, *J* = 5.6 Hz, 0.5H), 1.51 (s, 15H), 1.47 (s, 7.5H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 175.75, 175.04, 151.30, 150.89, 148.68, 148.08, 144.11, 143.75, 142.50, 141.77, 140.44, 139.39, 128.97, 128.90, 128.50, 128.42, 128.37, 128.19, 128.10, 128.04, 127.60, 127.27, 127.18, 126.62, 113.64, 113.40, 108.83, 108.66, 100.14, 99.87, 88.89, 88.23, 79.04, 78.14, 72.05, 71.18, 9.80, 9.45 (due to the overlapping of ^{13}C signals, 38 out of 40 peaks of the

two diastereomers can be observed); **HRMS for $C_{32}H_{31}BrIrN_2O_2$ [M-Cl]$^+$:** m/z calcd 747.1193 and 747.1173; found: 747.1196 and 747.1175.



Complex 25: A mixture of two isomers (3:1 ratio); **^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm):** 7.55 – 7.28 (m, 12H), 7.14 (s, 1H), 6.82 (s, 0.33H), 6.80 (s, 0.33H), 6.78 (s, 1H), 6.15 (s, 1H), 6.04 (s, 0.33H), 6.04 (s, 0.33H), 6.00 (s, 1H), 5.07 (d, *J* = 5.4 Hz, 0.33H), 5.02 (d, *J* = 11.3 Hz, 1H), 4.78 (d, *J* = 11.2 Hz, 1H), 4.66 (d, *J* = 5.9 Hz, 0.33H), 1.46 (s, 15H), 1.43 (s, 5H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 151.60, 147.96, 147.90, 144.33, 144.27, 140.52, 139.54, 139.30, 128.95, 128.90, 128.45, 128.37, 128.29, 128.12, 127.56, 127.26, 112.88, 109.27, 100.44, 96.24, 96.17, 95.75, 95.68, 78.09, 77.22, 70.99, 9.80, 9.47, 9.41 (due to the overlapping and the low intensity of ^{13}C signals, 29 out of 40 peaks from the two diastereomers can be observed); **HRMS for $C_{32}H_{31}BrRhN_2O_2$ [M-Cl]$^+$:** m/z calcd 657.0619 and 659.0598; found: 657.0624 and 659.0610.

The enantiopurity of compound **26** was determined by HPLC analysis on a Chiralpak OJ-H column, *n*-hexane/*i*-PrOH = 90:10, flow rate = 0.5 mL/min., wavelength = 250 nm, t = 8.0 min (minor), t = 9.4 min (major).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.016	BV	0.1971	5281.72559	424.64911	45.0829
2	9.417	BB	0.3137	6433.86523	318.43326	54.9171

4.6 References

[1] D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557–2590.

[2] M. Rubiralta, E. Giralt, A. Diez, *Piperidine: Structure, Preparation and Synthetic Applications of Piperidine and Its Derivatives*, Elsevier:Amsterdam, **1991**.

[3] H.-U. Blaser, H. Hönig, M. Studer, C. Wedemeyer-Exl, *J. Mol. Catal. A Chem.* **1999**, *139*, 253–257.

[4] A. Lei, M. Chen, M. He, X. Zhang, *Eur. J. Org. Chem.* **2006**, *2006*, 4343–4347.

[5] S. A. Raynor, J. M. Thomas, R. Raja, B. F. G. Johnson, R. G. Bell, M. D. Mantle, *Chem. Commun.* **2000**, 1925–1926.

[6] F. Glorius, N. Spielkamp, S. Holle, R. Goddard, C. W. Lehmann, *Angew. Chem. Int. Ed.* **2004**, *43*, 2850–2852.

[7] M. Studer, C. Wedemeyer-Exl, F. Spindler, H.-U. Blaser, *Monatsh. Chem.* **2000**, *131*, 1335–1343.

[8] X.-B. Wang, W. Zeng, Y.-G. Zhou, *Tetrahedron Lett.* **2008**, *49*, 4922–4924.

[9] W. Tang, Y. Sun, L. Xu, T. Wang, Q. Fan, K.-H. Lam, A. S. C. Chan, *Org. Biomol. Chem.* **2010**, *8*, 3464–3471.

[10] W.-J. Tang, J. Tan, L.-J. Xu, K.-H. Lam, Q.-H. Fan, A. S. C. Chan, *Adv. Synth. Catal.* **2010**, *352*, 1055–1062.

[11] B. Balakrishna, J. L. Núñez-Rico, A. Vidal-Ferran, *Eur. J. Org. Chem.* **2015**, *2015*, 5293–5303.

[12] A. N. Kim, B. M. Stoltz, *ACS Catal.* **2020**, *10*, 13834–13851.

[13] C. Y. Legault, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 8966–8967.

[14] A. Cadu, P. K. Upadhyay, P. G. Andersson, *Asian J. Org. Chem.* **2013**, *2*,

1061–1065.

[15] Z.-S. Ye, M.-W. Chen, Q.-A. Chen, L. Shi, Y. Duan, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2012**, *51*, 10181–10184.

[16] Y. Kita, A. Iimuro, S. Hida, K. Mashima, *Chem. Lett.* **2014**, *43*, 284–286.

[17] M.-W. Chen, Y. Ji, J. Wang, Q.-A. Chen, L. Shi, Y.-G. Zhou, *Org. Lett.* **2017**, *19*, 4988–4991.

[18] S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563.

[19] G. Zassinovich, G. Mestroni, S. Giadiali, *Chem. Rev.* **1992**, *92*, 1051–1069.

[20] J. Hannedouche, G. J. Clarkson, M. Wills, *J. Am. Chem. Soc.* **2004**, *126*, 986–987.

[21] R. Guo, C. Elpelt, X. Chen, D. Song, R. H. Morris, *Chem. Commun.* **2005**, 3050–3052.

[22] A. M. Hayes, D. J. Morris, G. J. Clarkson, M. Wills, *J. Am. Chem. Soc.* **2005**, *127*, 7318–7319.

[23] J. S. M. Samec, J.-E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*, 237–248.

[24] X. Huang, J. Y. Ying, *Chem. Commun.* **2007**, 1825–1827.

[25] Y. Wei, X. Wu, C. Wang, J. Xiao, G. Zassinovich, G. Mestroni, S. Giadiali, R. A. W. Johnstone, A. H. Wilby, I. D. Entwistle, G. Brieger, T. J. Nestrick, *Chem. Rev.* **2007**, *92*, 567–580.

[26] J. Mao, D. C. Baker, *Org. Lett.* **1999**, *1*, 841–843.

[27] T. Thorpe, J. Blacker, S. M. Brown, C. Bubert, J. Crosby, S. Fitzjohn, J. P. Muxworthy, J. M. J. Williams, *Tetrahedron Lett.* **2001**, *42*, 4041–4043.

[28] J. Smith, A. Kacmaz, C. Wang, B. Villa-Marcos, J. Xiao, *Org. Biomol. Chem.* **2021**, *19*, 279–284.

Chapter 5: Rhodium-catalysed Transfer Hydrogenation of Aldehydes Using Methanol as Hydrogen Source

5.1 Introduction

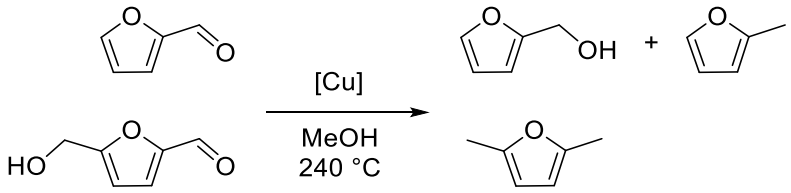
Reduction of unsaturated compounds is an important class of reactions in organic synthesis to produce valuable saturated products. In this chapter, we turn attention to the reduction of carbonyl compounds with rhodium catalysts. The reduction of carbonyl compounds is a fundamental synthetic method for alcohol production, and is extensively used in both laboratory and industry.[1] Traditionally, these type of transformations were performed using stoichiometric or excess amount of metal hydride reagents like sodium borohydride ($NaBH_4$) or lithium aluminium hydride ($LiAlH_4$). However, the use of such highly reactive reducing agents requires special care and generates stoichiometric wastes as by-products. Their almost universal reducing properties lead to difficulties in controlling regioselectivity during reduction. Catalytic hydrogenation with a pressure of molecular hydrogen (H_2) is also an employed strategy for reduction. TH has emerged as an alternative method in the past few decades for the preparation of saturated compounds like alcohols from carbonyls. Compared to the use of stoichiometric amount of hydride reagents or the hazardous hydrogen gas, TH has certain advantages in terms of safety, simplicity and low cost.[2–6] Various complexes based on transition metals such as Ru, Rh, Ir, Pd, Pt, Au, Fe, Co and Ni have been developed and applied in TH reactions.[7] Safe and easily available isopropanol and formic acid are commonly used hydrogen donors in TH.[7–17] In

contrast, the simplest and cheapest alcohol, methanol, has been less studied in TH reactions as hydrogen donor.

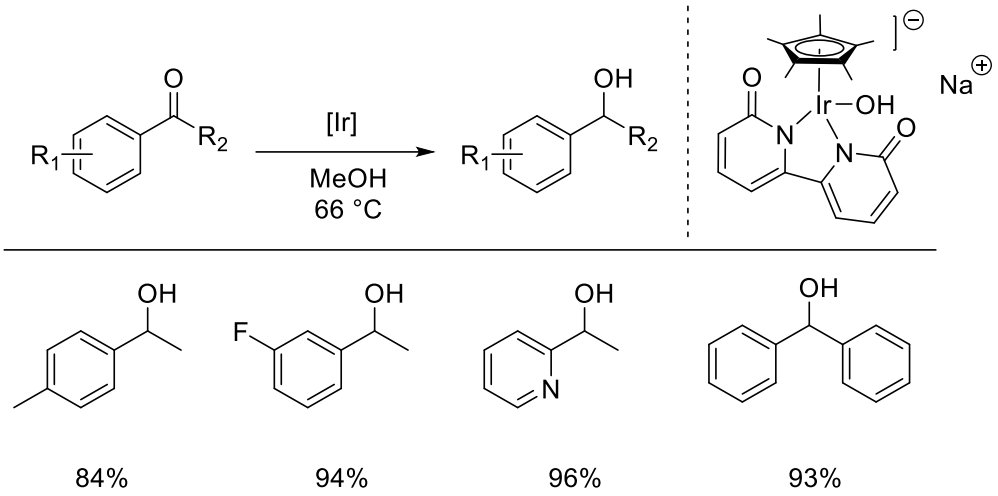
As a renewable energy source, methanol can be easily produced from oil, biomass and syngas with an annual global production capacity of over 110 million tons.[18] Methanol is the simplest aliphatic alcohol with a high hydrogen storage capacity of 12.6 wt% compared to other liquid fuels.[19] Thus, methanol is considered as one of the most significant chemical industrial materials especially when the global economy is shifting to carbon-neutral energy. Despite the importance of methanol as a future energy source, hydrogenation reactions using methanol as hydrogen donor are less studied. The main reason is that methanol is generally considered thermodynamically unfavourable to undergo dehydrogenation process for the generation of necessary metal hydride species (see Chapter 1.2.3).[20] Furthermore, the catalyst can be poisoned or deactivated by the dehydrogenation product aldehydes or decarbonylation product carbon monoxide (CO).[1]

So far, only limited reports have demonstrated the use of methanol as hydrogen donor in catalytic TH; however, none of the thermal catalytic reactions could be performed near room temperature. In 1985, Maitlis and co-workers reported homogeneous hydrogenation of ketones by ruthenium and rhodium complexes with methanol at 150 °C. Methanol was oxidised to methyl formate, and carbon dioxide was also detected.[21] The Chen group showed selective TH of

biomass-based furfural and 5-hydroxymethylfurfural over hydrotalcite-derived copper catalysts with methanol at over 200 °C (Scheme 5.1).[22] The García group demonstrated alkylation and TH of α,β-unsaturated enones by nickel catalyst with methanol at 180 °C.[23] The Crabtree group reported TH of aromatic ketones and imines with methanol by iridium *N*-heterocyclic carbine (NHC) complexes under microwave irradiation.[24] Very recently, lower temperature TH of ketones with methanol at 66 °C was reported by the Li group using an anionic iridium complex under base-free conditions (Scheme 5.2).[25] To the best of our knowledge, there are only two examples of TH with methanol at room temperature. In one report, the TH reaction is driven by light with Pd-Pt alloy,[26] while the other reaction is catalysed by an enzyme.[27]



Scheme 5.1: TH of biomass-based carbonyls using methanol as hydrogen donor



Scheme 5.2: Selected examples for TH of ketones using methanol as hydrogen donor

Both the thermodynamics and the literature results showed that it is challenging to perform TH using methanol as hydrogen donor at low temperature. In our previous study of TH reactions, we have reported the synthesis of various efficient cyclometalated iridium complexes and their applications in the reduction of carbonyls and imines.[28–30] Based on those studies, we found that a cyclometalated rhodium complex (rhodacycle) analogue is capable of reducing carbonyl compounds with methanol at 90 °C.[31,32] Further studies showed that the rhodium complex could dehydrogenate methanol at near room temperature for TH reactions. In this chapter, the rhodacycle-catalysed TH of aldehydes with methanol as hydrogen donor will be presented.

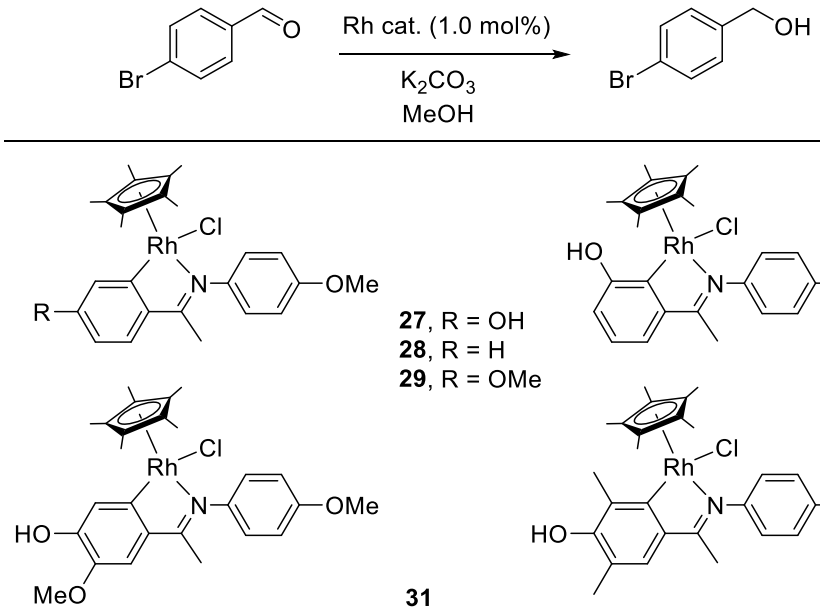
5.2 Results and discussion

5.2.1 Optimisation of reaction conditions

We chose 4-bromobenzaldehyde as the model substrate to conduct the rhodacycle-catalysed TH using methanol as both hydrogen donor and solvent. Surprisingly, an excellent yield (97%) was obtained in the presence of catalyst **27** and sodium carbonate (Na_2CO_3) at 30 °C for 1 h (Table 5.1, entry 1). A slightly lower yield (83%) was recorded when the reaction was performed at 25 °C (entry 2). A similar yield (91%) of alcohol product was obtained when methanol was replaced by ethanol (entry 3). Unexpectedly, the commonly used hydrogen donor, isopropanol, gave no conversion in this catalytic system (entry 4).

In order to select the most efficient catalyst, various rhodacycles were synthesised and tested in the methanol system within a shorter reaction time. The reactions were stopped at 20 min, and the catalyst **27** bearing a hydroxy group at the *para* position to the imino moiety of the ligand gave the highest yield (entry 5). Replacing the hydroxy group with hydrogen (**28**) or methoxy group (**29**) gave lower or no activity (entry 6-7). To our surprise, moving the hydroxyl group closer to the rhodium centre also led to decreased yield (entry 8). Pyridinyl ligands bearing a hydroxyl group at the *ortho* position to the metal centre have been shown to be effective for TH of ketones and imines by several research groups.[25,33–40] Complex **31** with an additional methoxy group showed a similar yield (entry 9), whilst only a trace amount of product was detected when two methyl groups were introduced to the complex **32** (entry 10).

Table 5.1: Optimisation of reaction conditions with cyclometalated rhodium complexes[a]



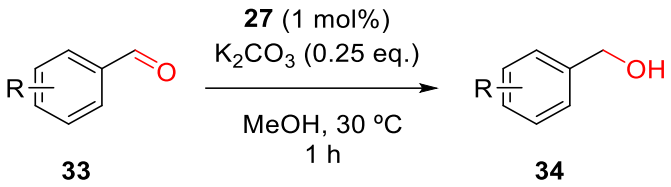
Entry	Catalyst	Solvent	Time	Yield %[b]
1	**27**	MeOH	1 h	97
2	**27**	MeOH	1 h	83[c]
3	**27**	EtOH	1 h	91
4	**27**	*i*-PrOH	1 h	N. R.
5	**27**	MeOH	20 min	87
6	**28**	MeOH	20 min	44
7	**29**	MeOH	20 min	N. R.
8	**30**	MeOH	20 min	43
9	**31**	MeOH	20 min	86
10	**32**	MeOH	20 min	< 5

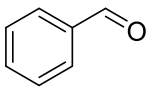
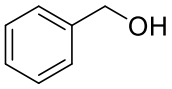
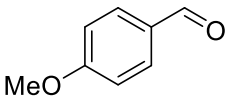
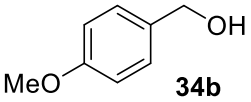
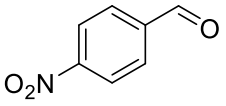
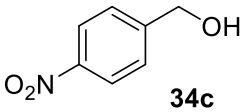
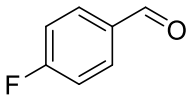
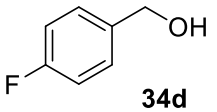
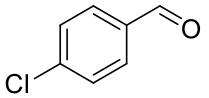
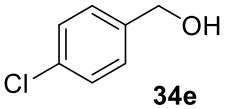
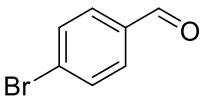
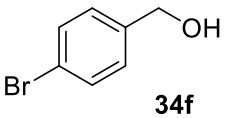
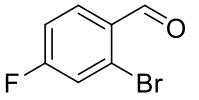
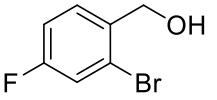
[a] Reaction condition: 4-bromobenzaldehyde (0.3 mmol), Rh catalyst (1 mol%), K_2CO_3 (0.075 mmol) and MeOH (1.5 mL), stirred at 30 ºC. [b] Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Reaction run at 25 °C.

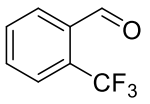
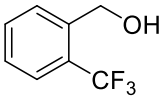
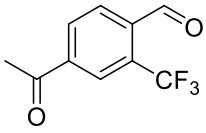
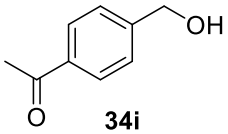
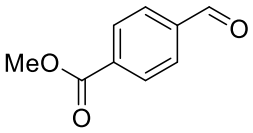
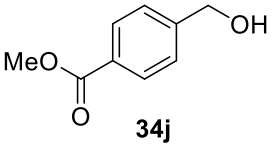
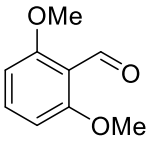
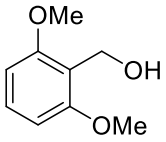
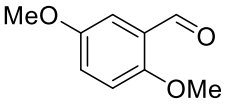
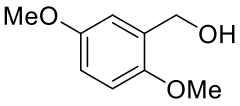
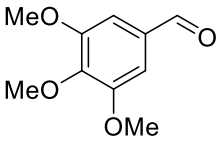
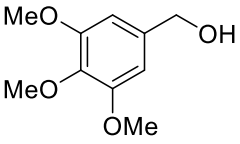
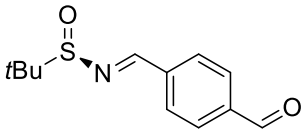
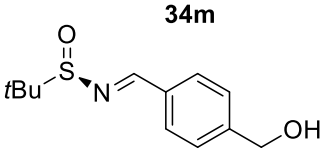
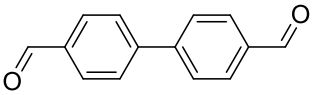
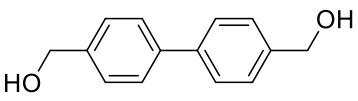
5.2.2 Substrate scope for TH of aldehydes with methanol

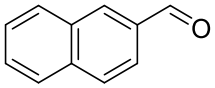
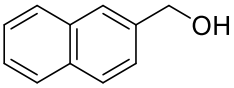
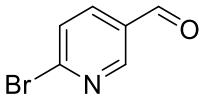
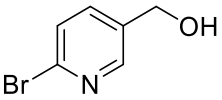
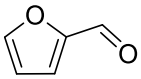
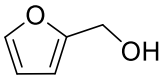
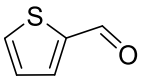
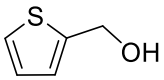
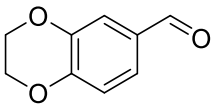
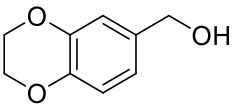
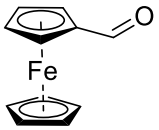
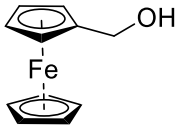
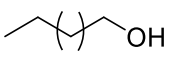
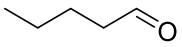
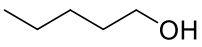
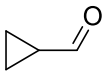
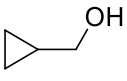
With the optimised reaction conditions in hand, we expanded the substrate scope of this protocol to various aromatic and aliphatic aldehydes to show the broader utility of the rhodium catalyst. Various aldehydes were transformed into the desired alcohol products in good to excellent yields (Table 5.2). Generally, substrates bearing electron-withdrawing groups, like nitro (**33c**), halide (**33d-g**) and trifluoromethyl (**33h**), gave slightly lower yields, compared with those bearing electron-donating groups (**33b**, **k-m**). Aldehydes with sterically bulky group at the *ortho* position, like (**33g**, **h**, **k**, **l**), had no effect on the high reduction yields. In addition, the potentially reducible functionalities, such as ester (**33j**), aldimine (**33n**) and ketones (**33i**, **z**), remained intact during the reduction process, demonstrating the high chemoselectivity of the reaction system. Heterocyclic aldehydes (**33q-u**) and aliphatic aldehydes (**33v-z**) were also well-tolerated to give their corresponding alcohols.

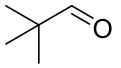
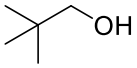
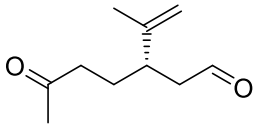
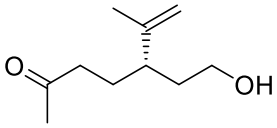
Table 5.2: Substrate scope for the reduction of aryl and aliphatic aldehydes with methanol [a]



Entry	Substrate	Product	Yield (%)[b]
1		 **34a**	85
2		 **34b**	92
3		 **34c**	67
4		 **34d**	87
5		 **34e**	90
6		 **34f**	93
7		 **34g**	90

Entry	Substrate	Product	Yield (%)[b]
8		 **34h**	81
9		 **34i**	84
10		 **34j**	89
11		 **34k**	85
12		 **34l**	93
13		 **34m**	92
14		 **34n**	84
15		 **34o**	87

Entry	Substrate	Product	Yield (%)[b]
16		 **34p**	99
17		 **34q**	74
18		 **34r**	85
19		 **34s**	73
20		 **34t**	93
21		 **34u**	99
22	 n=5	 n=5 **34v**	82
23		 **34w**	(76)
24		 **34x**	(83)

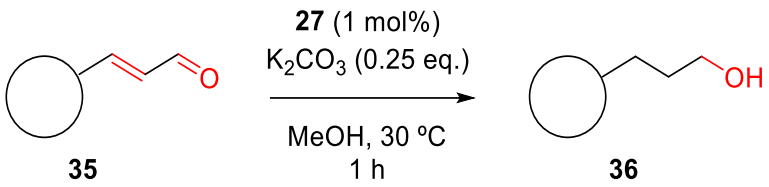
Entry	Substrate	Product	Yield (%)[b]
25		 **34y**	(80)
26		 **34z**	83

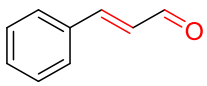
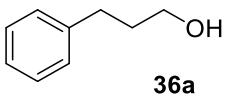
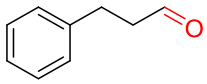
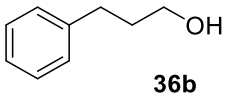
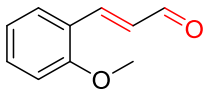
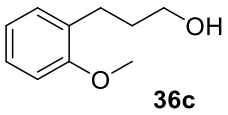
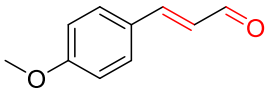
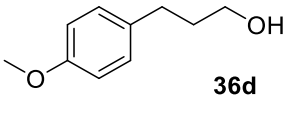
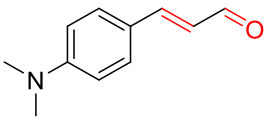
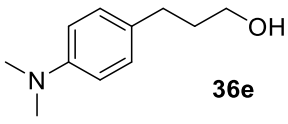
[a] Reaction condition: aldehyde (0.3 mmol), Rh catalyst **27** (1.0 mmol%), K_2CO_3 (0.25 eq.) and MeOH (1.5 mL), stirred at 30 ºC for 1 h. [b] Isolated Yields, values in parentheses are determined by GC.

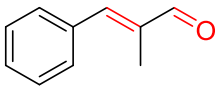
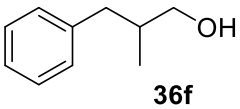
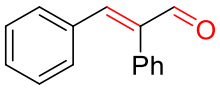
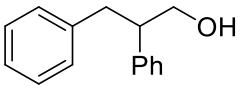
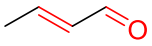
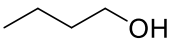
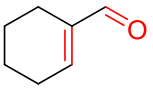
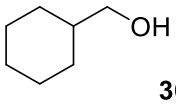
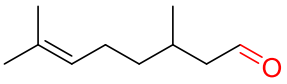
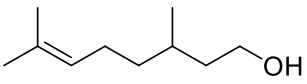
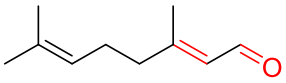
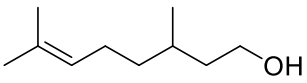
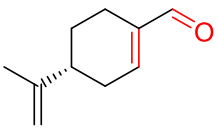
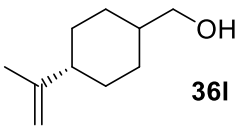
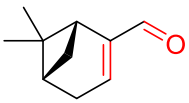
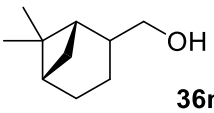
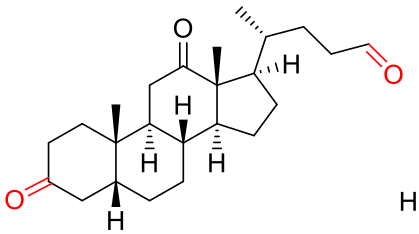
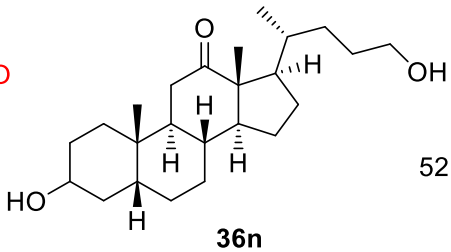
Next, the reaction system was successfully extended to a series of unsaturated aldehydes (Table 5.3). Under the standard conditions, reduction of α,β-unsaturated aldehydes, such as cinnamaldehyde **35a**, afforded saturated alcohol product with both C=O and C=C double bonds being reduced. Cinnamaldehydes bearing substituents at either *ortho* or *para* position gave excellent yields (**35c**-**e**). High yields were achieved even with the introduction of methyl or phenyl groups on the α carbon of cinnamaldehyde (**35f**, **g**). Aliphatic unsaturated aldehydes were also well-tolerated, including natural products, like terpene, citral, perillaldehyde and steroids. However, the nonconjugated C=C double bonds in these substrates remained intact during the reduction process. Surprisingly, ketone in the saturated cyclic steroid **35n** and **35o** derived from steroids like deoxycholic acid and lithocholic acid, respectively, were reduced along with aldehyde groups in fair

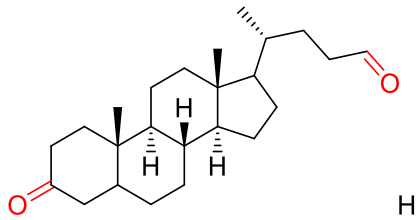
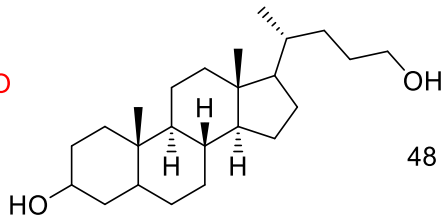
yields. It is noteworthy that in substrate **35n**, only the ketone moiety most remote from the aldehyde functionality was reduced, whilst the nearer one remained intact, possibly due to the difference in steric hindrance between the two ketone groups located at the two ends of one compound. The results indicate the potential for selective reduction of carbonyl groups in complex substrates due to steric effects.

Table 5.3: Substrate scope for the reduction of unsaturated aldehydes with methanol [a]



Entry	Substrate	Product	Yield (%)[b]
1		 **36a**	79
2		 **36b**	77
3		 **36c**	97
4		 **36d**	95
5		 **36e**	96

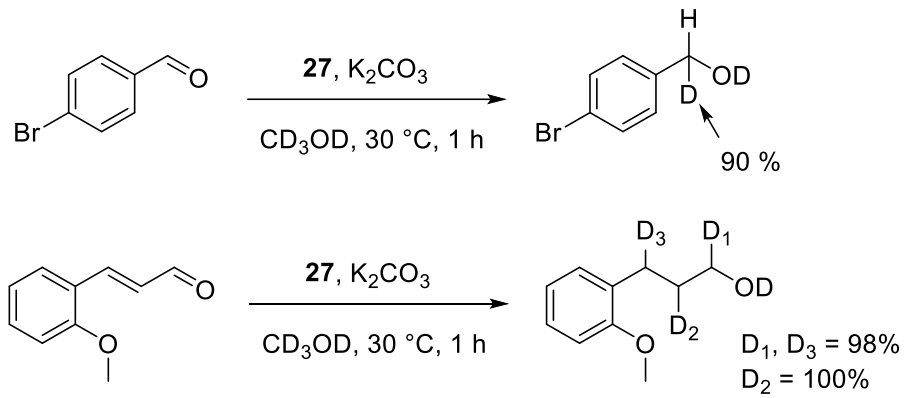
Entry	Substrate	Product	Yield (%)[b]
6		 **36f**	86
7		 **36g**	96
8		 **36h**	(72)
9		 **36i**	86
10		 **36j**	92
11		 **36k**	86
12		 **36l**	83
13		 **36m**	98
14		 **36n**	52

Entry	Substrate	Product	Yield (%)[b]
15		 **36o**	48

[a] Reaction condition: aldehyde (0.3 mmol), Rh catalyst **27** (1.0 mmol%), K_2CO_3 (0.25 eq.) and MeOH (1.5 mL), stirred at 30 ºC for 1 h. [b] Isolated Yields, values in parentheses are determined by GC.

5.2.3 Mechanistic investigations

The reduction of aldehydes in deuterated methanol (CD_3OD) was conducted to verify that methanol was the hydrogen source during the TH reactions. The ^1H NMR spectra confirmed the incorporation of deuterium at each aliphatic carbon of products (Scheme 5.3). The result is consistent with the normal transfer hydrogenation mechanism, in which β-hydride elimination from methanol occurs at rhodium to form a rhodium hydride. Then the hydride is transferred to the carbonyl carbon of a benzaldehyde or the β carbon of a cinnamaldehyde followed by proton and hydride transfer to generate the saturated alcohol products.[30–32,35]



Scheme 5.3: TH of benzaldehyde and cinnamaldehyde with deuterated methanol.

Further investigations with ^{1}H NMR were conducted to elucidate the mechanism of the TH reaction (Figure 5.1). No hydride resonance was observed on dissolution of catalyst **27** in CD_2Cl_2 or upon introducing a few drops of methanol to the NMR tube. After addition of 1 equivalent of sodium carbonate, the resulting solution turned from yellow to dark brown. The immediate change in colour may be caused by either the deprotonation of hydroxyl group from the ligand or the formation of the rhodium hydride species. At the same time, a triplet at -13.2 ppm ($J_{Rh\text{-}H}$ = 30.3 Hz) appeared in the hydride region of ^{1}H NMR spectrum, indicating the formation of a hydride-bridged dimeric rhodium species.[41] As the reaction proceeded, a monomeric hydride, characterised by a doublet peak at -12.02 ppm, grew and then disappeared. A new triplet peak formed and replaced the previous one, suggesting the formation of a more stable dimeric rhodium species. When a benzaldehyde substrate was added to the resulting mixture in the NMR tube, this

new hydride peak showed no observable changes in the ^{1}H NMR spectrum, implying the hydride species is catalytically inactive for the TH reaction.

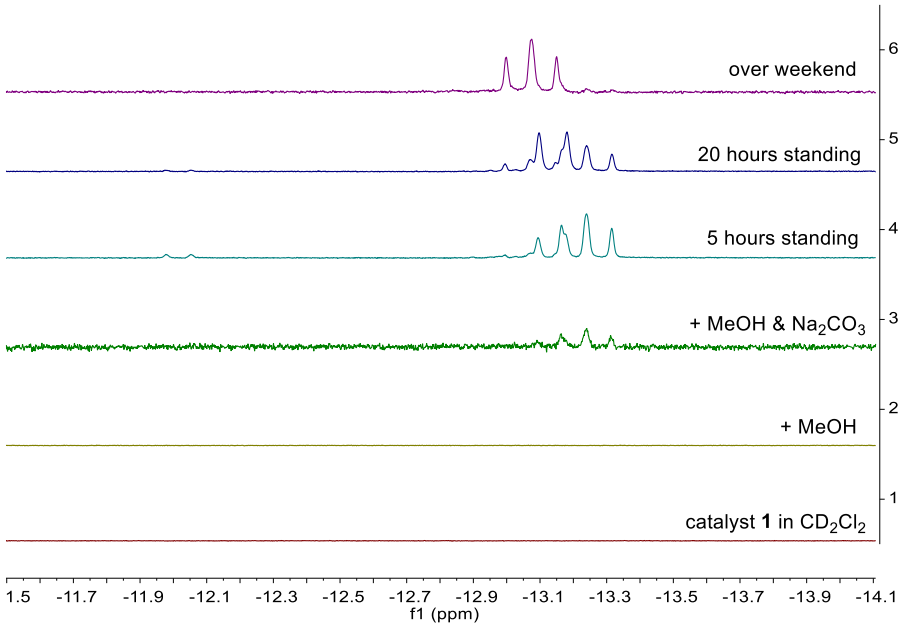


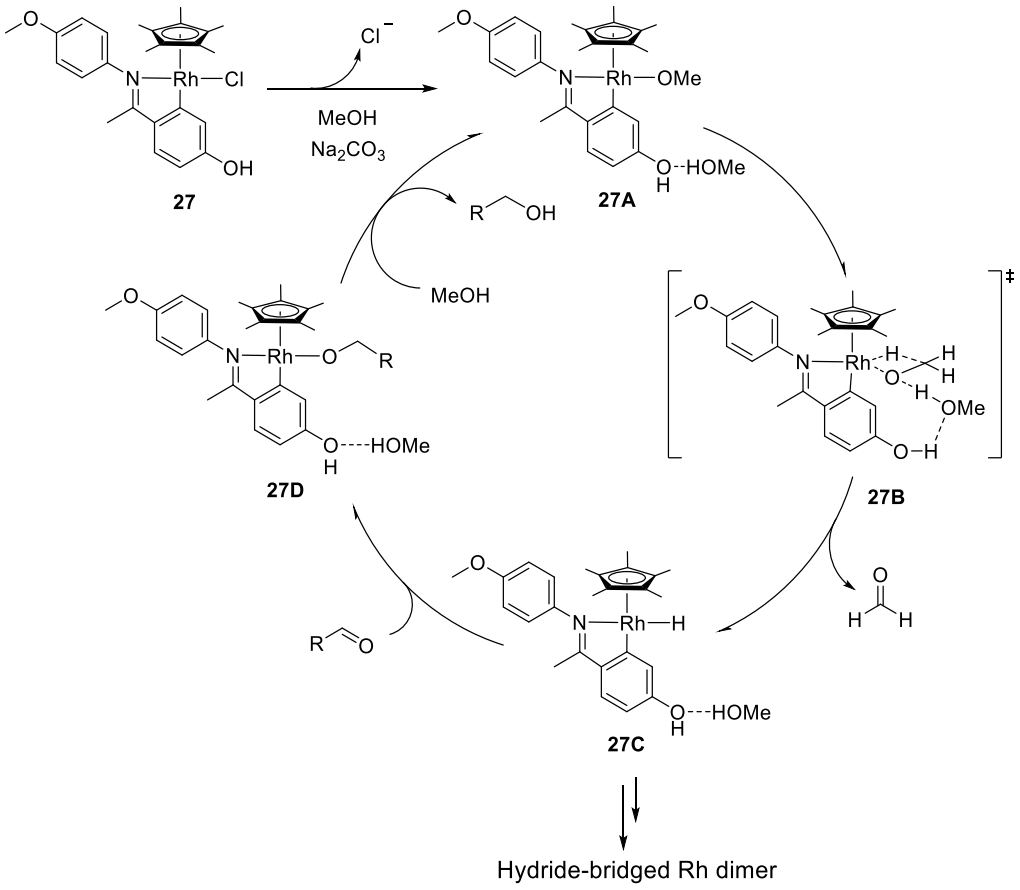
Figure 5.1： Stacked ^{1}H NMR spectra of the hydride region from the catalyst **27**

In contrast, when complex **28** was treated under the same conditions, no hydride was observed. This observation emphasises the key role of the *para*-hydroxy functionality of the ligand in facilitating the dehydrogenation of methanol. The low activity of complex **32** further highlights the importance of the *p*-OH group, as it introduces a methyl group between the rhodium centre and the hydroxy group, which may hinder the methanol dehydrogenation process that we assumed to be achieved *via* hydrogen bonding.

Based on the experimental results and previous studies on rhodium-catalysed TH of carbonyl compounds,[30–32,35] we have proposed a plausible mechanism (Scheme 5.4). At first, methanol reacts with the chloride-dissociated form of catalyst **27** to generate a rhodium methoxide complex **27A**. Then, β-hydride elimination occurs *via* the possible transition state **27B**, producing the active rhodium hydride species **27C** and releasing formaldehyde.[31,42,43] The hydride migrates from **27C** to the aldehyde substrate to give the alkoxide complex **27D**. Finally, the saturated alcohol product is formed with the regeneration of methoxide complex **27A** to close the catalytic cycle.

The base required in the reaction system may facilitate the generation of the methoxide complex **27A** or deprotonate the *para*-OH moiety. Although we cannot exclude the possibility of deprotonation during the reduction, the loss of catalytic activity in **32**, in which the *para*-OH is sterically inaccessible for a transition state like **27B**, suggests that deprotonation of the imino ligand, if it occurs, may be less relevant to the catalysis. Similarly, the low activity of catalyst **30**, where the OH is closer to the rhodium centre, also emphasises that the position of hydroxy functionality is most important for the effective TH reaction to proceed. Therefore, we suggest that the *para*-OH provides a hydrogen bonding network including a solvent methanol molecule in a transition state **27B**. This network may lower the energy barrier for the transfer of β-hydride from MeOH to rhodium, thus making the low-temperature dehydrogenation possible. This hydrogen bonding network may also facilitate the hydride transfer from **27C** to the aldehyde substrate. The

hydride may yield a catalytically inactive dimeric species, as indicated by the dominant triplet in Figure 5.1; however, the structure of the species is unclear so far.



Scheme 5.4: Proposed mechanism for rhodium-catalysed TH of aldehydes with methanol

5.3 Conclusion

This chapter shows that a cyclometalated rhodium complex enables the dehydrogenation of methanol at room temperature. The catalytic protocol

developed allows for the TH of various aldehydes with methanol as both hydrogen donor and solvent. Few molecular catalysts are known of being able to dehydrogenate methanol under such mild conditions. The key to the ability of the identified catalyst is the introduction of a hydroxy functionality and its appropriate positioning in the ligand.

5.4 Experimental

5.4.1 General information

Chemicals were purchased from Sigma-Aldrich, Alfa Aesar or Fluorochem and used without further purification. Silica gel plates (GF254) were used for TLC monitoring and silica gel (230- 400 mesh) was used for running column chromatography. Methanol was purchased from Sigma-Aldrich. NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer with TMS as the internal standard. The mass spectra were obtained by chemical ionization (CI).

5.4.2 General procedure for the imine ligands preparation

Imine ligands were prepared based on our previous work. In a 250 mL round bottomed flask, ketone (5.0 mmol), amine (5.5 mmol) and $NaHCO_3$ (420 mg, 5 mmol) were dissolved in toluene (80 mL), and 4Å molecular sieves (1.2 g) were introduced. The resulting mixture was fitted with a Dean-Stark condenser and heated to reflux for 24 h. After completion, solid residues were removed, followed

by removal of solvent in vacuo. The imine ligand was obtained from crystallization by using DCM/hexane.

5.4.3 General procedure for the rhodium complexes preparation

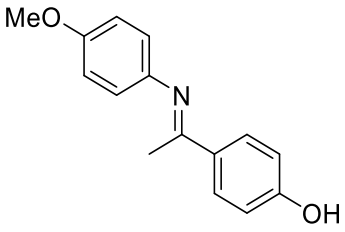
In a 50 mL round bottomed flask, $[Cp^*RhCl_2]_2$ dimer (100 mg, 0.16 mmol) (Cp* = pentamethylcyclopentadiene), imine ligand (2.2 eq.) and sodium acetate (10 eq.) were dissolved in DCM (10 mL). Then the reaction was stirred overnight under a nitrogen atmosphere at room temperature. The resulting mixture was then filtered to remove insoluble materials, dried over $MgSO_4$, and filtered, and the solvent was removed in vacuo. The crude solid product was then washed with diethyl ether/hexane to afford an air and moisture stable pure compound.[44]

5.4.4 General procedures for TH of aldehydes

A Schlenk tube containing a magnetic stirring bar, the rhodium catalyst (1.5 mg, 0.003 mmol), aldehyde substrate (0.3 mmol) and potassium carbonate (10 mg, 0.075 mmol) in 1.5 mL of methanol was sealed and placed in a carousel reactor. The reaction mixture was stirred at 30 °C for 1 h, after which it was cooled to room temperature, and washed with H_2O. The resulting mixture was extracted with ethyl acetate and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the product was purified by flash column chromatography using hexane/ethyl acetate as eluent.

5.5 Analytical data

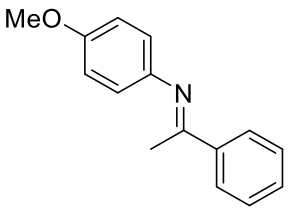
5.5.1 Data of imine compounds



4-(1-((4-Methoxyphenyl)imino)ethyl)phenol:

The titled compound was synthesised according to general procedure for the imine ligands preparation. The product was obtained from crystallization by using DCM/hexane.

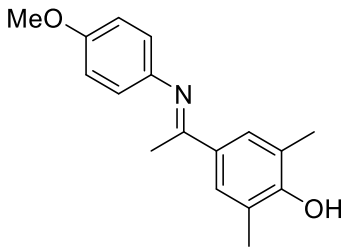
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.82 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 2.22 (s, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 166.03, 158.20, 155.98, 144.44, 132.02, 129.00, 121.09, 115.21, 114.29, 55.50, 17.47; **HRMS for $C_{15}H_{16}NO_2$ [M + H]$^+$:** m/z calcd 242.1176; found 242.1173.



N-(4-methoxyphenyl)-1-phenylethan-1-imine:

The titled compound was synthesised according to general procedure for the imine ligands preparation. The product was obtained from crystallization by using DCM/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.03 – 7.91 (m, 2H), 7.50 – 7.38 (m, 3H), 6.96 – 6.87 (m, 2H), 6.81 – 6.71 (m, 2H), 3.82 (s, 3H), 2.26 (s, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 165.79, 155.91, 144.78, 139.73, 130.34, 128.35, 127.10, 120.75, 114.21, 55.49, 17.36; **HRMS for $C_{15}H_{16}NO$ $[M + H]^+$:** m/z calcd 226.1226; found 226.1236.

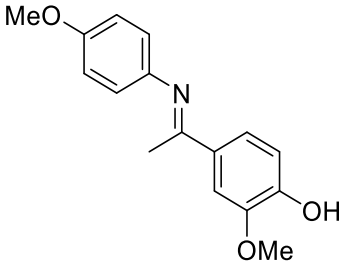


4-(1-((4-Methoxyphenyl)imino)ethyl)-2,6-dimethylphenol:

The titled compound was synthesised according to general procedure for the imine ligands preparation. The product was obtained from crystallization by using DCM/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.64 – 7.58 (m, 2H), 6.93 – 6.86 (m, 2H), 6.77 – 6.69 (m, 2H), 3.81 (s, 3H), 2.29 (d, *J* = 0.7 Hz, 6H), 2.19 (s, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 165.47, 155.74, 154.38, 145.09, 131.85, 127.79,

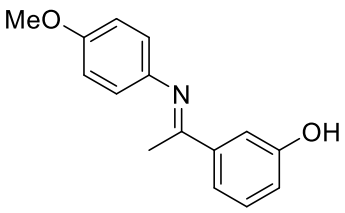
122.76, 120.89, 114.21, 55.49, 17.19, 15.98; **HRMS for $C_{17}H_{20}NO_2$ $[M + H]^+$:** m/z calcd 270.1489; found 270.1494.



2-Methoxy-4-(1-((4-methoxyphenyl)imino)ethyl)phenol:

The titled compound was synthesised according to general procedure for the imine ligands preparation. The product was obtained from crystallization by using DCM/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.71 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.92 – 6.87 (m, 2H), 6.77 – 6.71 (m, 2H), 3.97 (s, 3H), 3.82 (s, 3H), 2.21 (s, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 164.96, 155.81, 148.04, 146.58, 144.97, 132.27, 121.42, 120.84, 114.26, 113.58, 108.95, 56.07, 55.50, 17.10; **HRMS for $C_{16}H_{18}NO_2$ $[M + H]^+$:** m/z calcd 272.1281; found 272.1277.

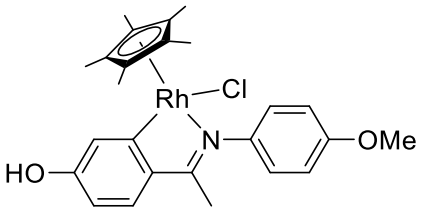


3-(1-((4-Methoxyphenyl)imino)ethyl)phenol:

The titled compound was synthesised according to general procedure for the imine ligands preparation. The product was obtained from crystallization by using DCM/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.46 (d, *J* = 2.2 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.33 – 7.25 (m, 1H), 6.93 (td, *J* = 5.1, 4.5, 2.8 Hz, 3H), 6.80 (d, *J* = 8.4 Hz, 2H), 3.84 (d, *J* = 1.1 Hz, 3H), 2.23 (d, *J* = 1.1 Hz, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 166.87, 156.17, 156.07, 144.13, 141.16, 129.57, 120.99, 119.48, 117.82, 116.68, 114.85, 114.33, 113.94, 55.50, 17.82. **HRMS for $C_{15}H_{16}NO_2$ [M + H]$^+$:** m/z calcd 242.1176; found 242.1181.

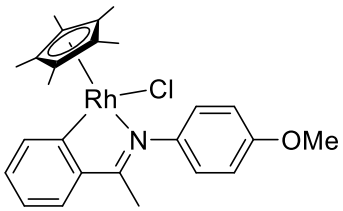
5.5.2 Data of cyclometalated rhodium complexes



Rhodium complex (27):[31]

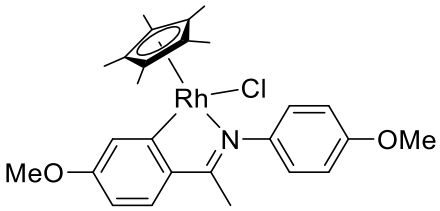
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.26 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 2.3 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.42 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.85 (s, 3H), 2.24 (s, 3H), 1.38 (s, 15H); ^{1}H NMR at low temperature (213 K) could be found in our previous study.[31] **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 185.32, 178.25, 157.97, 157.43, 143.66, 140.19, 129.11, 124.36, 122.98, 110.53, 99.99, 96.08, 96.01, 55.52,

17.02, 8.76; **HRMS for $C_{25}H_{29}RhNO_2$ [M-Cl]$^+$:** m/z calcd 478.1248; found 478.1255.



Rhodium complex (28):

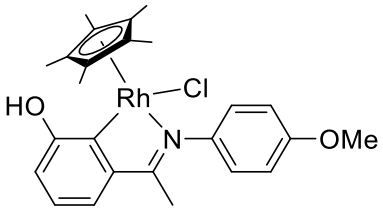
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.83 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.31 – 7.23 (m, 2H), 7.05 (td, *J* = 7.4, 1.2 Hz, 1H), 6.99 – 6.89 (m, 2H), 3.85 (s, 3H), 2.32 (s, 3H), 1.39 (s, 15H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 183.96, 183.64, 179.28, 157.66, 147.29, 143.54, 136.28, 131.15, 127.75, 124.02, 122.19, 113.85, 96.24, 96.18, 55.53, 17.06, 8.77; **HRMS for $C_{25}H_{29}{}^{35}ClRhNONa$ [M + Na]$^+$:** m/z calcd 520.0885; found 520.0891.



Rhodium complex (29):[31]

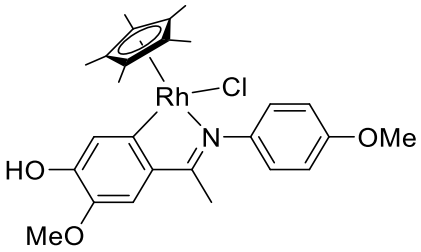
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.41 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 2.3 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.58 (dd, *J* = 8.5, 2.3 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 2.27 (s, 3H), 1.39 (s, 15H); Due to the fluxionality, two of the aromatic

hydrogens appeared very broad and featureless at rt. ^{1}H NMR at low temperature (213 K) could be found in our previous study.[31] **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 182.38, 182.06, 178.06, 157.38, 156.64, 143.75, 140.18, 130.39, 124.45, 122.37, 118.21, 95.91, 95.85, 55.54, 53.42, 17.03, 15.69, 8.79; **HRMS for $C_{26}H_{31}{}^{35}ClRhNO_2Na$ [M + Na]$^+$:** m/z calcd 550.0996; found 550.0988.



Rhodium complex (30):

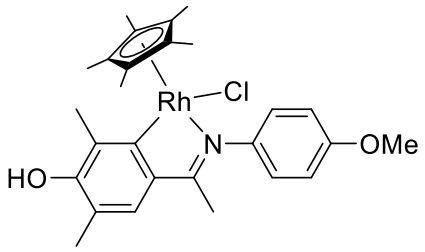
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.41 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.05 – 6.99 (m, 1H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 7.7 Hz, 1H), 3.86 (s, 3H), 2.38 (s, 3H), 1.40 (s, 15H); **HRMS for $C_{25}H_{29}{}^{35}ClRhNO_2Na$ [M + Na]$^+$:** m/z calcd 536.0834; found 536.0834.



Rhodium complex (31):

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.37 (s, 1H), 7.00 (s, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 5.90 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.27 (s, 3H), 1.39 (s, 15H); **^{13}C**

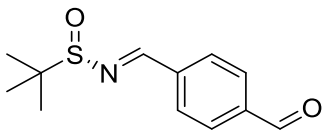
NMR ($CDCl_3$, 100 MHz) δ (ppm): 157.45, 148.19, 143.78, 142.80, 138.72, 128.98, 124.08, 121.31, 110.44, 95.99, 95.93, 77.33, 56.22, 55.54, 17.19, 8.77; **HRMS for $C_{26}H_{31}{}^{35}ClRhNO_3Na$ $[M + Na]^+$:** m/z calcd 566.0940; found 566.0937.



Rhodium complex (32):

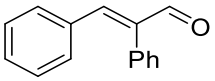
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.50 (d, *J* = 8.3 Hz, 2H), 7.17 (s, 1H), 6.94 – 6.87 (m, 2H), 3.84 (s, 3H), 2.58 (s, 3H), 2.33 (s, 3H), 2.22 (d, *J* = 0.8 Hz, 3H), 1.32 (s, 15H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 157.55, 154.70, 143.32, 140.17, 138.57, 137.78, 129.14, 127.38, 125.42, 117.71, 113.39, 96.42, 96.36, 55.51, 19.55, 15.86, 8.88; **HRMS for $C_{27}H_{33}{}^{35}ClRhNO_2Na$ $[M + Na]^+$:** m/z calcd 564.1147; found 564.1143.

5.5.3 Data of starting materials and alcohol products



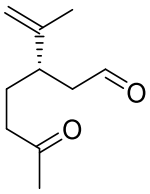
(S,E)-N-(4-formylbenzylidene)-2-methylpropane-2-sulfinamide:[45]

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.10 (s, 1H), 8.66 (s, 1H), 8.11 – 7.88 (m, 4H), 1.29 (s, 9H).



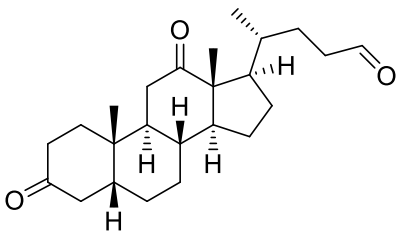
(E)-2,3-Diphenylacrylaldehyde:[46]

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 9.68 (s, 1H), 7.36 – 7.27 (m, 4H), 7.23 – 7.17 (m, 1H), 7.17 – 7.08 (m, 6H).



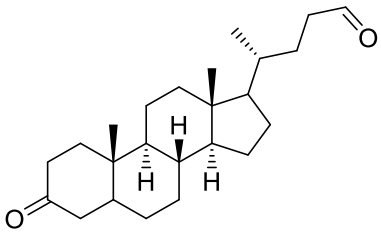
(S)-6-Oxo-3-(prop-1-en-2-yl)heptanal:[47]

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 9.67 (t, *J* = 2.3 Hz, 1H), 4.83 (t, *J* = 1.7 Hz, 1H), 4.78 (dt, *J* = 1.8, 0.9 Hz, 1H), 2.68 (dtd, *J* = 9.8, 7.3, 4.9 Hz, 1H), 2.54 – 2.36 (m, 4H), 2.13 (s, 3H), 1.82 – 1.55 (m, 5H).



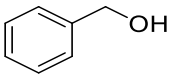
Corresponding aldehyde obtained from deoxycholic acid:[48]

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 9.76 (t, *J* = 1.8 Hz, 1H), 2.58 (q, *J* = 14.6, 13.3 Hz, 2H), 2.51 – 2.25 (m, 3H), 2.22 – 2.12 (m, 1H), 2.12 – 1.98 (m, 3H), 1.96 – 1.71 (m, 8H), 1.65 – 1.55 (m, 1H), 1.48 – 1.20 (m, 8H), 1.09 (s, 3H), 1.04 (s, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 214.04, 212.01, 202.92, 58.52, 57.54, 46.50, 44.25, 43.68, 42.11, 41.15, 38.35, 36.90, 36.78, 35.59, 35.55, 35.42, 27.55, 27.43, 26.58, 25.45, 24.30, 22.13, 18.68, 11.72; **HRMS for $C_{24}H_{36}NO_3Na$ [M + Na]$^+$:** m/z calcd 395.2557; found 395.2556



Corresponding aldehyde obtained from lithocholic acid:[48]

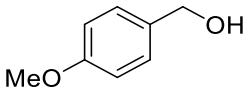
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 9.75 (s, 1H), 2.63 – 2.51 (m, 1H), 2.45 – 2.36 (m, 1H), 2.35 – 2.25 (m, 2H), 2.20 – 2.01 (m, 3H), 1.92 – 1.76 (m, 2H), 1.76 – 1.56 (m, 5H), 1.56 – 1.12 (m, 10H), 1.04 (s, 3H), 1.03 – 0.96 (m, 2H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.82 (s, 3H), 0.81 – 0.74 (m, 2H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 213.29, 203.08, 56.41, 55.99, 44.30, 42.79, 42.35, 40.91, 40.71, 40.03, 37.20, 37.00, 35.51, 35.30, 34.88, 28.21, 27.92, 26.61, 25.76, 24.15, 22.65, 21.18, 18.38, 12.08.; **HRMS for $C_{24}H_{38}NO_2Na$ [M + Na]$^+$:** m/z calcd 381.2764; found 381.2760.



Benzyl alcohol (34a):[49]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a colourless oil (27.6 mg, 85%).

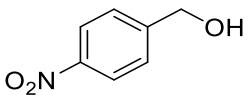
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.30 – 7.24 (m, 5H), 4.53 (d, *J* = 5.7 Hz, 2H), 2.92 (t, *J* = 5.8 Hz, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 140.87, 128.56, 127.65, 127.00, 65.31.



4-Methoxybenzyl alcohol (34b):[49]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a colourless oil (38.1 mg, 92%).

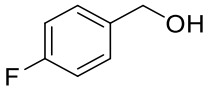
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.28 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.61 (s, 2H), 3.81 (s, 3H), 1.62 (s, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 159.21, 133.12, 128.65, 113.96, 65.04, 55.31.



4-Nitrobenzyl alcohol (34c):[50]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a yellow solid (30.8 mg, 67%).

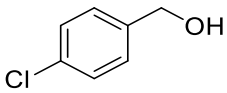
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.19 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 4.83 (s, 2H), 2.16 (s, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 147.18, 146.24, 125.97, 122.70, 62.97.



4-Fluorobenzyl alcohol (34d):[50]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a colourless oil (32.9 mg, 87%).

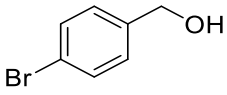
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.31 (m, 2H), 7.03 (m, 2H), 4.62 (s, 2H), 2.09 (s, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 162.29 (d, $J_{C\text{-}F}$ = 245.6 Hz), 136.57 (d, $J_{C\text{-}F}$ = 3.2 Hz), 128.75 (d, $J_{C\text{-}F}$ = 8.1 Hz), 115.36 (d, $J_{C\text{-}F}$ = 21.4 Hz), 64.56.



4-Chlorobenzyl alcohol (34e):[50]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a white solid (38.3 mg, 85%).

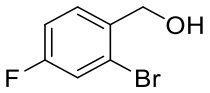
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.37 – 7.27 (m, 4H), 4.67 (d, *J* = 5.1 Hz, 2H), 1.73 (s, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 139.24, 133.36, 128.67, 128.27, 64.55.



4-Bromobenzyl alcohol (34f):[50]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a white solid (51.9 mg, 93%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.48 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 4.64 (s, 2H), 1.82 (s, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 139.75, 131.62, 128.58, 121.45, 64.56.

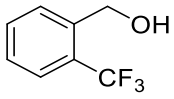


(2-Bromo-4-fluorophenyl)methanol (34g):[51]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a white solid (55.0 mg, 90%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.43 (dd, *J* = 8.5, 6.0 Hz, 1H), 7.28 (dd, *J* = 8.2, 2.6 Hz, 1H), 7.03 (td, *J* = 8.3, 2.6 Hz, 1H), 4.68 (d, *J* = 5.4 Hz, 2H), 2.37 (t, *J* = 5.9 Hz, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 161.76 (d, $J_{C\text{-}F}$ = 250.2

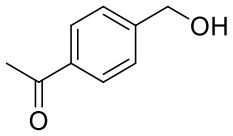
Hz), 135.66 (d, $J_{C\text{-}F}$ = 3.4 Hz), 129.86 (d, $J_{C\text{-}F}$ = 8.5 Hz), 122.46 (d, $J_{C\text{-}F}$ = 9.6 Hz), 119.86 (d, $J_{C\text{-}F}$ = 24.6 Hz), 114.63 (d, $J_{C\text{-}F}$ = 20.8 Hz), 64.29.



(2-(Trifluoromethyl)phenyl)methanol (34h):[52]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a white solid (42.8 mg, 81%).

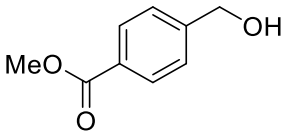
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.70 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 4.87 (s, 2H), 2.17 (s, 1H**); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 139.1, 132.1, 128.7, 128.4, 127.2 (q, $J_{C\text{-}F}$ = 31 Hz), 125.7 (q, $J_{C\text{-}F}$ = 31 Hz), 124.4 (q, $J_{C\text{-}F}$ = 272.2 Hz), 61.2 (q, $J_{C\text{-}F}$ =2.6 Hz).



4-Acetyl phenylmethanol (34i):[53]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a yellow solid (37.8 mg, 84%).

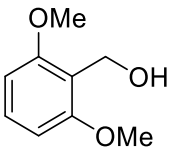
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.93 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 4.76 (s, 2H), 2.59 (s, 3H), 2.22 (brs, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 198.14, 146.41, 136.40, 128.74, 126.73, 64.69, 26.78.



Methyl 4-(hydroxymethyl)benzoate (34j):[53]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a yellow solid (44.3 mg, 89%).

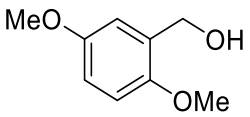
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.98 (d, *J* = 8.3 Hz, 2H), 7.45 – 7.32 (m, 2H), 4.72 (s, 2H), 3.89 (s, 3H), 2.45 (s, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 167.06, 146.10, 129.79, 129.18, 126.44, 64.57, 52.12.



(2,6-Dimethoxyphenyl)methanol (34k):[52]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a yellow solid (42.8 mg, 85%).

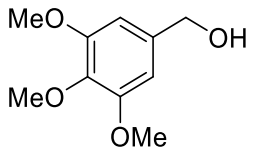
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.21 (t, *J* = 8.3 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 2H), 4.79 (s, 1H), 3.83 (s, 6H), 2.50 (s, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 158.41, 129.15, 117.04, 103.82, 55.75, 54.72.



(2,5-Dimethoxyphenyl)methanol (34l):[54]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a yellow solid (46.9 mg, 93%).

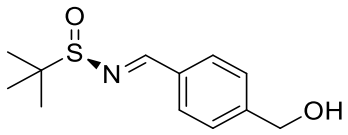
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.88 (d, *J* = 2.5 Hz, 1H), 6.84 – 6.73 (m, 2H), 4.65 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 2.44 (s, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 153.61, 151.50, 130.11, 114.78, 112.99, 111.14, 62.01, 56.25, 55.77.



(3,4,5-Trimethoxyphenyl)methanol (34m):[54]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a yellow solid (54.6 mg, 92%).

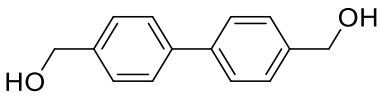
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.51 (s, 2H), 4.53 (s, 2H), 3.77 (s, 6H), 3.75 (s, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 153.28, 137.17, 136.75, 103.76, 65.36, 60.83, 56.05.



(R,E)-N-(4-(hydroxymethyl)benzylidene)-2-methylpropane-2-sulfinamide (34n):

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a white solid (56.7 mg, 84%).

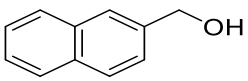
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.43 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), δ 4.74 (s, 2H), 2.79 (s, 1H), 1.24 (s, 9H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 162.40, 145.99, 133.16, 129.58, 127.09, 64.59, 57.84, 22.59.



4,4'-Biphenyldiyldimethanol (34o):[56]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a white solid (55.8 mg, 87%).

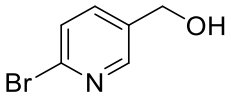
^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.61 (d, *J* = 8.2 Hz, 4H), 7.40 (d, *J* = 8.0 Hz, 4H), 5.22 (t, *J* = 5.7 Hz, 2H), 4.54 (d, *J* = 5.6 Hz, 4H); **^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm):** 142.05, 138.93, 127.48, 126.69, 63.09.



2-Naphthalenemethanol (34p):[52]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a white solid (46.9 mg, 99%).

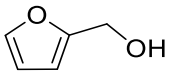
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.93 – 7.72 (m, 4H), 7.56 – 7.38 (m, 3H), 4.84 (d, *J* = 3.2 Hz, 2H), 2.04 (d, *J* = 4.9 Hz, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 138.32, 133.38, 132.95, 128.34, 127.90, 127.73, 126.20, 125.91, 125.44, 125.18, 65.45.



(6-Bromopyridin-2-yl)methanol (34q):[57]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a yellow solid (41.5 mg, 74%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.55 (t, *J* = 7.7 Hz, 1H), 7.39 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.28 (dd, *J* = 7.6, 0.9 Hz, 1H), 4.74 (s, 2H), 3.14 (brs, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 161.19, 141.40, 139.06, 126.67, 119.30, 64.20.

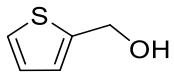


Furan-2-ylmethanol (34r):[52]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a yellow oil (25.0 mg, 85%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.40 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.35 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.30 (dd, *J* = 3.2, 0.7 Hz, 1H), 4.62 (d, *J* = 5.7 Hz, 2H), 1.70 (t,

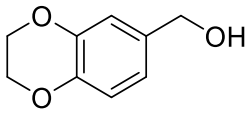
J = 6.0 Hz, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 153.97, 142.59, 110.36, 107.77, 57.48.



Thiophen-2-ylmethanol (34s):[52]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a yellow oil (24.9 mg, 73%).

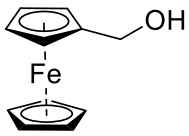
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.27 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.05 – 6.92 (m, 2H), 4.80 (s, 2H), 2.12 (s, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 143.98, 126.88, 125.60, 125.49, 59.96.



2,3-Dihydrobenzo[b][1,4]dioxin-6-methanol (34t):[58]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a white solid (46.3 mg, 93%).

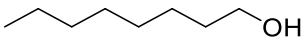
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.93 – 6.73 (m, 3H), 4.54 (s, 2H), 4.24 (s, 4H), 1.94 (s, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 143.48, 143.06, 134.36, 120.29, 117.30, 116.21, 64.91, 64.36, 64.22.



Ferrocenemethanol (34u):[59]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a yellow solid (64.1 mg, 99%).

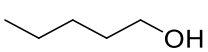
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.33 (s, 2H), 4.24 (t, *J* = 1.8 Hz, 2H), 4.18 (d, *J* = 2.1 Hz, 7H), 1.66 (s, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 88.38, 68.31, 68.29, 67.90, 60.77.



1-Octanol (34v):

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a colourless oil (32.0 mg, 82%).

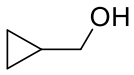
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.61 (t, *J* = 6.7 Hz, 2H), 1.71 (s, 1H), 1.61 – 1.46 (m, 2H), 1.39 – 1.15 (m, 10H), 0.96 – 0.76 (m, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 62.98, 32.77, 31.81, 29.39, 29.27, 25.74, 22.64, 14.06.



1-Pentanol (34w):

Following the general procedure, the reaction was conducted at 0.3 mmol scale, giving the titled compound in 76% GC yield as a colourless oil.

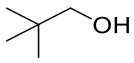
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.63 (d, *J* = 2.7 Hz, 2H), 1.77 (d, *J* = 4.3 Hz, 1H), 1.57 (ddt, *J* = 9.5, 7.6, 4.6 Hz, 2H), 1.34 (tdd, *J* = 7.2, 4.6, 3.1 Hz, 4H), 1.01 – 0.81 (m, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 62.95, 32.44, 27.90, 22.47, 14.01.



Cyclopropylmethanol (34x):[60]

Following the general procedure, the reaction was conducted at 0.3 mmol scale, giving the titled compound in 83% GC yield as a colourless oil.

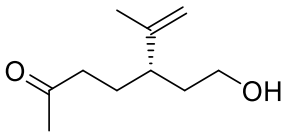
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.24 (d, *J* = 7.0 Hz, 2H), 0.90 (ddt, *J* = 10.3, 7.6, 3.8 Hz, 1H), 0.32 (dt, *J* = 7.9, 3.0 Hz, 2H), 0.01 (d, *J* = 5.0 Hz, 2H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 67.71, 13.54, 2.69.



2,2-Dimethylpropan-1-ol (34y):[61]

Following the general procedure, the reaction was conducted at 0.3 mmol scale, giving the titled compound in 80% GC yield as a colourless solid.

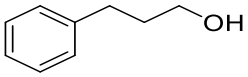
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.30 (s, 2H), 0.91 (d, J = 1.0 Hz, 9H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 73.52, 32.62, 26.00.



(S)-5-(2-Hydroxyethyl)-6-methylhept-6-en-2-one (34z):[55]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a colourless oil (42.3 mg, 83%).

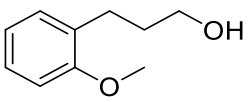
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.84 – 4.75 (m, 1H), 4.72 (d, *J* = 2.2 Hz, 1H), 3.59 (qt, *J* = 10.8, 6.5 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.24 – 2.14 (m, 1H), 2.11 (s, 3H), 1.75 – 1.61 (m, 3H), 1.60 – 1.59 (m, 3H), 1.58 – 1.50 (m, 1H), 1.24 (d, *J* = 1.6 Hz, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 209.09, 146.61, 112.84, 61.16, 43.56, 41.35, 36.10, 30.08, 26.59, 17.55.



3-Phenylpropan-1-ol (36a):[62]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a colourless oil (32.2 mg, 79%).

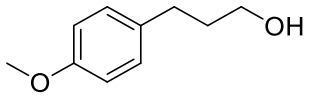
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.32 – 7.14 (m, 5H), 3.65 (t, *J* = 6.4 Hz, 2H), 2.70 (t, *J* = 7.6 Hz, 2H), 1.94 – 1.83 (m, 2H), 1.68 (s, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 141.85, 128.44, 128.41, 125.88, 62.24, 34.23, 32.10.



3-(2-Methoxyphenyl)propan-1-ol (36c):[63]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a colourless oil (48.3 mg, 97%).

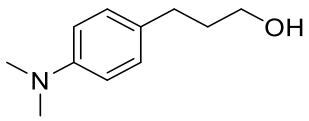
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.24 – 7.11 (m, 2H), 6.98 – 6.81 (m, 2H), 3.84 (s, 3H), 3.61 (t, *J* = 6.3 Hz, 2H), 2.73 (t, *J* = 7.3 Hz, 2H), 2.01 (s, 1H), 1.91 – 1.80 (m, 2H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 157.40, 130.12, 129.99, 127.19, 120.72, 110.33, 61.96, 55.36, 32.93, 25.95.



3-(4-Methoxyphenyl)propan-1-ol (36d):[64]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a colourless oil (47.3 mg, 95%).

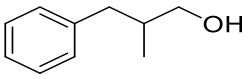
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.12 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 3.79 (s, 3H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 7.7 Hz, 2H), 1.92 – 1.81 (m, 2H), 1.43 (s, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 157.80, 133.86, 129.30, 113.83, 62.27, 55.27, 34.45, 31.15.



3-(4-(Dimethylamino)phenyl)propan-1-ol (36e):[65]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a yellow oil (51.6 mg, 96%).

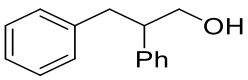
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.10 (d, *J* = 8.2 Hz, 2H), 6.73 (d, *J* = 8.2 Hz, 2H), 3.67 (t, *J* = 6.5 Hz, 2H), 2.93 (s, 6H), 2.63 (t, *J* = 7.7 Hz, 2H), 1.94 – 1.78 (m, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 149.13, 130.10, 129.02, 113.19, 62.39, 40.99, 34.54, 31.07.



2-Methyl-3-phenylpropan-1-ol (36f):[66]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a colourless oil (38.7 mg, 86%).

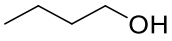
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.33 – 7.24 (m, 2H), 7.22 – 7.12 (m, 3H), 3.59 – 3.38 (m, 2H), 2.75 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.41 (dd, *J* = 13.4, 8.1 Hz, 1H), 2.03 – 1.84 (m, 1H), 1.65 (s, 1H), 0.91 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 140.74, 129.25, 128.36, 125.97, 67.72, 39.81, 37.89, 16.57.



2,3-Diphenylpropan-1-ol (36g):[67]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a colourless solid (61.1 mg, 96%).

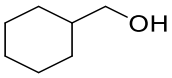
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.36 – 7.03 (m, 10H), 3.78 (ddd, *J* = 6.8, 5.5, 1.4 Hz, 2H), 3.15 – 2.97 (m, 2H), 2.90 (dd, *J* = 13.3, 7.3 Hz, 1H), 1.33 (t, *J* = 6.1 Hz, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 141.92, 139.92, 129.06, 128.65, 128.26, 128.10, 126.86, 126.04, 66.38, 50.20, 38.72.



1-Butanol (36h):

Following the general procedure, the reaction was conducted at 0.3 mmol scale, giving the titled compound in 72% GC yield as a colourless oil.

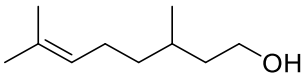
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.64 (t, *J* = 6.7 Hz, 2H), 1.84 (s, 1H), 1.62 – 1.47 (m, 2H), 1.47 – 1.30 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 62.60, 34.82, 18.87, 13.82.



Cyclohexylmethanol (36i):[68]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a colourless oil (29.4 mg, 86%).

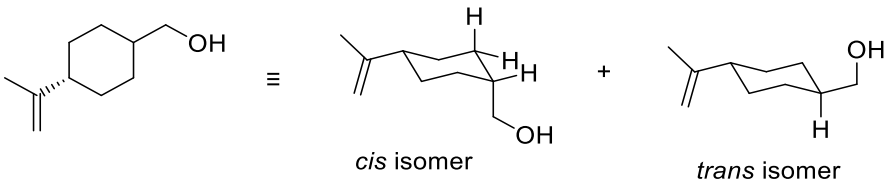
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.43 (d, *J* = 6.4 Hz, 2H), 1.87 – 1.58 (m, 5H), 1.54 – 1.38 (m, 2H), 1.32 – 1.06 (m, 3H), 1.02 – 0.82 (m, 2H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 68.76, 40.49, 29.56, 26.59, 25.84.



3,7-Dimethyloct-6-en-1-ol (36j):[69]

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a pale yellow oil (43.1 mg, 92%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 5.09 (t, *J* = 7.2 Hz, 1H), 3.66 (q, *J* = 7.6, 7.0 Hz, 2H), 1.98 (td, *J* = 17.1, 16.1, 7.5 Hz, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.63 – 1.53 (m, 3H), 1.43 – 1.28 (m, 2H), 1.23 – 1.10 (m, 1H), 0.89 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 131.23, 124.70, 61.13, 39.89, 37.21, 29.17, 25.70, 25.45, 19.51, 17.62.

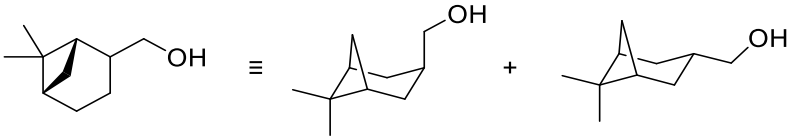


4-(1-Methylethenyl)-cyclohexanemethanol (36l):[70]

Following the general procedure, the reaction was conducted at 0.3 mmol scale, a mixture of diastereomers were isolated in 83% yield (38.3 mg) with the *cis* diastereomer as the major product (d.r. 15:1).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.67 (d, *J* = 1.4 Hz, 2H), 3.46 (d, *J* = 6.3 Hz, 2H), 1.83 (tdd, *J* = 10.8, 4.3, 2.2 Hz, 5H), 1.72 (d, *J* = 1.2 Hz, 3H), 1.47 (dt, *J* = 5.8, 2.8 Hz, 1H), 1.29 – 1.14 (m, 3H), 1.02 (td, *J* = 12.2, 3.2 Hz, 2H); **^{13}C NMR**

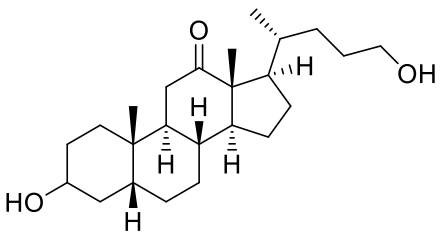
(CDCl$_3$, 100 MHz) δ (ppm): 150.74, 108.11, 68.69, 45.46, 40.33, 31.15, 29.54, 20.98.



((1S,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methanol (36m):[71]

Following the general procedure, the reaction was conducted at 0.3 mmol scale, giving the titled compound in 98% yield (45.3 mg) with d.r. 7:1.

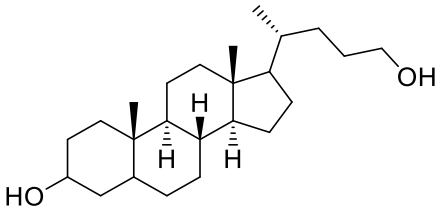
^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 3.47 – 3.33 (m, 2H), 2.22 – 2.10 (m, 1H), 2.04 (tdd, *J* = 5.8, 3.6, 1.2 Hz, 1H), 1.96 – 1.69 (m, 5H), 1.69 – 1.54 (m, 1H), 1.31 (d, *J* = 10.0 Hz, 1H), 1.22 (s, 3H), 0.85 (s, 3H); **^{13}C NMR (CDCl$_3$, 100 MHz) δ (ppm):** (major *trans* product) 66.74, 42.18, 40.99, 37.64, 26.65, 24.11, 23.42, 23.32, 20.15, 18.18. (minor *cis* product) 67.72, 44.41, 42.88, 41.47, 39.17, 38.62, 33.14, 27.96, 25.99, 18.78.



(5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-hydroxy-17-((*R*)-5-hydroxypentan-2-yl)-10,13 dimethylhexadecahydro-12H-cyclopenta[a]phenanthren-12-one (36n):

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a yellow solid (58.7 mg, 52%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.14 – 4.04 (m, 1H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.50 (t, *J* = 12.4 Hz, 1H), 2.09 – 1.97 (m, 2H), 1.97 – 1.60 (m, 8H), 1.56 – 1.11 (m, 17H), 1.04 (s, 3H), 1.02 (s, 3H), 0.85 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 215.28, 66.71, 63.52, 58.91, 57.59, 46.68, 43.62, 38.45, 36.08, 35.94, 35.54, 33.38, 31.41, 30.17, 29.86, 29.83, 27.69, 27.66, 26.58, 25.99, 24.38, 23.28, 18.98, 11.73; **HRMS for $C_{24}H_{40}O_3Na$ [M +Na^+]:** m/z calcd 399.2875; found 399.2870.



(8*R*,9*S*,10*S*,13*R*,14*S*)-17-((*R*)-5-hydroxypentan-2-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (36o):

The titled compound was synthesised according to general procedure at 0.3 mmol scale. The product was isolated as a yellow solid (52.2 mg, 48%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.03 (t, *J* = 3.0 Hz, 1H), 3.54 (td, *J* = 6.6, 3.1 Hz, 2H), 2.06 – 1.70 (m, 4H), 1.70 – 1.17 (m, 19H), 1.13 – 0.92 (m, 7H), 0.89 (s, 3H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.58 (s, 3H); **^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):** 67.17, 63.58, 56.65, 56.22, 42.75, 40.26, 39.75, 36.58, 35.65, 35.57, 35.13,

33.53, 31.85, 29.94, 29.39, 28.32, 27.84, 26.67, 26.29, 24.21, 23.92, 21.11, 18.66, 12.08; **HRMS for $C_{24}H_{42}O_2Na$ [M + Na^+]:** m/z calcd 385.3083; found 385.3077.

5.6 References

[1] R. A. W. Johnstone, A. H. Wilby, I. D. Entwistle, *Chem. Rev.* **1985**, *85*, 129–170.

[2] G. Brieger, T. J. Nestrick, *Chem. Rev.* **1974**, *74*, 567–580.

[3] G. Zassinovich, G. Mestroni, S. Giadiali, *Chem. Rev.* **1992**, *92*, 1051–1069.

[4] S. E. Clapham, A. Hadzovic, R. H. Morris, *Coord. Chem. Rev.* **2004**, *248*, 2201–2237.

[5] Y. Wei, X. Wu, C. Wang, J. Xiao, G. Zassinovich, G. Mestroni, S. Giadiali, R. A. W. Johnstone, A. H. Wilby, I. D. Entwistle, G. Brieger, T. J. Nestrick, *Chem. Rev.* **2007**, *92*, 567–580.

[6] Y. Wei, X. Wu, C. Wang, J. Xiao, *Catal. Today* **2015**, *247*, 104–116.

[7] D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621–6686.

[8] Y. Sasson, J. Blum, *Tetrahedron Lett.* **1971**, *12*, 2167–2170.

[9] P. Yang, H. Xu, J. S. Zhou, *Angew. Chem. Int. Ed.* **2014**, *53*, 12210–12213.

[10] J. Blum, Y. Sasson, S. Iflah, *Tetrahedron Lett.* **1972**, *13*, 1015–1018.

[11] Y. Na, S. Park, S. B. Han, H. Han, S. Ko, S. Chang, *J. Am. Chem. Soc.* **2004**, *126*, 250–258.

[12] A. M. Hayes, D. J. Morris, G. J. Clarkson, M. Wills, *J. Am. Chem. Soc.* **2005**, *127*, 7318–7319.

[13] D. J. Morris, A. M. Hayes, M. Wills, *J. Org. Chem.* **2006**, *71*, 7035–7044.

[14] F. K. Cheung, C. Lin, F. Minissi, A. L. Crivillé, M. A. Graham, D. J. Fox, M. Wills, *Org. Lett.* **2007**, *9*, 4659–4662.

[15] G. Wienhöfer, I. Sorribes, A. Boddien, F. Westerhaus, K. Junge, H. Junge, R. Llusar, M. Beller, *J. Am. Chem. Soc.* **2011**, *133*, 12875–12879.

[16] G. Wienhöfer, F. A. Westerhaus, R. V Jagadeesh, K. Junge, H. Junge, M. Beller, *Chem. Commun.* **2012**, *48*, 4827–4829.

[17] A. McSkimming, M. M. Bhadbhade, S. B. Colbran, *Angew. Chem. Int. Ed.* **2013**, *52*, 3411–3416.

[18] The Methanol Industry by Methanol Institute, http://www.methanol.org/the-methanol-industry/, accessed Sep 2021.

[19] A. Monney, E. Barsch, P. Sponholz, H. Junge, R. Ludwig, M. Beller, *Chem. Commun.* **2014**, *50*, 707–709.

[20] R. H. Crabtree, *Chem. Rev.* **2017**, *117*, 9228–9246.

[21] T. A. Smith, P. M. Maitlis, *J. Organomet. Chem.* **1985**, *289*, 385–395.

[22] J. Zhang, J. Chen, *ACS Sustain. Chem. Eng.* **2017**, *5*, 5982–5993.

[23] N. Castellanos-Blanco, M. Flores-Alamo, J. J. García, *Organometallics* **2012**, *31*, 680–686.

[24] J. Campos, L. S. Sharninghausen, M. G. Manas, R. H. Crabtree, *Inorg. Chem.* **2015**, *54*, 5079–5084.

[25] R. Wang, X. Han, J. Xu, P. Liu, F. Li, *J. Org. Chem.* **2020**, *85*, 2242–2249.

[26] Y. Zhao, F. Pan, H. Li, G. Q. Xu, W. Chen, *ChemCatChem* **2014**, *6*, 454–458.

[27] Y. Shen, Y. Zhan, S. Li, F. Ning, Y. Du, Y. Huang, T. He, X. Zhou, *Chem. Sci.* **2017**, *8*, 7498–7504.

[28] D. Talwar, N. P. Salguero, C. M. Robertson, J. Xiao, *Chem. Eur. J.* **2014**, *20*, 245–252.

[29] H.-Y. T. Chen, C. Wang, X. Wu, X. Jiang, C. R. A. Catlow, J. Xiao, *Chem. Eur. J.* **2015**, *21*, 16564–16577.

[30] C. Wang, J. Xiao, *Chem. Commun.* **2017**, *53*, 3399–3411.

[31] A. H. Aboo, E. L. Bennett, M. Deeprose, C. M. Robertson, J. A. Iggo, J. Xiao, *Chem. Commun.* **2018**, *54*, 11805–11808.

[32] A. H. Aboo, R. Begum, L. Zhao, Z. H. Farooqi, J. Xiao, *Chinese J. Catal.*

2019, *40*, 1795–1799.

[33] R. Kawahara, K. Fujita, R. Yamaguchi, *J. Am. Chem. Soc.* **2012**, *134*, 3643–3646.

[34] R. Kawahara, K. Fujita, R. Yamaguchi, *Angew. Chem. Int. Ed.* **2012**, *51*, 12790–12794.

[35] K. Fujita, R. Kawahara, T. Aikawa, R. Yamaguchi, *Angew. Chem. Int. Ed.* **2015**, *54*, 9057–9060.

[36] F. Jiang, M. Achard, T. Roisnel, V. Dorcet, C. Bruneau, *Eur. J. Inorg. Chem.* **2015**, *2015*, 4312–4317.

[37] R. Wang, H. Fan, W. Zhao, F. Li, *Org. Lett.* **2016**, *18*, 3558–3561.

[38] Z. Xu, P. Yan, H. Li, K. Liu, X. Liu, S. Jia, Z. C. Zhang, *ACS Catal.* **2016**, *6*, 3784–3788.

[39] S.-M. Lu, Z. Wang, J. Li, J. Xiao, C. Li, *Green Chem.* **2016**, *18*, 4553–4558.

[40] K. Sordakis, C. Tang, L. K. Vogt, H. Junge, P. J. Dyson, M. Beller, G. Laurenczy, *Chem. Rev.* **2018**, *118*, 372–433.

[41] M. J. Chen, L. M. Utschig, J. W. Rathke, *Inorg. Chem.* **1998**, *37*, 5786–5792.

[42] P. Hu, Y. Diskin-Posner, Y. Ben-David, D. Milstein, *ACS Catal.* **2014**, *4*,

2649–2652.

[43] N. Govindarajan, V. Sinha, M. Trincado, H. Grützmacher, E. J. Meijer, B. de Bruin, *ChemCatChem* **2020**, *12*, 2610–2621.

[44] C. Wang, A. Pettman, J. Bacsa, J. Xiao, *Angew. Chem. Int. Ed.* **2010**, *49*, 7548–7552.

[45] Z.-Y. Jiang, W. H. Chan, A. W. M. Lee, *J. Org. Chem.* **2005**, *70*, 1081–1083.

[46] T. Knaus, F. G. Mutti, L. D. Humphreys, N. J. Turner, N. S. Scrutton, *Org. Biomol. Chem.* **2015**, *13*, 223–233.

[47] T. D. Haddad, L. C. Hirayama, J. J. Buckley, B. Singaram, *J. Org. Chem.* **2012**, *77*, 889–898.

[48] V. C. Edelsztein, P. H. Di Chenna, G. Burton, *Tetrahedron* **2009**, *65*, 3615–3623.

[49] Y.-N. Duan, X. Du, Z. Cui, Y. Zeng, Y. Liu, T. Yang, J. Wen, X. Zhang, *J. Am. Chem. Soc.* **2019**, *141*, 20424–20433.

[50] S. R. Roy, S. C. Sau, S. K. Mandal, *J. Org. Chem.* **2014**, *79*, 9150–9160.

[51] B. Xue, H. Sun, X. Li, *RSC Adv.* **2015**, *5*, 52000–52006.

[52] H. Li, T. P. Gonçalves, J. Hu, Q. Zhao, D. Gong, Z. Lai, Z. Wang, J. Zheng, K.-W. Huang, *J. Org. Chem.* **2018**, *83*, 14969–14977.

[53] T. Osako, K. Torii, S. Hirata, Y. Uozumi, *ACS Catal.* **2017**, *7*, 7371–7377.

[54] Z. Yang, Z. Zhu, R. Luo, X. Qiu, J. Liu, J.-K. Yang, W. Tang, *Green Chem.* **2017**, *19*, 3296–3301.

[55] G. Sui, Q. Lv, X. Song, H. Guo, J. Dai, L. Ren, C.-S. Lee, W. Zhou, H.-D. Hao, *New J. Chem.* **2019**, *43*, 15793–15796.

[56] A. Feiz, A. Bazgir, A. M. Balu, R. Luque, *Sci. Rep.* **2016**, *6*, 32719.

[57] S. Ulrich, E. Buhler, J.-M. Lehn, *New J. Chem.* **2009**, *33*, 271–292.

[58] J. J. Marugan, W. Zheng, O. Motabar, N. Southall, E. Goldin, W. Westbroek, B. K. Stubblefield, E. Sidransky, R. A. Aungst, W. A. Lea, A. Simeonov, W. Leister, C. P. Austin, *J. Med. Chem.* **2011**, *54*, 1033–1058.

[59] J. M. Casas-Solvas, A. Vargas-Berenguel, L. F. Capitán-Vallvey, F. Santoyo-González, *Org. Lett.* **2004**, *6*, 3687–3690.

[60] G. Tavakoli, M. H. G. Prechtl, *Catal. Sci. Technol.* **2019**, *9*, 6092–6101.

[61] T. V Chciuk, W. R. Anderson, R. A. Flowers, *J. Am. Chem. Soc.* **2018**, *140*, 15342–15352.

[62] L. Shi, Y. Liu, Q. Liu, B. Wei, G. Zhang, *Green Chem.* **2012**, *14*, 1372–1375.

[63] X. Chen, Y. Zhang, H. Wan, W. Wang, S. Zhang, *Chem. Commun.* **2016**, *52*, 3532–3535.

[64] T. Wendling, E. Risto, T. Krause, L. J. Gooßen, *Chem. Eur. J.* **2018**, *24*, 6019–6024.

[65] H. Takakura, R. Kojima, M. Kamiya, E. Kobayashi, T. Komatsu, T. Ueno, T. Terai, K. Hanaoka, T. Nagano, Y. Urano, *J. Am. Chem. Soc.* **2015**, *137*, 4010–4013.

[66] B. Zhang, H. Li, Y. Ding, Y. Yan, J. An, *J. Org. Chem.* **2018**, *83*, 6006–6014.

[67] D. Lichosyt, Y. Zhang, K. Hurej, P. Dydio, *Nat. Catal.* **2019**, *2*, 114–122.

[68] A. Cocq, B. Léger, S. Noël, H. Bricout, F. Djedaïni-Pilard, S. Tilloy, E. Monflier, *ChemCatChem* **2020**, *12*, 1013–1018.

[69] A. M. López-Vinasco, L. M. Martínez-Prieto, J. M. Asensio, P. Lecante, B. Chaudret, J. Cámpora, P. W. N. M. van Leeuwen, *Catal. Sci. Technol.* **2020**, *10*, 342–350.

[70] G. Fronza, C. Fuganti, M. Pinciroli, S. Serra, *Tetrahedron: Asymmetry* **2004**, *15*, 3073–3077.

[71] M. J. P. Ferreira, V. P. Emerenciano, G. A. R. Linia, P. Romoff, P. A. T. Macari, G. V Rodrigues, *Prog. Nucl. Magn. Reson. Spectrosc.* **1998**, *33*, 153–206.

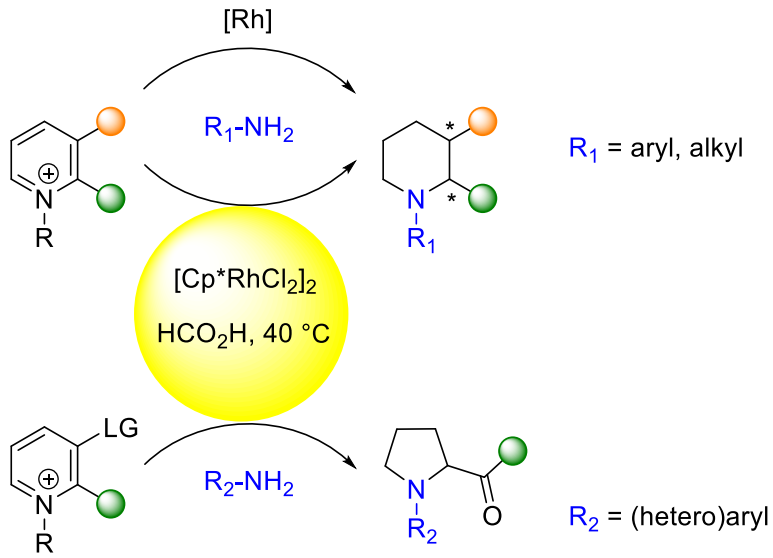
Chapter 6: Conclusions and Perspectives

This thesis describes the investigations on rhodium-catalysed transfer hydrogenation and transamination. In Chapter 1, we summarised the current status on the reduction of *N*-heteroaromatics and carbonyls. Although these types of reactions have been extensively studied by many research groups, a number of limitations and challenges still remain, such as the limited examples in the reduction of *N*-heterocycles *via* TH, especially with high enantioselectivity, and the reduction with the use of inexpensive and safe hydrogen sources that could perform under milder reaction conditions.

A novel and efficient reaction protocol, ART, was developed for the preparation of a wide range of chiral piperidines from pyridinium salts with excellent diastero- and enantioselectivities. Key to this reaction is the introduction of a chiral amine which undergoes transamination with the original nitrogen moiety under reducing conditions, while induing the chirality on the ring. By introducing fluorine into the pyridine substrate, we have overcome the challenges of accessing chiral fluorinated piperidines, compounds of importance in pharmaceuticals.

By employing (hetero)aryl amines in the modified ART reaction system, we have extended its application to the synthesis of *N*-aryl piperidines, bypassing the limitations of traditional C-N cross-coupling reactions (Scheme 6.1). Surprisingly, the introduction of a leaving group into the pyridine substrate led to the formation of pyrrolidines, allowing for a switchable synthesis of two classes of high-value *N*-heterocyclic compounds from one parent substrate. Currently, AH of

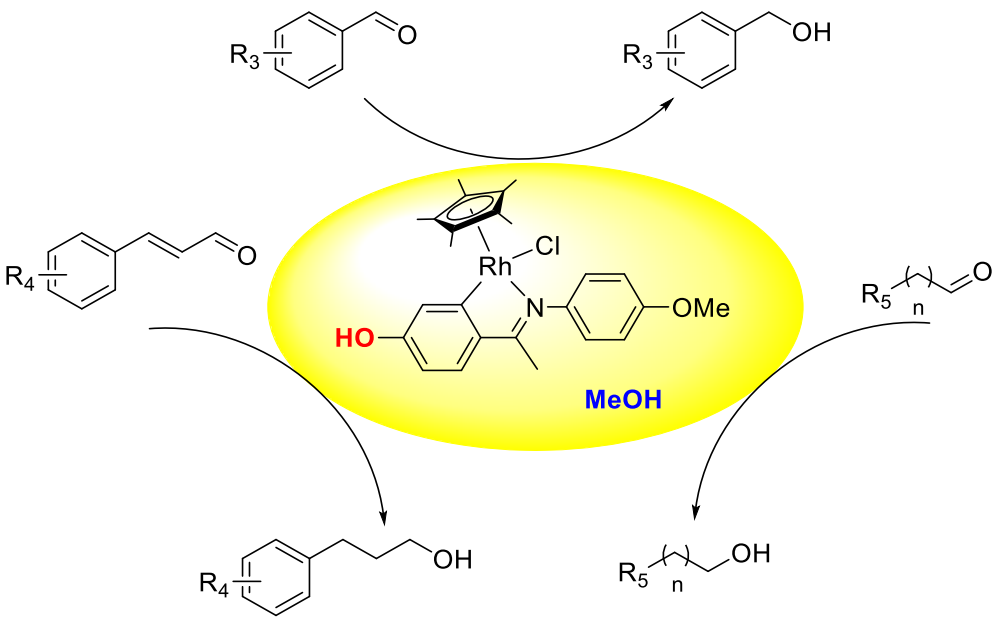
pyridines is the most efficient pathway to access chiral piperidines, whilst methodologies like ATH is still underexploited. Our preliminary studies have shown that the desired chiral piperidine products can be obtained by using chiral catalysts *via* reductive transamination. Although the yields and enantioselectivities are relatively low compared with commonly used AH protocols, it is a method of great promise considering the ease availability and diversity of various chiral ligands in AH and ATH reactions.



Scheme 6.1: Summary of rhodium catalysed transamination in this thesis with the ART with achiral amines yet to be fully established (LG = leaving group)

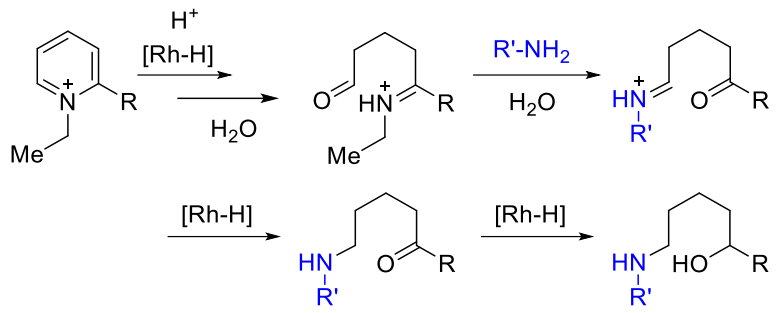
A cyclometalated rhodium complex has been found to be highly efficient on the TH of carbonyl compounds at room temperature using methanol as hydrogen source. Few molecular catalysts are capable of dehydrogenating methanol under

such mild conditions. Further studies showed the importance of the hydroxy functionality in the imino ligand.



Scheme 6.2: Summary of rhodium catalysed TH of aldehydes using methanol in this thesis

Given the fact that the rhodium catalyst shows high reactivity in the reductive transamination of pyridines, future work may aim at developing more efficient chiral rhodium catalysts to fulfil the current industrial technical need for chiral piperidine *via* ATH of pyridine derivatives. By understanding the mechanism of the reductive transamination process, we may also obtain amino ketone or alcohol products before the ring-closing step (Scheme 6.3).



Scheme 6.3: Envisioned ring-opening amine product *via* reductive transamination

Cyclometalated rhodium complexes have shown great potential towards the TH of imines and *N*-heteroaromatics (Chapter 2, 3 and 4).[1,2] In the field of hydrogen borrowing reactions, the advantage of this complex in methanol dehydrogenation may allow it to be used for methylation reactions. Preliminary studies in our group have shown complex **25** to be active for the monomethylation of aniline compounds.

In the field of catalytic hydrogenation, catalysts based on non-noble metals, such as manganese[3–5], iron[6,7], cobalt[8–10], nickle[11,12], etc, have continued to be investigated over the last decade.[13] The search for more efficient metal catalysts could be a future direction of more environmentally friendly transfer hydrogenation and transamination processes.

References

[1] C. Wang, B. Villa-Marcos, J. Xiao, *Chem. Commun.* **2011**, *47*, 9773–9785.

[2] Y.-F. Han, G.-X. Jin, *Chem. Soc. Rev.* **2014**, *43*, 2799–2823.

[3] V. Papa, Y. Cao, A. Spannenberg, K. Junge, M. Beller, *Nat. Catal.* **2020**, *3*, 135–142.

[4] K. Azouzi, D. A. Valyaev, S. Bastin, J.-B. Sortais, *Curr. Opin. Green Sustain. Chem.* **2021**, *31*, 100511.

[5] W. Yang, I. Y. Chernyshov, R. K. A. van Schendel, M. Weber, C. Müller, G. A. Filonenko, E. A. Pidko, *Nat. Commun.* **2021**, *12*, 12.

[6] S. Enthaler, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2008**, *47*, 3317–3321.

[7] W. Zuo, R. H. Morris, *Nat. Protoc.* **2015**, *10*, 241–257.

[8] M. R. Friedfeld, M. Shevlin, J. M. Hoyt, S. W. Krska, M. T. Tudge, P. J. Chirik, *Science* **2013**, *342*, 1076–1080.

[9] T. Dombray, C. Helleu, C. Darcel, J.-B. Sortais, *Adv. Synth. Catal.* **2013**, *355*, 3358–3362.

[10] R. V Jagadeesh, D. Banerjee, P. B. Arockiam, H. Junge, K. Junge, M.-M. Pohl, J. Radnik, A. Brückner, M. Beller, *Green Chem.* **2015**, *17*, 898–902.

[11] D. Tavor, I. Gefen, C. Dlugy, A. Wolfson, *Synth. Commun.* **2011**, *41*,

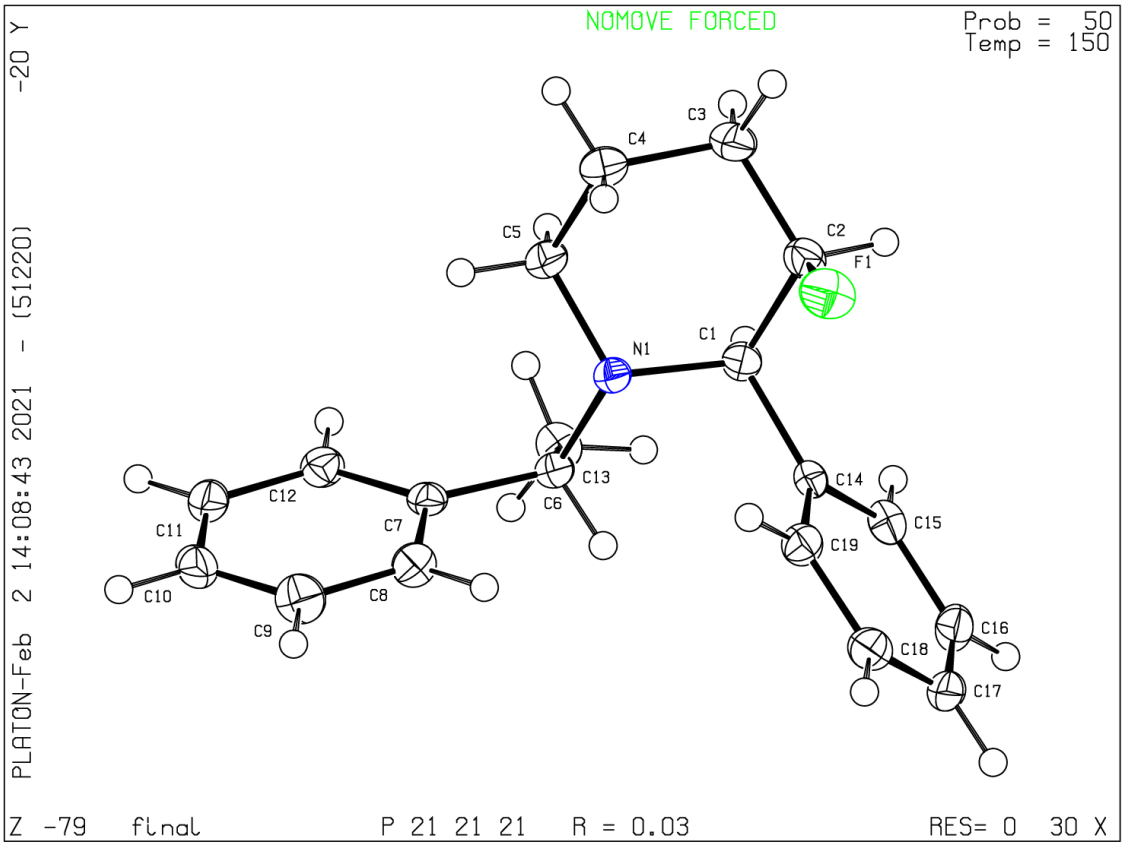
3409–3416.

[12] H. Xu, P. Yang, P. Chuanprasit, H. Hirao, J. (Steve) Zhou, *Angew. Chem. Int. Ed.* **2015**, *54*, 5112–5116.

[13] D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621–6686.

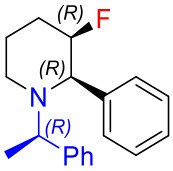
APPENDIX

X-ray crystallographic data



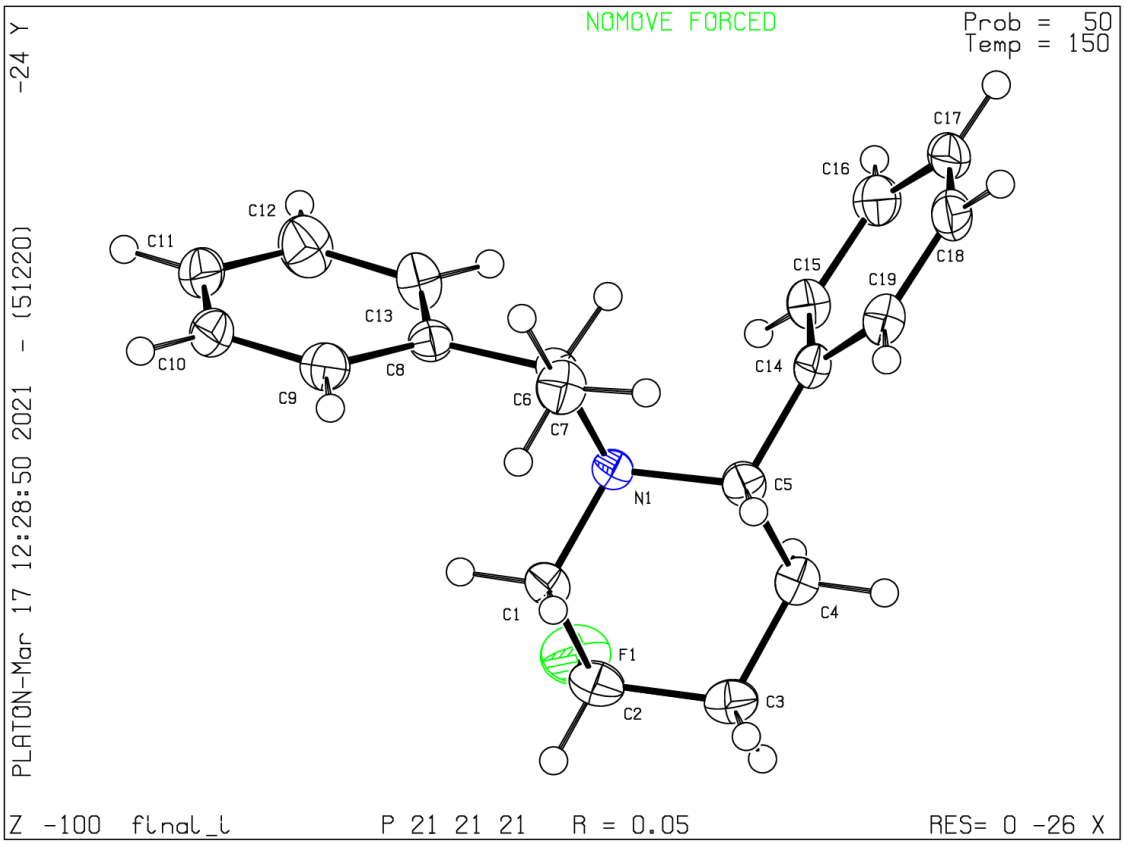
Crystal structure of compound **17a** from **Table 2.1**

CCDC number: 2073098



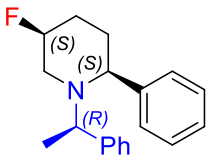
17a

Bond precision: C-C = 0.0023 Å			Wavelength=1.54178
Cell:	a=7.9010(3)	b=10.2650(4)	c=18.8453(7)
	alpha=90	beta=90	gamma=90
Temperature:	150 K		
	Calculated		Reported
Volume	1528.43(10)		1528.42(10)
Space group	P 2_1 2_1 2_1		P 2_1 2_1 2_1
Hall group	P 2ac 2ab		P 2ac 2ab
Moiety formula	C_{19} H_{22} F N		C_{19} H_{22} F N
Sum formula	C_{19} H_{22} F N		C_{19} H_{22} F N
Mr	283.38		283.37
Dx,g cm^{-3}	1.232		1.231
Z	4		4
Mu (mm^{-1})	0.626		0.626
F000	608.0		608.0
F000’	609.70		
h,k,lmax	9, 12, 22		9, 12, 22
Nref	2730[1592]		2655
Tmin,Tmax	0.882, 0.975		0.691, 0.753
Tmin’	0.882		
Correction method= EMPIRICAL			
Data completeness= 1.67/0.97			Theta(max)= 66.908
R(reflections)= 0.0286(2616)			wR2(reflections)= 0.0758(2655)
S = 1.085			Npar= 191



Crystal structure of compound **17x** from **Table 2.1**.

CCDC number: 2073099



17x

Bond precision: C-C = 0.0046 Å			Wavelength=1.54178
Cell:	a=7.8287(2)	b=10.3685(3)	c=19.0249(5)
	alpha=90	beta=90	gamma=90
Temperature:	150 K		
	Calculated		Reported
Volume	1544.293(7)		1544.29(7)
Space group	P 2_1 2_1 2_1		P 2_1 2_1 2_1
Hall group	P 2ac 2ab		P 2ac 2ab
Moiety formula	C_{19} H_{22} F N		C_{19} H_{22} F N
Sum formula	C_{19} H_{22} F N		C_{19} H_{22} F N
Mr	283.38		283.37
Dx,g cm^{-3}	1.219		1.219
Z	4		4
Mu (mm^{-1})	0.620		0.620
F000	608.0		608.0
F000’	609.70		
h,k,lmax	9, 12, 22		9, 12, 22
Nref	2755[1606]		2727
Tmin,Tmax	0.949, 0.989		0.658, 0.753
Tmin’	0.872		
Correction method= EMPIRICAL			
Data completeness= 1.70/0.99			Theta(max)= 66.710
R(reflections)= 0.0488(2518)			wR2(reflections)= 0.1014(2727)
S = 1.113			Npar= 192