UNIVERSITY OF LIVERPOOL

HYDROGENATION AND DEHYDROGENATION WITH CYCLOMETALATED IRIDIUM (III) COMPLEXES

Thesis submitted in accordance with the requirements of
the University of Liverpool for the degree of Doctor in
Philosophy

by

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In memory of my dear mother and father

You will be missed forever & always

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Abstract

The selective hydrogenation and dehydrogenation of organic molecules is a fundamentally challenging and an attractive transformation for both, industry and academia. However, catalysts capable of undergoing both transformations under environmentally benign conditions are rare. In this thesis, our contribution to the development of a "universal" catalyst capable of achieving both hydrogenation and dehydrogenation of a wide range of organic compounds under mild conditions is presented.

A general introduction covering the recent developments in the area of transfer hydrogenation of C=X (X = O, N) bonds, relevant applications of cyclometalated half-sandwich complexes and previous work in the area developed within our group is described in Chapter 1. In Chapter 2, Cyclometalated iridium complexes are shown to be highly efficient and chemoselective catalysts for the transfer hydrogenation of a wide range of carbonyl groups with formic acid in water. Examples include α-substituted ketones (α-ether, α-halo, α-hydroxy, α-amino, α-nitrile, α-ester), α-keto esters, β-keto esters, and α,β-unsaturated aldehydes. The reduction was carried out at substrate/catalyst ratios of up to 50000 at pH 4.5, requiring no organic solvent. The protocol provides a practical, easy and efficient way for the synthesis of β-functionalised secondary alcohols, such as β-hydroxyethers, β-hydroxyamines and β-hydroxyhalo compounds, which are valuable intermediates in pharmaceutical, fine chemical, perfume and agrochemical synthesis.

In Chapter 3, the cyclometalated iridium complexes are shown to catalyse the transfer hydrogenation of various nitrogen heterocycles, including but not limited to quinolines, isoquinolines, indoles and pyridiniums, in aqueous solution under mild

conditions. The catalyst shows excellent functional group compatibility and high turnover number (up to 7500), with loading as low as 0.01% being feasible.

In Chapter 4, cyclometalated iridium complexes are found to be versatile catalysts for the direct reductive amination of carbonyls to give primary amines under transfer hydrogenation conditions with ammonium formate as both the nitrogen and hydrogen source. The activity and chemoselectivity of the catalyst towards primary amines is excellent, with a substrate to catalyst ratio of 1000 being feasible. Both aromatic and aliphatic primary amines were obtained in high yields. Moreover, a first example of a homogeneously catalysed transfer hydrogenative direct reductive amination (DRA) has been achieved for β-keto ethers, leading to the corresponding β-amino ethers. In addition, non-natural α-amino acids could also be obtained in excellent yields with this method.

Following the success of hydrogenation, cyclometalated iridium complexes were also found to be versatile catalysts for the oxidant-free, acceptorless dehydrogenation of various N-heterocycles, including tetrahydroquinolines, tetrahydroisoquinolines, tetrahydroquinoxalines and indolines. This protocol was also successfully applied to the total synthesis of alkaloids as presented in Chapter 5.

Chapter 6 describes the development of a new strategy for the oxidant- and base-free dehydrogenative coupling of N-heterocycles at mild conditions. Under the action of an iridium cyclometalated catalyst, N-heterocycles undergo multiple sp^3 C-H activation, generating a nucleophilic enamine that reacts in situ with various electrophiles to give highly functionalised products. The dehydrogenative coupling can be cascaded with Friedel-Crafts addition, resulting in double functionalisation of the N-heterocycles. The dehydrogenation products could also be saturated under

either hydrogenation or transfer hydrogenation conditions, giving rise to structurally diverse products.

Final conclusion and perspectives of the research covered in this PhD thesis are presented in Chapter 7.

Publications and Patents

- **Versatile Iridicycle Catalysts for Highly Efficient and Chemoselective Transfer Hydrogenation of Carbonyl Compounds in Water**

  D. Talwar, X. Wu, O. Saidi, N. P. Salguero, J. L. Xiao, *Chem. Eur. J.* **2014**, 20, 12835-12842.

- **Primary Amines by Transfer Hydrogenative Reductive Amination of Ketones by Using Cyclometalated Ir[III] Catalysts**

  D. Talwar, N. P. Salguero, C. M. Robertson, J. L. Xiao, *Chem. Eur. J.* **2014**, 20, 245-252.

- **Fast Reductive Amination by Transfer Hydrogenation "on Water"**

  Q. Li, Y. Wei, D. Talwar, C. Wang, D. Xue, J. L. Xiao, *Chem. Eur. J.* **2013**, 19, 4021-4029.

- **Robust Cyclometalated Ir(III) Catalysts for the Homogeneous Hydrogenation of *N*-Heterocycles Under Mild Conditions**

  J. Wu, J. H. Barnard, Y. Zhang, D. Talwar, C. M. Robertson, J. L. Xiao, *Chem. Commun.* **2013**, 49, 7052-7054.

- **Acceptorless Dehydrogenation of Nitrogen Heterocycles with a Versatile Iridium Catalyst**

  J. Wu[†], D. Talwar[†], S. Johnston, M. Yan, J. L. Xiao, *Angew. Chem. Int. Ed.*, **2013**, 52, 6983-6987.

  † Joint first author

- **Regioselective Acceptorless Dehydrogenative Coupling of *N*-Heterocycles Towards Functionalized Quinolines, Phenanthrolines and Indoles**

  D. Talwar, A. Gonzalez-de-Castro, H. Y. Li, J. L. Xiao, *J. Am. Chem. Soc.* Manuscript submitted.

- **A Simple and Environmentally Friendly Approach for the Transfer Hydrogenation of *N*-Heterocycles in Water**

  D. Talwar, H. Y. Li, E. Durham, J. L. Xiao, manuscript in preparation.

- D. Talwar, W. Tang, C. Wang, B. V. Marcos, J. L. Xiao, GB 1206572.8; *WO2013/153407A1*, **2013**.

- B. V. Marcos, W. Tang, D. Talwar, C. Wang, J. Wu, J. L. Xiao, GB 1206573.6; *WO2013/153408A1*, **2013**.

  Catalysts (Iridicycles) are now commercially available from Strem Chemicals Inc. – Catalogue no. 77-0424, 77-0418, 77-0430 and 77-0428.

Abbreviations

α	alpha
β	beta
δ	chemical shift
Å	amstrong
ADC	acceptorless dehydrogenative coupling
aq	aqueous
Ar	aryl
ATH	asymmetric transfer hydrogenation
atm	atmosphere
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
bs	broad singlet
°C	Celsius degree
^{13}C	carbon 13
CDH	catalytic dehydrogenation
CI	chemical ionisation
cm	centimetre(s)
COD	1,5-cyclooctadiene
conv.	conversion
Cp*	pentamethylcyclopentadiene
Cy	cyclohexyl
d	doublet

dd	doublet of doublets
DCM	dichloromethane
DFE	2,2-difluoroethanol
DKR	dynamic kinetic resolution
DPEN	1,2-diphenylethylenediamine
DPPB	1,4-bis(diphenylphosphino)butane
DRA	direct reductive amination
dt	doublet of triplets
ee	enantiomeric excess
EI	electron ionisation
eq	equation
equiv.	equivalent(s)
ESI	electrospray ionisation
FAB	fast atom bombardment
F/T	formic acid/triethylamine azeotrope
g	gram(s)
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
h	hour(s)
^{1}H	proton
H_2	molecular hydrogen
HEH	Hantzsch 1,4-dihydropyridine
HRMS	high resolution mass spectroscopy

Hz	hertz
i.e.	*id est* (that is to say)
IR	infrared
J	coupling constant value
m	meta
m	multiplet
MeCN	acetonitrile
mg	milligram(s)
min	minute(s)
mL	millilitre
mmol	milimole(s)
MS	mass spectrometry
NAD^+	nicotinamide adenine dinucleotide
NADH	nicotinamide adenine dinucleotide hydride
NADPH	nicotinamide adenine dinucleotide phosphate hydride
NEt_3	triethylamine
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
o	ortho
p	para
PhMe	toluene
ppm	parts per million
q	quartet

RA	reductive amination
rt	room temperature
s	singlet
S/C	substrate to catalyst ratio
t	triplet
TFE	2,2,2-tifluoroethanol
TH	transfer hydrogenation
THF	tetrahydrofuran
TMS	tetramethylsilane
TOF	turnover frequency
TON	turnover number
TsDPEN	*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine
vide infra	see below
vide supra	see above
vs	versus

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Chapter 6: Regioselective Acceptorless Dehydrogenative Coupling of *N*-Heterocycles

Chapter 7: Conclusion and perspectives

Chapter 1

Introduction

1.1 Introduction

The reduction of C=X (X = O, N) bonds is one of the most important transformations in both academia and industry.[1] The resulting products, alcohols and amines, are both important intermediates in fine chemicals, agrochemicals, pharmaceuticals and advanced material synthesis.[2] In fact, these functional groups are present in numerous bioactive molecules and natural products (Scheme 1.1).[3,4]
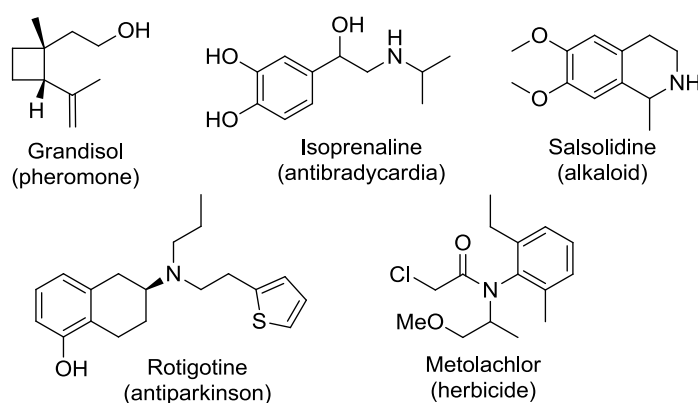
Scheme 1.1: Representative examples of bioactive molecules containing alcohol and amine moiety.

Such reactions are typically performed with a stoichiometric reducing agent such as metal hydrides based on boron or aluminium. Since their discovery both LiAlH$_4$ and NaBH$_4$ have been the choice of reducing agents for the carbonyl reduction.[5] They have been routinely implemented in the pharmaceutical industry with numerous applications due to their robustness and reliability.[6] NaBH$_4$ is cheaper and tolerates more functional groups (i.e. esters, amides, nitriles) than LiAlH$_4$; thus it is the preferred reagent on large scale synthesis.[7] However, for the reductive amination (RA), NaBH(OAc)$_3$ is preferred as it is more selective than NaBH$_4$.[8,9] NaBH(OAc)$_3$, at pH 5-6, reduces imines but not ketones whereas NaBH$_4$ reduces both imines and ketones. Although these metal hydrides are robust, the stoichiometric inorganic waste that is generated after the work up is an environmental concern, especially in industrial or scale up processes. Work up also

includes an aqueous quench, sometimes acidic to destroy the residual borohydride. This process is exothermic and evolves hydrogen gas that raises safety issues.[10] Thus other reduction systems have been developed as greener alternatives, which are catalytic and encourage waste minimisation.[11] These include biocatalytic[12] and organocatalytic[13] systems, but heterogeneous and homogeneous catalysts based on transition metals are the most promising and widely studied systems.[14,15] Heterogeneous catalysts are widely applied to the reduction of carbonyl and imino bonds; however these catalysts are beyond the scope of this chapter and have been highlighted in excellent reviews.[15,16] Homogeneous catalysts, depending on the hydride source used, can be divided into two categories:

- Metal catalysed hydrogenation where H_2 gas is used as the hydrogen source.

- Metal catalysed transfer hydrogenation where hydride source other than H_2 is used (typically HCO_2H or ^{i}PrOH).

The latter is more desirable as it circumvents the use of potentially explosive H_2 and the handling of high pressure reactors.[17] Moreover, hydrogen sources such as formates and ^{i}PrOH are cheap, air stable, easy to handle and do not require any specialised equipments to conduct reactions.[18] Thus this chapter will focus on advances in homogeneous transition metal catalysed transfer hydrogenation (TH) of C=X (X = O, N) bonds.

1.2 TH of ketones in organic media

The first TH of carbonyls to alcohols was reported in 1925, known as Meerwein-Ponndorf-Verley (MPV) reduction.[19] The reaction proceeds via a six-membered transition state, where a hydride from an α carbon of the alcohol is transferred to the

carbonyl (Scheme 1.2).[20] The reaction is catalysed by $Al(O^iPr)_3$ and the reverse of such reaction is known as Oppenauer oxidation (OPP).[19,20]
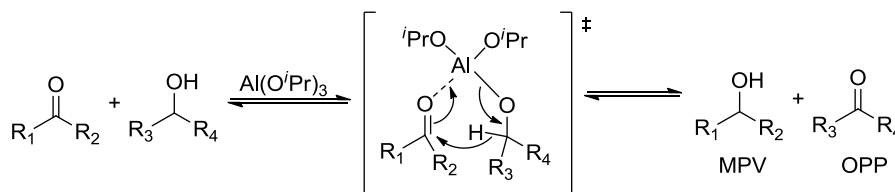

Scheme 1.2: Meerwein-Ponndorf-Verley (MPV) reduction.

Since then, much attention was devoted to the development of heterogeneous catalysis based on various transition metals. However the homogeneous catalysts for TH of ketones did not gain much attention until the early 1980's, when ruthenium complexes were shown to catalyse the dehydrogenation of alcohols.[2] It was also reported that the addition of a base such as NaOH significantly improved the dehydrogenation of alcohols. Thus, Bäckvall and co-workers reported that $[RuCl_2(PPh_3)_3]$ could catalyse the TH of ketones in ^iPrOH using catalytic amounts of NaOH under mild conditions (82 °C).[21] The yields obtained were moderate and no reduction proceeded in the absence of NaOH (Scheme 1.3). These results however presented a significant improvement when using ^iPrOH as a hydride source, as the earlier examples reported with Ru required elevated temperatures (150-200 °C).[21] When ^iPrOH is used as the hydrogen source, the equilibrium involving the ^iPrOH and acetone sets a limit to the conversion of ketones. Therefore, to achieve useful conversions the reaction is usually carried out in large excess of ^iPrOH (low substrate concentration of about 0.1 M) or by removal of acetone from the reaction mixture in situ.[2]
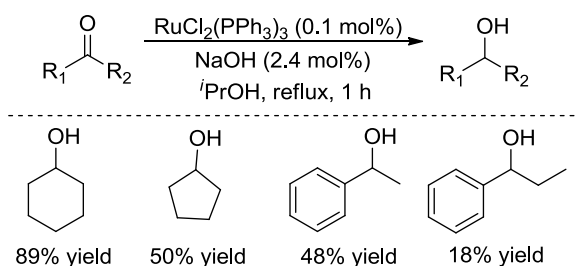
**Scheme 1.3**: TH of ketones catalysed by [RuCl$_2$(PPh$_3$)$_3$] in ^{i}PrOH.

Highly active catalysts for the TH of ketones started emerging by the end of 1990's, prior to that the reaction rate and the productivity of the catalysts were low. Van Koten and co-workers reported the Ru(II) pincer complexes containing a terdentate bis(phosphanyl)aryl (PCP) ligand (Scheme 1.4).[22] TOFs of up to 10000 h^{-1} were achieved for the TH of cyclohexanone using just 0.01 mol% **1**, with KOH as the promoter in ^{i}PrOH at 82 °C. In contrast, when the cationic variant **2** was used TOFs of up to 27000 h^{-1} were achieved. These values were superior to those obtained earlier with Ru(II) complexes bearing only monodentate phosphane ligands, such as [RuCl$_2$(PPh$_3$)$_3$].[21] The reaction only proceeded under inert atmosphere and a low KOH concentration was necessary to inhibit the side aldol products.
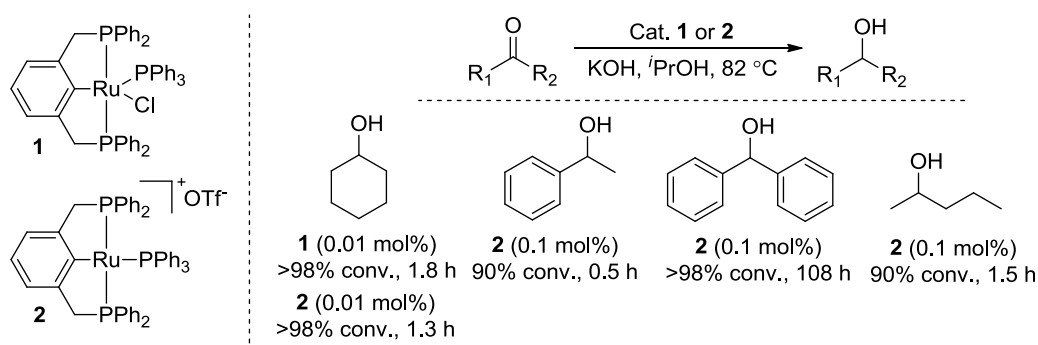
Scheme 1.4: Pincer-type Ru(II) complexes containing terdentate PCP ligands.

In addition, Barrata and co-workers independently prepared a diverse series of cyclometalated Ru(II) complexes (Scheme 1.5), and subsequently applied them to the TH of ketones in ^{i}PrOH under basic conditions.[23,24] Complex **3**, containing a

bidentate ethylendiamine coligand at 0.1 mol% loading, was found to transfer-hydrogenate acetophenone in quantitative yields in 30 min, using NaOH as a base in ^{i}PrOH. Remarkably, considerable rate acceleration was observed when ethylendiamine coligand was replaced with 1-(pyridin-2-yl)methanamine (Pyme); the same reaction finished in only 5 min using only 0.05 mol % **4** with TOF reaching up to 60000 h^{-1}. However, when the analogous 2-(pyridine-2-yl)ethanamine was used as coligand instead of Pyme, this resulted in much less active reduction (TOF 4000 h^{-1}),[23] suggesting that the Pyme coligand is essential for the catalytic activity. Their system was also applicable on a gram scale as demonstrated by the TH of benzophenone with 0.01 mol% catalyst loading (90% isolated yield of benzhydrol).[23]
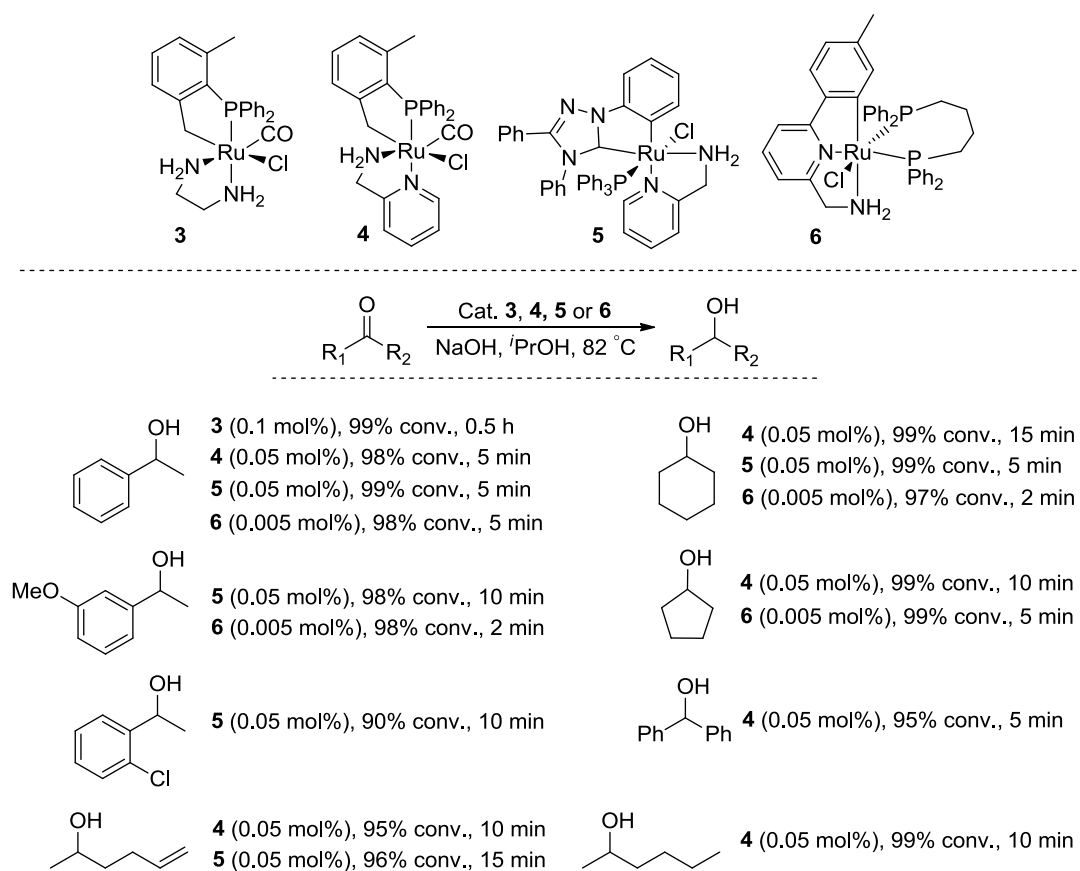
Scheme 1.5: Series of diverse cyclometalated Ru(II) complexes and their activity in TH of ketones.

Subsequently, the cyclometalated carbene Pyme and terdentate CNN ruthenium complexes **5** and **6** were reported (Scheme 1.5).[24,25] Complex **5** is highly efficient in the reduction of numerous ketones, including alkyl and dialkyl ketones with TOF up to 1.2×10^5 h^{-1} using 0.05 mol% catalyst.[24] This high activity could be ascribed to the relative strong bonding of the carbene ligand. Complex **6** is also highly robust. For example at an S/C ratio of 20000:1, 1-phenylethanol was quantitatively obtained within 5 min of TH of acetophenone with a remarkable TOF of up to 1.1×10^6 h^{-1} in ^{i}PrOH.[25] Addition of further amounts of acetophenone into the reaction mixture also resulted in complete reduction, showing the high catalytic activity of the catalyst. This TH was also demonstrated on a gram scale at S/C of 100000:1. The high catalytic activity is probably due to the role of the NH_2 group in assisting the TH of ketone. The NH_2 group offers metal-ligand bifunctionality; thus when it was replaced with NMe_2 group the activity decreased. Rigid framework built by the CNN ligand together with chelating diphosphine retarded the deactivation of catalyst.[25]

Complexes based on iridium and rhodium are also known to be effective for the TH of ketones by ^{i}PrOH.[26-34] Inspired by the seminal work of Bianchini on Ir complexes featuring aminodiphosphine ligands,[26] Rashid and co-workers developed the bifunctional pincer complex **7**.[27] Indeed, complex **7** was found to be highly active for the TH of ketones in the absence of a base in ^{i}PrOH, with acetophenone being converted into the corresponding alcohol using only 0.001 mol% catalyst loading (Scheme 1.6). The high activity of this complex was due to the availability of the hydrogen on the nitrogen donor, which plays an important role for the reactivity with concerted hydrogen transfer from both NH and Ir-H to the ketone.[27] Earlier Bianchini and co-workers had reported similar aminodiphosphine ligands with a NR moiety (where R represents an alkyl substituent) instead of an NH;

however the catalytic performance was much lower, highlighting the importance of NH.[26,27]
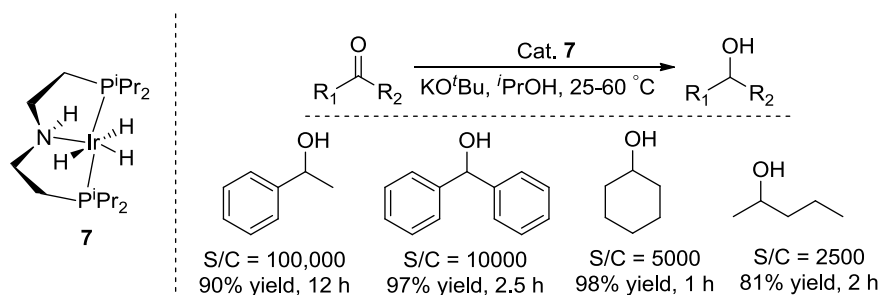
Scheme 1.6: Iridium catalysed TH of ketones.

Nolan and co-workers reported the use of cationic Ir(I) mono-carbene complex **8** for the TH of ketones.[28] This catalyst is analogous to Crabtree's [Ir(cod)(py)(PCy$_3$)]PF$_6$ hydrogenation catalyst.[29] Complex **8** catalysed the reduction of simple ketones using ^{i}PrOH/KOH under reflux, with a low catalyst loading and short reaction times (Scheme 1.7). The same catalyst also exhibits activity toward the reduction of C=C bond and NO$_2$ group. Consequently, Crabtree and co-workers developed a series of bis(*N*-heterocyclic carbene) complexes based on Rh(III)[30] and Ir(III)[31] that are air and moisture stable. The two carbene moieties were linked by a methylene bridge. The stability of the complexes was attributed to the chelate effect of the bis-carbene that resists degradation under catalytic conditions. Ir(III) complexes were much more active than their Rh(III) counterparts for the TH of ketones. The catalytic activity was highly influenced by the nature of the R group on the carbene (Scheme 1.8).[31] For example when complex **9a** (R = Me) was used for the TH of benzophenone in ^{i}PrOH under reflux condition, the corresponding alcohol was achieved in 98% conversion after 90 min with a TOF of up to 2000 h^{-1}. In contrast, when **9c** (R = neopentyl) was used under the same condition, the reaction was completed in only 4 min with a TOF of up to 50000 h^{-1} being achieved at 50% conversion. With complex

9b (R = Bn) the reaction was much slower (98% conversion in 20 h), however. The activity of these bis-carbene complexes is significantly higher than that observed for related mono-carbene complex **8**.[28]
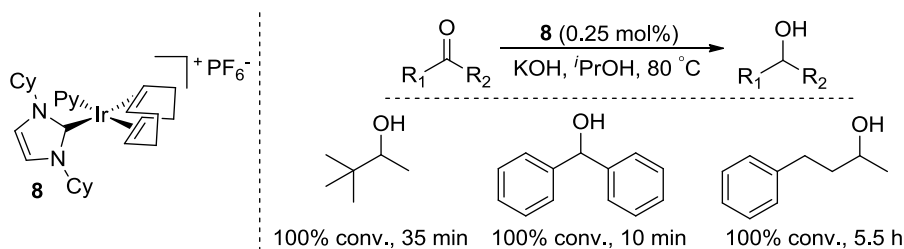

Scheme 1.7: TH of simple ketones catalysed by [Ir(cod)(py)ICy]PF$_6$ in ^{i}PrOH.
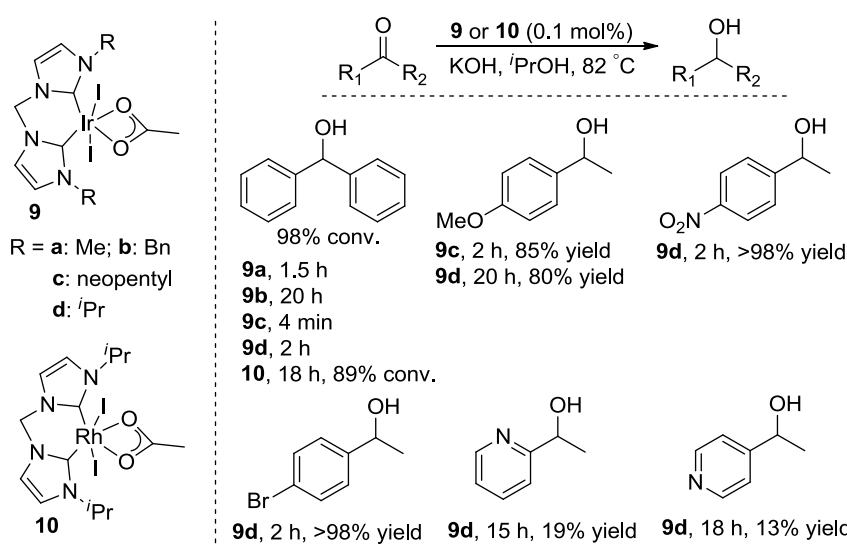
Scheme 1.8: TH of ketones with Ir and Rh bis(*N*-heterocyclic carbene) complexes.

Among the half-sandwich Ir(III) NHC complexes, complex **11**, reported by Peris and co-workers is an interesting catalyst.[32] The Cp* is tethered to the NHC leaving the complex with two possible vacant coordination sites. Thus, complex **11** was found to be much more active than its analogous complex **12**,[33] providing the reduction of a range of ketones at low catalyst loading (0.1 mol% compared with 1 mol% when using **12**). Rh(III) CNC pincer complex **13**, with two NHC donor moieties, was also reported to be active for TH of cyclohexanone, acetophenone and benzophenone with low catalyst loadings (Scheme 1.9).[34]
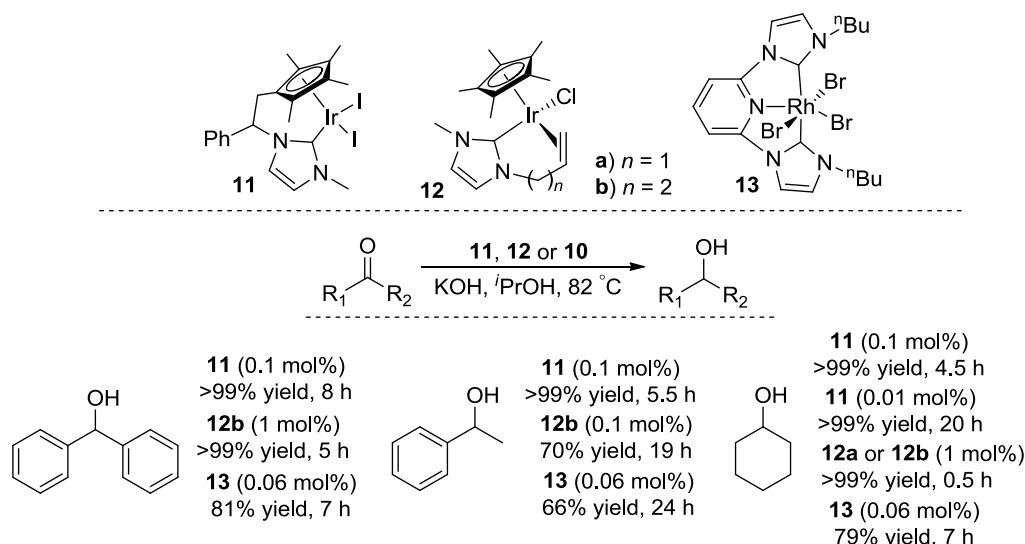
Scheme 1.9: TH of ketones with Ir half-sandwich NHC complexes and Rh-CNC complex.

Three main pathways have been proposed for the metal catalysed TH between alcohols (^{i}PrOH) and ketones (Scheme 1.10);[35]

- Pathway A involves direct hydrogen transfer where simultaneous hydride transfer takes place between the alkoxide and ketone, while both are coordinated to the metal centre. A typical example that follows such pathway is Meerwein-Ponndorf-Verley reduction.

- Pathway B is a typical example of metal-ligand bifunctional catalyst such as **7**, where the metal hydride transfers one hydrogen atom to the carbon of C=O bond, while the acidic amine provides the second hydrogen atom to the oxygen, usually via six membered transition state.

- Meanwhile in pathway C once the metal hydride species is formed the reaction proceeds by the coordination of ketone to the metal and then the hydride transfer takes place. Complex **9** follows this pathway as suggested by Crabtree and co-workers.
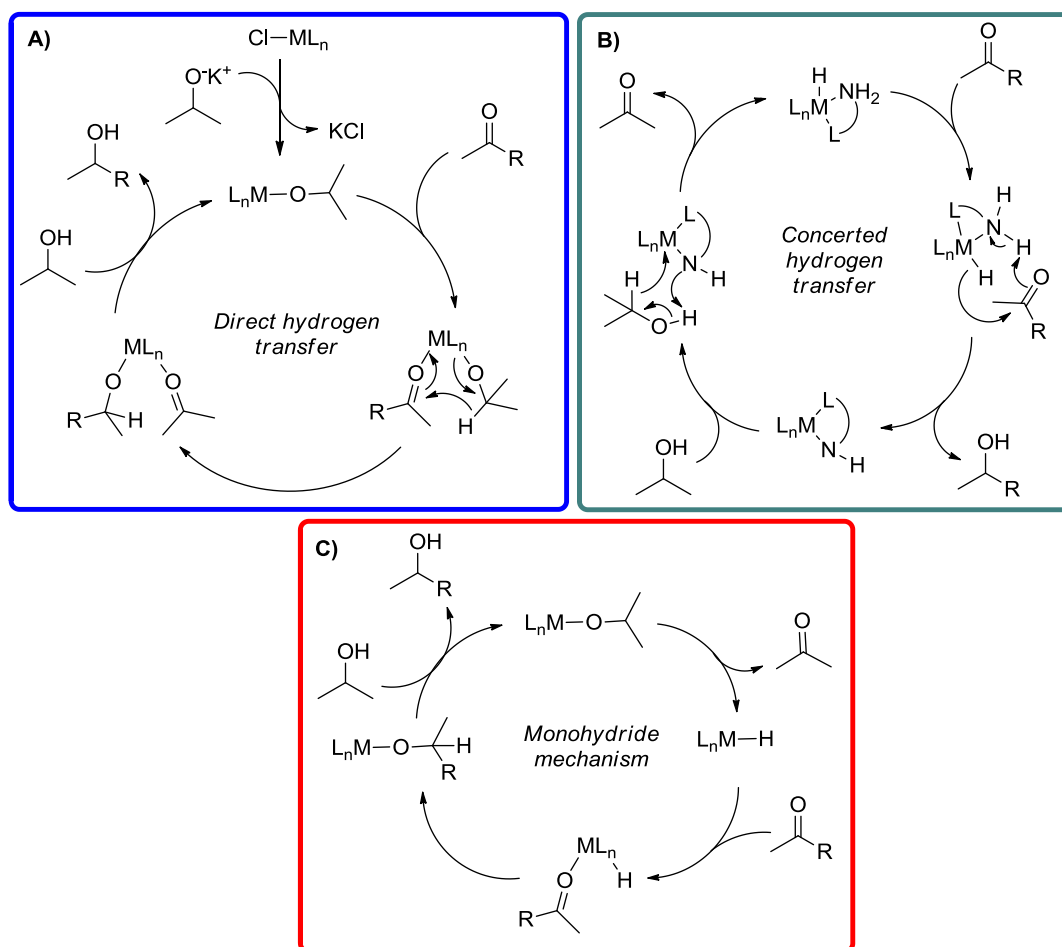
Scheme 1.10: Reaction pathways proposed for the metal catalysed TH of ketones by ^{i}PrOH.

1.3 TH of ketones in aqueous media

The TH of carbonyls can also be conducted in an aqueous media using formate salts as the hydride source as demonstrated by the seminal work of Sasson and Blum,[36,37] and later by Joo[38,39] and co-workers in the 1980's. A number of aromatic aldehydes were reduced in moderate to good yields by HCO_2Na at 90 °C using $RuCl_2(PPh_3)_3$ as the catalyst. In the case of ketone reduction analogous $RhCl(PPh_3)_3$ proved to have a higher activity, although a large excess of PPh_3 was required for a sufficient reaction.[36] Later studies by Joo revealed that the reactions in aqueous media are pH dependent.[39] For example in a study using Ru and a water soluble (3-sulfonatophenyl)diphenylphosphane (*m*-TPPMS) ligand in excess, TH of

cinnamaldehyde at pH 9 resulted in the formation of cinnamyl alcohol exclusively; however, at pH 3 the same reaction afforded 3-phenylpropanal as the major product (Scheme 1.11).[39,40]
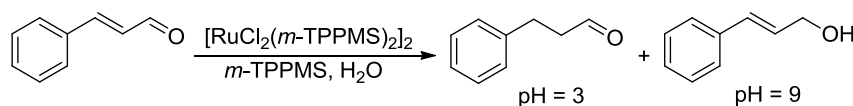
Scheme 1.11: Selectivity of the hydrogenation of cinnamaldehyde as a function of pH value.

The in situ NMR experiments conducted revealed the formation of various Ru(II) hydrides; [HRuCl(m-TPPMS)$_3$] and [RuH$_2$(m-TPPMS)$_4$] were the dominant species detected in acidic and basic solutions, respectively. [HRuCl(m-TPPMS)$_2$], which is formed in acidic solution by the dissociation of phosphine from [HRuCl(m-TPPMS)$_3$] was reported to be the active species for the selective reduction of C=C bond. Conversely, [RuH$_2$(m-TPPMS)$_4$] formed under basic conditions is selective for C=O bond reduction (Scheme 1.12).[39-41] The coordinative saturation of [RuH$_2$(m-TPPMS)$_4$] probably prevents the coordination of C=C bond to the metal centre, but allows the reduction of C=O bond by intermolecular nucleophilic hydride transfer.
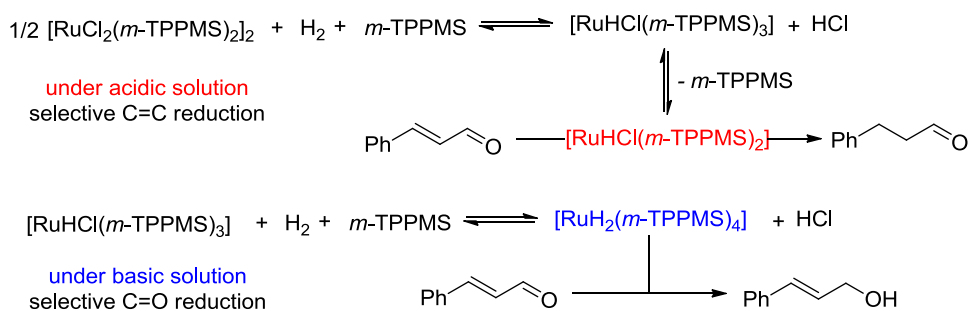
Scheme 1.12: Formation of Ru-hydride species and their selectivity towards unsaturated bonds.

Recently, water-soluble half-sandwich Ir(III),[42] Rh(III)[43] and Ru(II)[44] complexes have shown to be active in carbonyl TH using HCO$_2$Na or HCO$_2$H (Scheme 1.13). For the reduction, the active hydride species is generated in situ from the decarboxylation of formate. Ogo and co-workers have reported that Ir complexes **14**,

15 and **16** are effective for the TH of carbonyls under acidic conditions.[42,45,46] The reaction is highly pH dependent and only works in a certain pH interval and is also dependent on the catalyst used. For example, in the case of **16** the optimum TOF is achieved when the reaction is conducted between pH 2.0-3.0 for both water soluble (cyclohexanone) and water insoluble (acetophenone) substrates using HCO_2H. The reaction is faster because under these acidic conditions the carbonyl groups are activated by the protons; hence hydride transfer is easier.[42,45] The formation of the active hydride catalyst **16a** is also pH dependent, as high concentrations of it are only observed between the pH values of 2.0-6.0. Below pH 2.0, the protonation of **16a** occurs with H_2 evolution. Above pH 6.0, **16** is predominantly deprotonated to form a hydroxo complex **16b** that is inactive and hardly reacts with formic acid (Scheme 1.14).[45] In comparison, complexes **14** and **15** were less active than **16**.[42,45] The aqua complex **17**, a Rh analogue of **14** was also less active.[46,47] In contrast, Ru(II) catalyst **18** performed best at the pH of 4.0 with TOF up to 153 h^{-1} being achieved.[44]
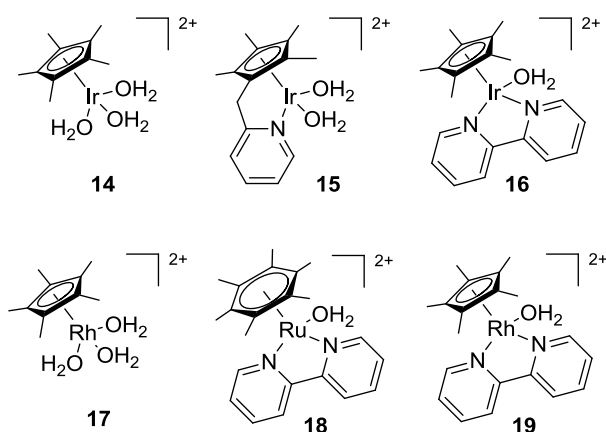
Scheme 1.13: Water-soluble half-sandwich complexes.
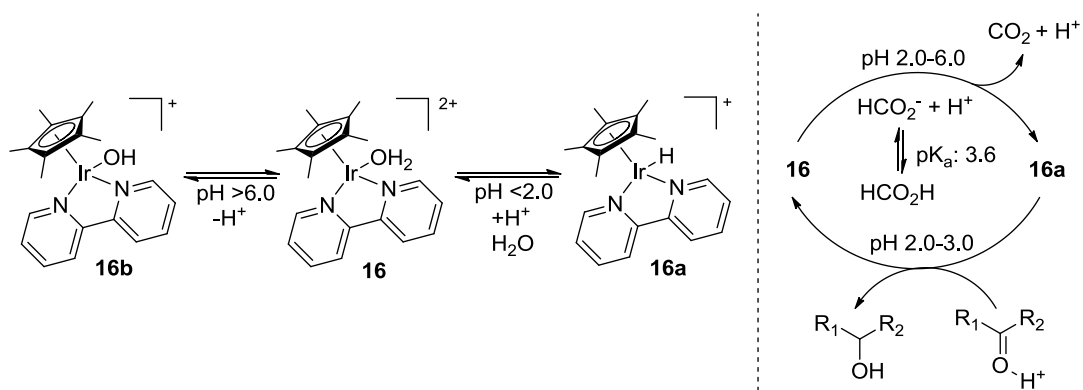
Scheme 1.14: Species observed at different pH values.

Some of these complexes can also be used in conjunction with enzymes for the enantioselective reduction. Redox enzymes such as alcohol dehydrogenases require a cofactor such as nicotinamide adenine dinucleotide hydride (NADH) or nicotinamide adenine dinucleotide phosphate hydride (NADPH) as the hydride source. However, the in situ regeneration of these cofactors is expensive; thus efforts have been made to develop cheaper non-enzymatic regeneration systems. Steckhan and co-workers reported the use of half-sandwich $[Cp*Rh(bpy)H]^+$ for the regioselective reduction of NAD^+ to 1,4-NADH.[48] The active hydride catalyst $[Cp*Rh(bpy)H]^+$, which is an analogue of $[Cp*Rh(bpy)OH_2]^{2+}$ **19**, was generated in situ from the decarboxylation of HCO_2Na. This system was successfully applied for the cofactor regeneration process in enzymatic reduction of ketones.[49] Later, Fish and co-workers elucidated the mechanism of this important reaction.[50] They proposed that once the hydride catalyst is formed, the amide functionality of the NAD^+ coordinates to the Rh metal centre. This coordination site occurs by the ring slippage mechanism of the Cp* ring, where the coordination mode of the Cp* changes from η^5 to η^3. Next, the selective hydride transfer at C4 of the NAD^+ occurs via six-membered transition state, which simultaneously includes the reversion of the coordination of Cp* from η^3 to η^5.

Finally, H_2O displaces the NADH and gives the precursor catalyst **19** (Scheme 1.15).[50]
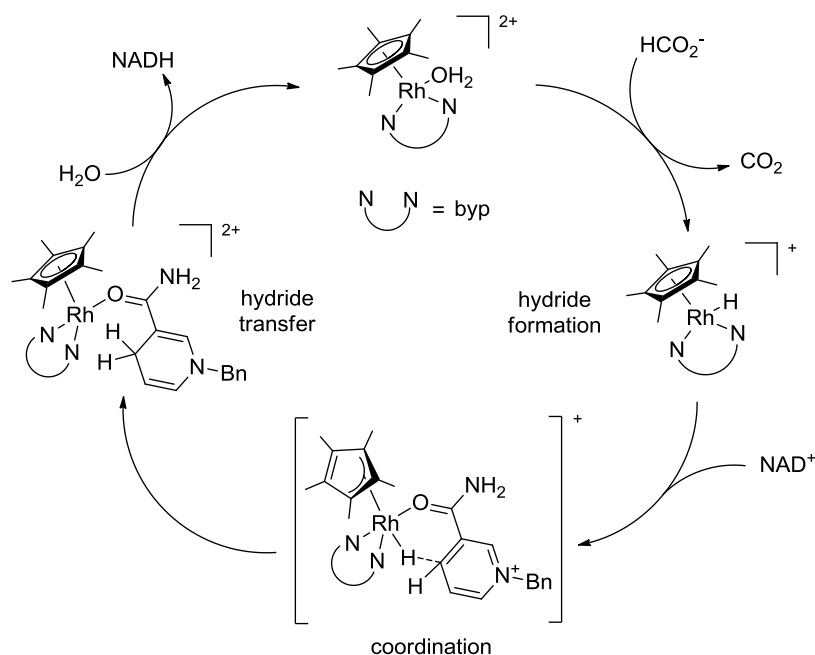
Scheme 1.15: Proposed mechanism for the regioselective, catalytic reduction of NAD^+ model.

Inspired by Ogo's work,[42-44] Süss-Fink and co-workers reported a series of complexes containing chelating 1,10-phenanthroline ligands.[51,52] However, the activity of these complexes was lower in comparison to bipyridine complexes.[44] For example using **18**, a TON of 196 was achieved after 4 h at 70 °C for the TH of acetophenone using HCO_2H, whereas under the same condition a TON of 144 was achieved after 48 h when 1,10-phenanthroline ligand was used.[44,51] Subsequently, the Rh cationic chlorido complex **20**, which was reported by the same group, was found to be highly active in the TH of NAD^+ in aqueous media. TOF of up to 2000 h^{-1} was obtained using only 0.1 mol% catalyst. It was also compatible for the NADH regeneration for the stereoselective TH of ketones with alcohol dehydrogenase (Scheme 1.16).[52]
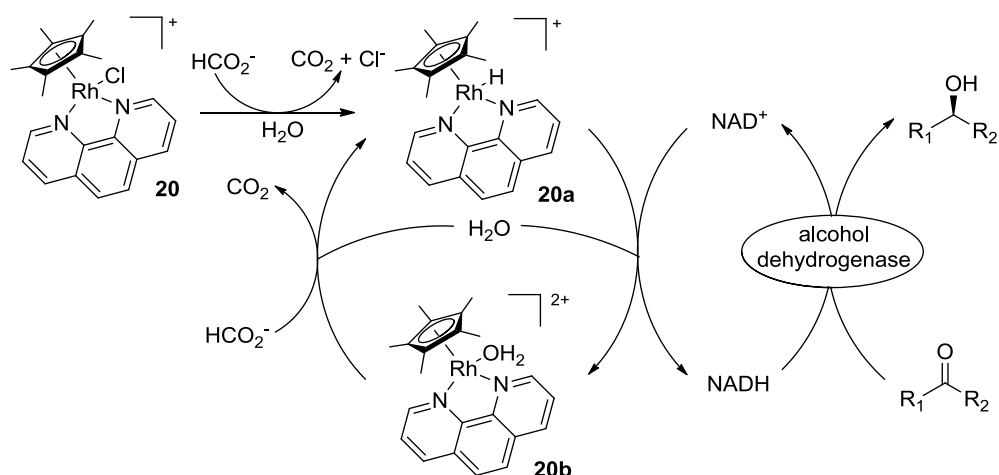
Scheme 1.16: Proposed mechanism for the chemoenzymatic ATH of ketones.

1.4 TH of aldehydes

Compared to ketones, the TH of aldehydes is less explored. Phosphine ligands have been traditionally used on transition metal catalysts for the TH of aldehydes. However, their conversions remained moderate.[53,54] Catalytic TH of aldehydes is often challenging and several reasons may apply for the low conversion usually obtained;

I.   When reduction is carried out in ^{i}PrOH under basic conditions, the α-CH group to the carbonyl can be deprotonated and lead to the formation of aldol product.

II.   Substrate decarbonylation that may deactivate the catalyst through coordination of the resulting carbonyl.

Crabtree and co-workers have recently reported that NHC ligands, being a stronger electron donors, can enhance the reactivity of the transition metal.[55] The Ir-NHC complex **21**, catalysed the TH of various aldehydes, achieving TOF's of up to 3000 h^{-1}, in ^{i}PrOH (Scheme 1.17).
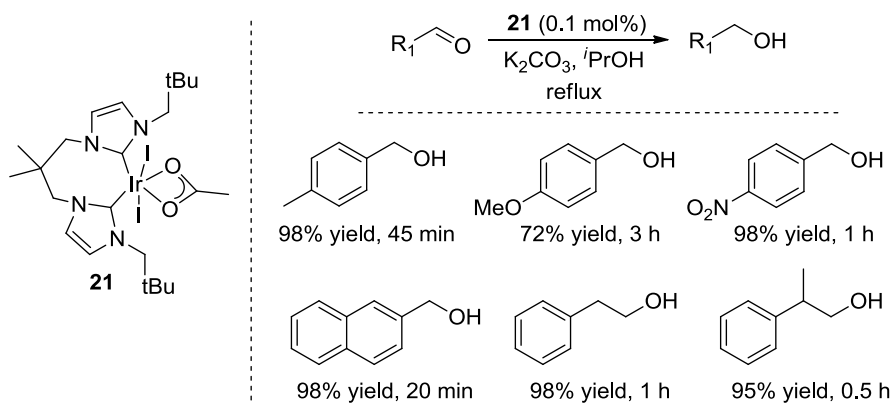
Scheme 1.17: TH of aldehydes by Ir-NHC complex in ^{i}PrOH.

More recently, Baratta and co-workers reported the most efficient system for the TH of aldehydes using tridentate CNN ruthenium complex **22**.[56] ^{i}PrOH served as both the solvent and hydride donor and a TOF up to 5.0 x 10^5 h^{-1} was achieved for the reduction of benzaldehyde using only a 0.05 mol% catalyst loading (Scheme 1.18). The association of a CNN ligand with the bulky diphosphane was considered to hinder the substrate decarbonylation. The system was also effective in reducing aliphatic aldehydes in high yield.
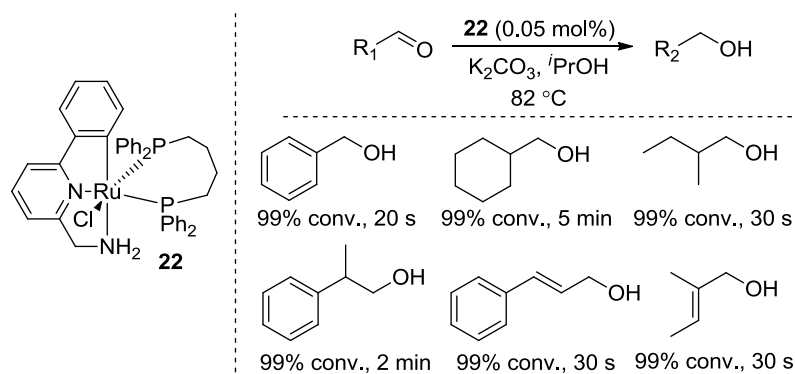
Scheme 1.18: TH of aldehydes in ^{i}PrOH by Ru-CNN complex.

Xiao and co-workers demonstrated that the TH of aldehydes can be enhanced when conducted in aqueous media in an "on water" fashion.[57] The half-sandwich catalyst **23** was prepared in situ using [Cp*IrCl$_2$]$_2$ and monotosylated ethylenediamine ligand. Although the catalyst was insoluble in water, it afforded a TOF of up to 1.3 x

10^5 h^{-1} for the reduction of benzaldehdye in neat water (Scheme 1.19). Interestingly, when the same reaction was carried using F/T or ^{i}PrOH, only a conversion up to 3% was achieved. This system was highly chemoselective towards aldehyde reduction when the TH of a substrate containing both an aldehyde and a ketone functionality was attempted. Moreover, the catalyst was also chemoselective towards the TH of α,β-unsaturated aldehydes giving allylic alcohols in high yields. An ample variety of functional groups were tolerated and reduction of aliphatic aldehydes was also viable.
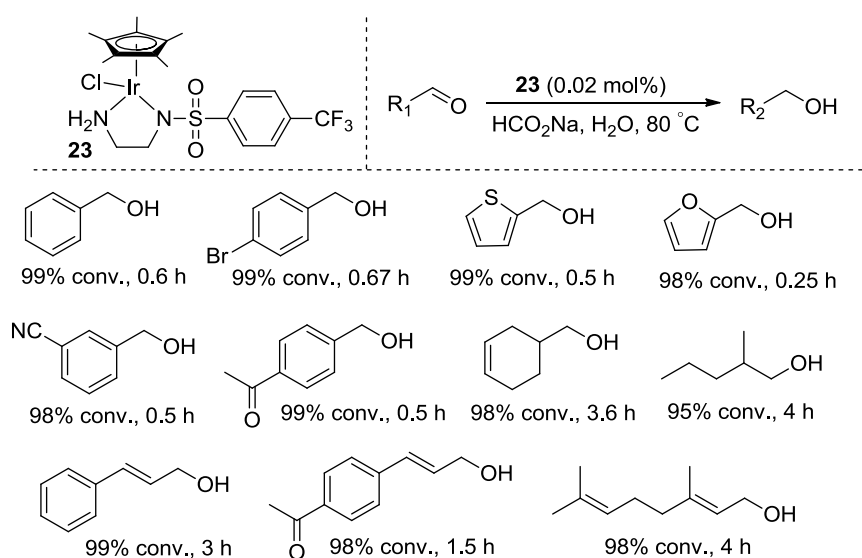
Scheme 1.19: TH benzaldehyde in water.

1.5 ATH of ketones in organic media

Asymmetric transfer hydrogenation (ATH) of ketones has also been developed in both organic and aqueous media. In early studies chiral monophosphine ligands were employed for the ATH of ketones, though the enantioselectivities achieved were generally low.[2] Pfaltz and co-workers reported that Ir(I) complexes prepared in situ from [Ir(COD)Cl$_2$] and tetrahydrobi(oxazoles) **24** can catalyse the reduction of ketones with ^{i}PrOH under reflux conditions (Scheme 1.20).[58] Alkyl aryl ketones

were smoothly reduced giving optically active alcohols in moderate to good enantioselectivities, whereas aliphatic substrates were found unreactive. Since then, several other chiral systems were developed by Genêt (Ru),[59] Evans (Sm)[60] and Lemaire (Rh),[61] although the enantioselectivity was generally lower than 90%.
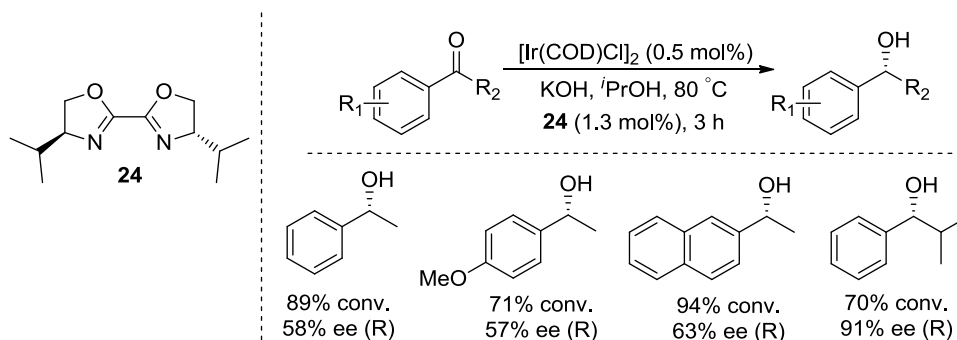
Scheme 1.20: ATH using tetrahydrobi(oxazole) ligand.

The pioneering work by Noyori, Ikariya and co-workers in 1995 led to a Ru(II) catalyst bearing a *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (Ts-DPEN) ligand, which was found to be highly efficient for the ATH of ketones.[62] The enantioselectivities achieved were excellent (>95%), which was a significant breakthrough, as for the earlier reported systems the enantioselectivities were generally moderate. *i*PrOH was used as the hydride source and the reaction was conducted at room temperature. It was important to run the reaction with a low substrate concentration (0.1 M) to achieve high enantioselectivity. At high concentration the enantiomeric purity of the chiral product deteriorated due to the occurrence of the reverse process originating from the structural similarity of the hydrogen donor (*i*PrOH) and product, both secondary alcohols. Subsequently, the same group reported that this problem could be avoided by substituting *i*PrOH with F/T azeotrope as the hydrogen source.[63] As a result, the reaction could be conducted with much higher substrate concentration (2-10 M) in comparison with the *i*PrOH

reaction (<0.1 M), with almost quantitative yields and excellent enantioselectivities (Scheme 1.21).
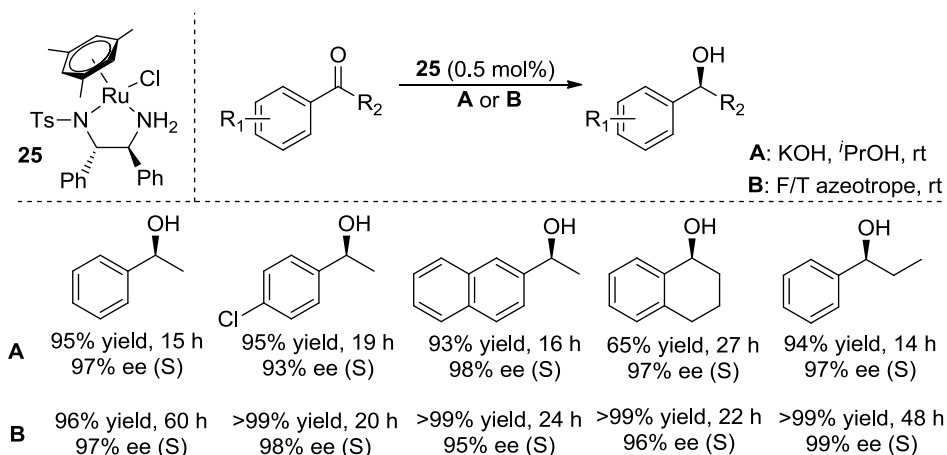
Scheme 1.21: ATH of acetophenone using Ru-TsDPEN.

Since its discovery these Noyori-Ikariya type catalysts have found broad applications and inspired intense research into ATH. Many ligands have been developed that offer metal-ligand bifunctionality, such as bidentate,[64] terdentate[65] and tetradentate ligands.[66] Some representative ligands are shown in Scheme 1.22, and their applications in the ATH of ketones have been summarised in many reviews.[2,14,35,67]
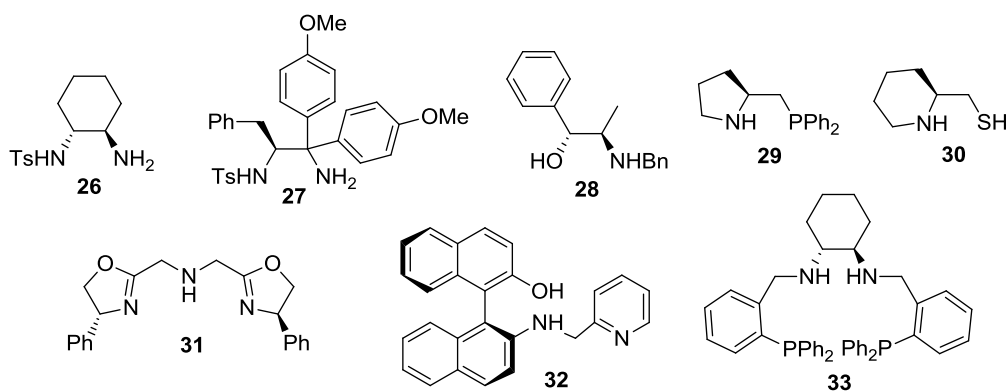
Scheme 1.22: Representative ligands for ATH.

Catalysts **25** and **34** are also efficient for the ATH of 1,2-diketones, giving the corresponding 1,2-diols in high yields and excellent enantioselectivities (up to 99%) in the presence of the F/T azeotrope.[68,69] For unsymmetrically substituted 1,2-

diketones the reduction took place at the less hindered carbonyl group first, and further reduction led to anti-1,2-diols. Under the same reaction conditions, racemic benzoin was also transformed into chiral diols via dynamic kinetic resolution (DKR).[69] ATH of α,β-unsturated ketones to allylic alcohols, and methyl 2-acylbenzoates to 3-alkylphtalides is also feasible with the same catalyst.[70,71] Using the isoelectronic Rh(III) catalyst **35**, a series of α-halo ketones, including heteroaryl ones, were reduced chemoselectively (Scheme 1.23).[72] These catalysts are much more reactive compared with Ru-TsDPEN complexes. For example with an S/C of 5000 the reduction of α-chloroacetophenone proceeded rapidly to give the corresponding chiral alcohol quantitatively with 96% ee (initial TOF, up to 2500h^{-1}). In contrast, complex **34**, which is highly effective for the ATH of simple ketones, exhibited no remarkable activity even at a lower S/C of 1000.
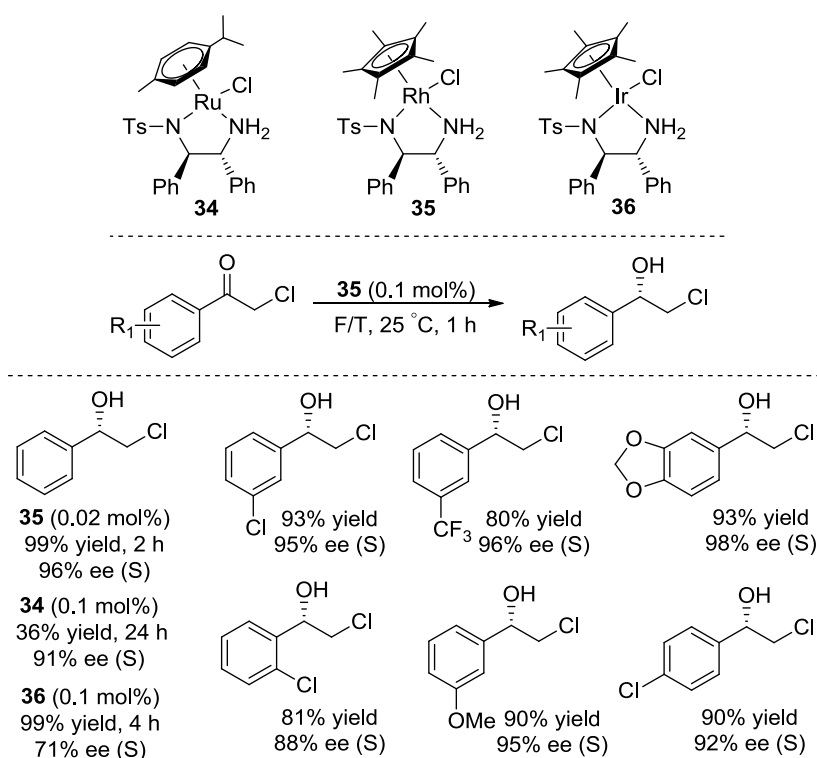
Scheme 1.23: Half-sandwich Noyori-Ikariya type catalysts and their reactivity towards ATH of α-chloroacetophenone.

An analogous Ir(III) complex **36** exhibited high reactivity but poor enantioselectivity (Scheme 1.23).[72] This remarkable difference in the reactivity could be attributed to the electronic properties of the central metals. The chiral halo-hydrins are useful intermediates for the synthesis of optically active styrene oxides and aminoethanols that serve as building blocks for the synthesis of various pharmaceuticals. The ATH is an attractive way to these halo-hydrins and using Noyori-Ikariya type catalysts, the reaction has been demonstrated on relatively large scale at Pfizer and Eli Lilly.[73]

Pfeffer and co-workers reported that ruthenacycles generated from [Ru(η^6-benzene)Cl$_2$]$_2$ and chiral amines (primary or secondary) are good catalyst precursors for the ATH of simple ketones.[74] Enantioselectivities ranging from 38 to 89% were achieved for the TH of acetophenone with such catalysts (Scheme 1.24). The main advantage is the use of simple commercially available chiral amines that could easily be complexed in one step.
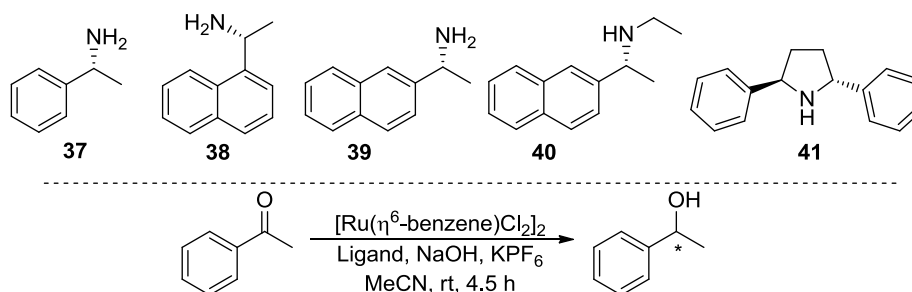
Entry	Ligand	Product yield (%)	ee(%)	Configuration
1	**37**	79	38	S
2	**38**	86	54	S
3	**39**	78	30	S
4	**40**	96	69	S
5	**41**	49	89	R

Scheme 1.24: Primary and secondary amine ligands for ATH of acetophenone.

Recently, the Ru(II)Pyme catalysts, which have previously shown good efficiency in the achiral TH of ketones, were also explored for asymmetric reduction (Scheme

1.25). Baratta and co-workers reported Ru(II) complex **42**, bearing a chiral phosphine ligand and Pyme, which was found to be highly active for the reduction of ketones in *i*PrOH, affording a TOF of up to 300000 h⁻¹ and enantioselectivities ranging from 85 to 94%. The use of chiral CNN ligand was also feasible; good enantioselectivity was obtained with the high activity retained.[75,76] Ru complexes **44** and **45** bearing unsymmetrical NNN ligands have been reported recently by Yu and co-workers (Scheme 1.26).[77] High yields with up to 97% ee are obtained for the corresponding alcohols in a few minutes at room temperature in *i*PrOH with just 0.1 mol% catalyst loading.
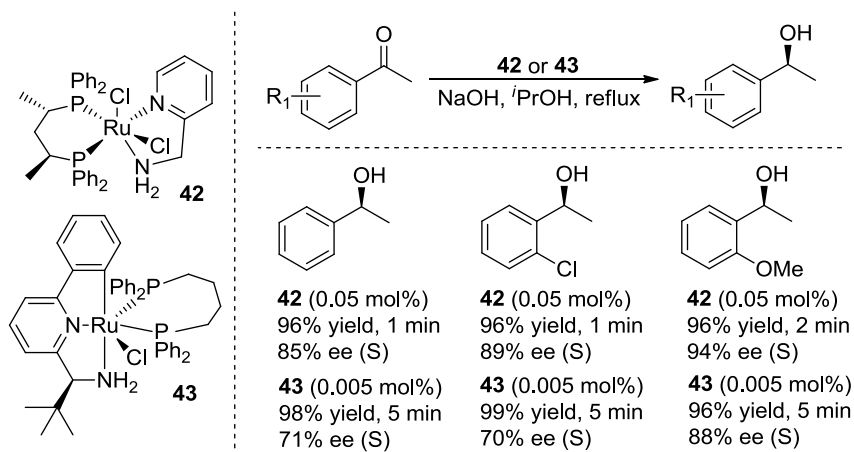
Scheme 1.25: ATH of ketones with Ru(II)Pyme complexes.
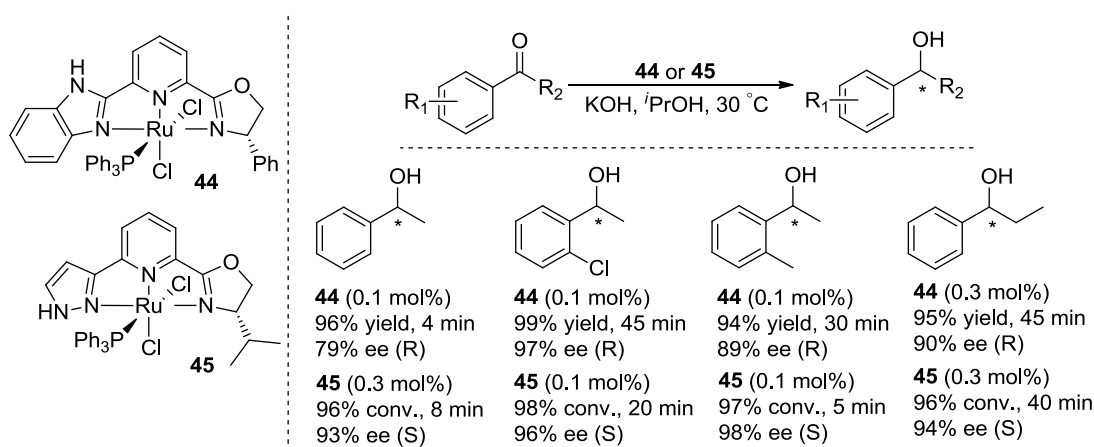
Scheme 1.26: ATH of ketones with Ru(II)-NNN complexes.

Wills and co-workers developed a series of structurally rigid, tethered complexes based on Rh and Ru (Scheme 1.27).[78-82] These catalysts are highly active for the ATH of ketones and generally provide faster reaction rate than the non-tethered analogous using F/T as the hydrogen source. The rigid framework stabilises the catalyst making it moisture and air insensitive and also offers an additional element in controlling the reaction enantioselectivity. Of particular note is the oxo-tethered Ru amido complex **48** with a three-legged piano-stool configuration, recently developed independently by Ikariya and Wills.[80,83] It exhibits excellent catalytic activity and selectivity for a wide range of ketones, affording up to >99% yield and 99% ee for the corresponding alcohols (Scheme 1.28). The reaction was also performed at loadings as low as S/C = 30000 without the loss of catalytic activity or enantioselectivity, thus providing the highest activity among a series of Ru-TsDPEN complexes. In addition, the catalytic performance of oxo-tethered Ru complex is much higher than that of carbon chain tethered Ru complex reported earlier by Wills.[83] Rh(III) complex **49**, like its non-tethered analogous **35**, is particularly good for the ATH of α-substituted aromatic ketones, affording the corresponding alcohols in quantitative yields and high enantioselectivities (up to 99.6%).[81] Of further interest is the Rh(III) catalyst **50**, which, containing a tethered monotosylated 1,2-diaminocyclohexane (TsDAC) ligand, represents one of the best ATH systems for aliphatic ketones, providing 87% ee in the case of cyclohexylmethyl ketone.[82]
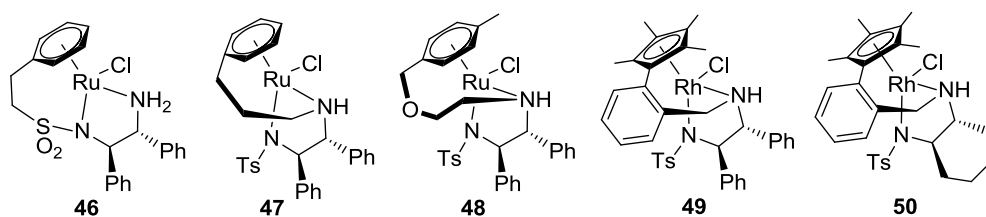
Scheme 1.27: Tethered complexes for ATH.
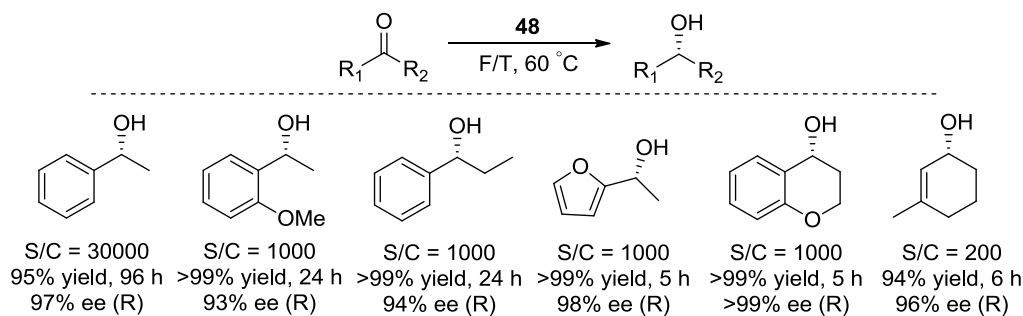
Scheme 1.28: ATH with oxo-tethered complex.

1.6 ATH of ketones in aqueous media

Transition metal catalysed ATH of ketones can be carried out efficiently in water. Significant advances have been made since the early 2000's for the exploration of Noyori-Ikariya type catalysts in water. Williams, Blacker and co-workers reported TsDPEN and TsDAC containing a sulfonic acid or sulfonic acid sodium salt group, which made these ligands water soluble (**51** and **52**, Scheme 1.29).[84] Subsequently, they tested these ligands for the ATH of simple ketones. The catalysts were prepared in situ by reacting the ligand with [Ru(*p*-cymene)Cl$_2$]$_2$ or [Cp*MCl$_2$]$_2$ (M = Rh, Ir). *i*PrOH was used both as a co-solvent and as a hydrogen source and the reactions were carried out at room temperature. Although good to excellent enantioselectivities (up to 96%) were achieved, the activity was much lower compared with the reaction reported earlier in organic media.[62,63]

Chung and co-workers reported the first examples of ATH of ketones in neat water without any organic co-solvents. The active catalyst was formed by combining [Ru(*p*-cymene)Cl$_2$]$_2$ with a water soluble (s)-proline amide ligand, **53** (Scheme 1.29).[85] Sodium formate was used as the hydrogen source and the catalyst could be recycled up to 6 times without the loss of activity. A highly water soluble ligand **54** has also been developed and found to have good activity in the presence of a surfactant sodium dodecyl sulfate (SDS).[86] Remarkably, this system is also capable

of reducing α-bromo acetophenone in good yield and enantioselectivity. This is a challenging substrate, as under homogeneous condition using F/T azeotrope as the hydrogen source usually only formate displacement is observed.[86]
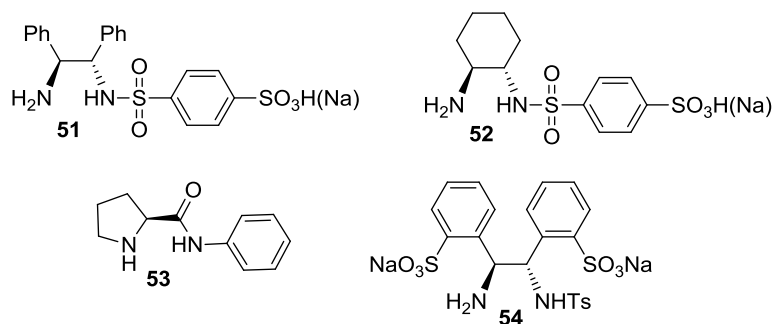
Scheme 1.29: Water soluble ligands for ATH of ketones.

A common focus in the research for the successful ATH of ketones in water has been the development of water soluble catalysts. However, Xiao and co-workers reported that water insoluble **34** and M-TsDAC (M = Ru, Rh, Ir) can also catalyse the reduction of ketones by HCO_2Na. Water was found to accelerate the asymmetric reduction of unfunctionalised ketones. For example using **34** at S/C = 100 acetophenone was fully reduced to its corresponding alcohol (95% ee) in 1 h at 40 °C by HCO_2Na in water. In comparison, the reaction run in F/T only afforded a conversion of 2% in 1 h (Scheme 1.30).[87] Further investigation revealed that the ATH of ketones promoted by the Ru-TsDPEN catalyst in water is pH dependent, with higher pH favouring higher rates and enantioselectivities.[88] The catalyst is partitioned in the substrate and water phase being more soluble in the former. Hence, it could be described as "on water" (biphasic) reaction. The tethered Rh-TsDAC complex **50** is also highly effective for the reduction of ketones in aqueous media including heterocyclic ketones.[82] Thus, 2-acetylfuran was reduced to its corresponding alcohol using only a 0.01 mol% catalyst loading at room temperature

with an enantioselectivity of 98%. The ATH of aliphatic ketones was also feasible in water, albeit with slightly lower enantioselectivities.
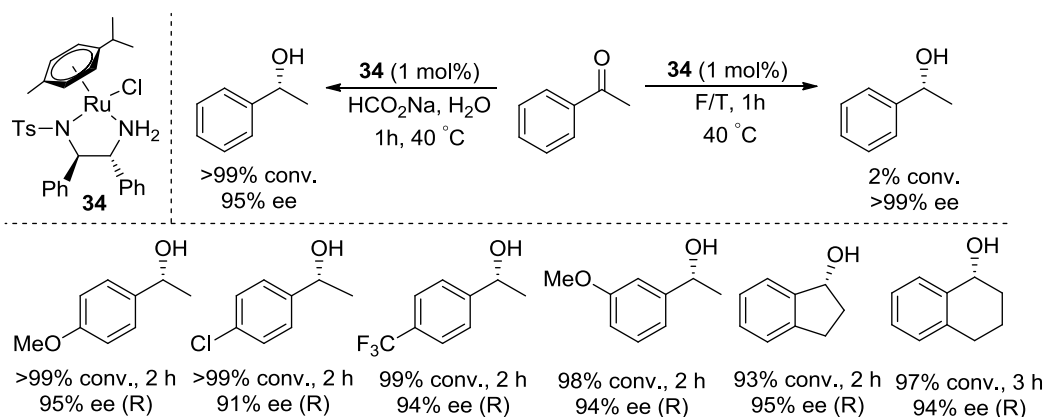
Scheme 1.30: Selected examples of alcohols obtained with Ru-TsDPEN in water.

Li and co-workers demonstrated the ATH of α-keto esters to the highly useful chiral α-hydroxy esters in water using Ru(II) catalysts.[89] They found that a bulkier tosyl variant afforded greater conversions and enantioselectivities compared with less bulky ligands. The use of surfactant was necessary for higher activity with the best results obtained in the presence of dodecyltrimethylammonium bromide (DTAB) (Scheme 1.31). There appears to be, however, some effects from the substituents on the aryl ring of the substrates. Thus, high enantioselectivities were obtained with electron donating substrates compared with substrates containing electron withdrawing groups. Other metals tested such as Ir and Rh were less active, however. Wang and co-workers showed that complex **34** enables efficient ATH of α-cyano aryl ketones, β-keto esters and β-keto amides when the reaction is performed in an emulsion of DCM and aqueous HCO_2Na in the presence of tetrabutylammonium iodide (TBAI).[90]
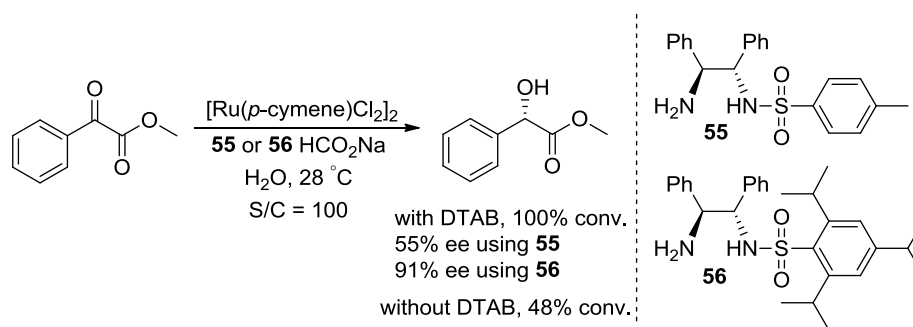
Scheme 1.31: The effect of bulkier Ts-DPEN on the ATH of methyl 2-oxo-2-phenylacetate.

Carreira and co-workers developed a series of chiral aqua complexes derived from Ir(III) trihydrate precatalysts (Scheme 1.32).[91-93] Screening of a range of sulfonamides revealed that ligands bearing strong electron deficient sulfonamides provided the highest selectivity and reactivity. Thus, catalyst **57**, bearing a perfluorinated sulfonamide reduced a range of α-cyano ketones using HCO_2H in water (pH = 3.5) at a low catalyst loading (0.25-0.5 mol%).[91] Substrates with electron donating and electron withdrawing groups did not adversely affect the selectivity or conversion, and substrates containing heteroaromatic ring were also viable (Scheme 1.33). Reduction of α-chloro and α-nitro ketones was also feasible albeit at lower pH of 2.0. Complex **58**, containing a chiral diamine, which can be seen as a simplified alternative to commonly used Ts-DPEN, was also found to be highly efficient for the ATH of both α-nitro and α-cyano aryl ketones with generally >92% enantioselectivities achieved in most cases. It is particularly selective for the *ortho*-substituted aryl ketones, which have been known to give lower enantiomeric excess in the past, with up to 99% ee achieved with the current system.[92] Further work revealed that the reaction is pH independent as it tolerates a wide pH range. For instance, the ATH of ethyl benzoylacetate proceeded with 100% conversion and 94% ee to its corresponding alcohol at pH = 5.0. Remarkably exactly same result was obtained when the reaction was conducted at higher pH = 10.5.[93]
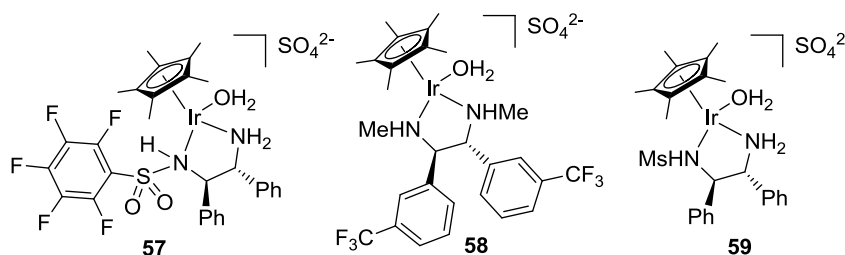
Scheme 1.32: Chiral aqua complexes.
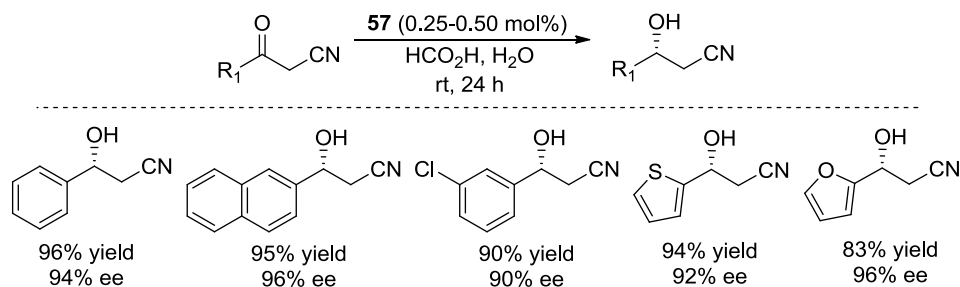
Scheme 1.33: Representative examples of ATH of various α-cyano ketones in water.

1.7 TH of imines

In contrast to the TH of ketones, the transition metal catalysed TH of imines is more challenging and a relatively underdeveloped transformation.[94,95] One of the main reasons for that is the competitive coordination of the reduced products (ability to coordinate to a metal: amine>alcohol) to the metal centre that may lead to undesired catalyst poisoning. Despite that some significant advances have been achieved in the area of imine TH in the past two decades. Ru, Rh and Ir-based complexes are still usual catalysts choice. Imines are most commonly prepared from the condensation of amines and carbonyls. If the imine formation and its subsequent reduction are carried out in one pot, the reaction is known as direct reductive amination (DRA). Consequently, imine reduction is sometimes referred as indirect reductive amination (Scheme 1.34).
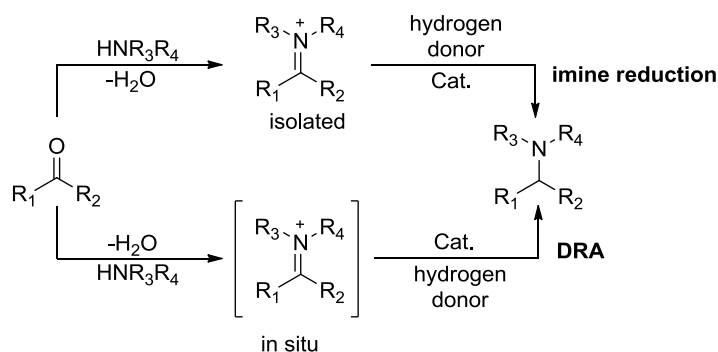
Scheme 1.34: Imine reduction and DRA.

Grigg and co-workers reported the first example of TH of imine using the Wilkinson's catalyst. A number of aldimines were reduced to their corresponding secondary amines in good yields in the presence of sodium carbonate in ^{i}PrOH.[96] In 1992, Bäckvall and co-workers showed that the Ru complex [RuCl$_2$(PPh$_3$)$_3$] can also catalyse the reduction of imines in ^{i}PrOH.[97] K$_2$CO$_3$ was essential for the reaction to proceed and aromatic imines gave better results than aliphatic ones. The reaction was sluggish when the monophosphine ligand was replaced by bidentate phosphine ligands such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) or 1,4-bis(diphenylphosphino)butane (dppb), which could be attributed to the higher steric demand of the imines. Later studies revealed that the dihydride [RuH$_2$(PPh$_3$)$_3$] was the active species and it catalysed the reduction of C=N bond in the absence of a base, indicating that this reaction proceeds through the hydride mechanism without ligand assistance (Scheme 1.35).[98]
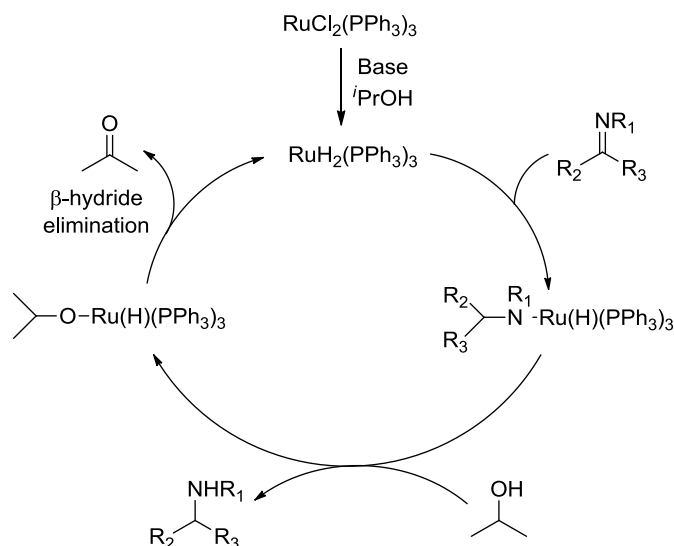
Scheme 1.35: Proposed mechanism of [RuCl$_2$(PPh$_3$)$_3$] catalysed TH of imine.

Catalytic TH of imines can also be realised with the half-sandwich dimeric Shvo's catalyst **60**, which had earlier shown to be effective in ketone reduction.[99] In solution, Shvo's catalyst dissociates into interchangeable species **60a** and **60b**, with the former active in hydrogenation and the latter in dehydrogenation of ^{i}PrOH (Scheme 1.36). The catalyst is highly active and reduces a range of *N*-aryl imines at very low catalyst loadings under mild conditions. The rate of imine reduction can be enhanced by carrying out the reaction under microwave irradiation.[100] Interestingly, Shvo's catalyst is also active for the racemisation of amines and alcohols.[101]
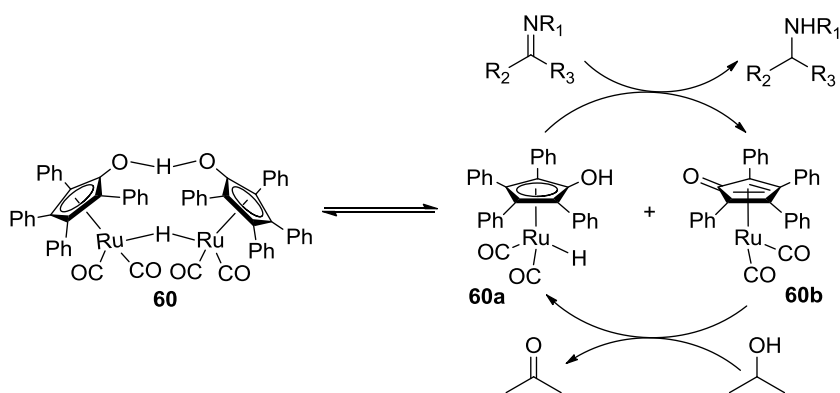
Scheme 1.36: TH of imines with Shvo's catalyst.

Casey and co-workers proposed an outer-sphere mechanism for the TH of imines with Shvo's catalyst, where the hydride and the proton from the OH group of the cyclopentadienyl (Cp) ring were transferred simultaneously to the C=N bond, without it being coordinated to the metal centre.[102] This mechanism is also consistent with ketone reduction. In contrast, Bäckvall and co-workers suggested an inner-sphere mechanism, where imine coordination is followed by the hydride transfer. A key step would involve the ring slippage of Cp from η^5 to η^3 to generate a coordinately unsaturated species, required for the imine to coordinate (Scheme 1.37).[103]
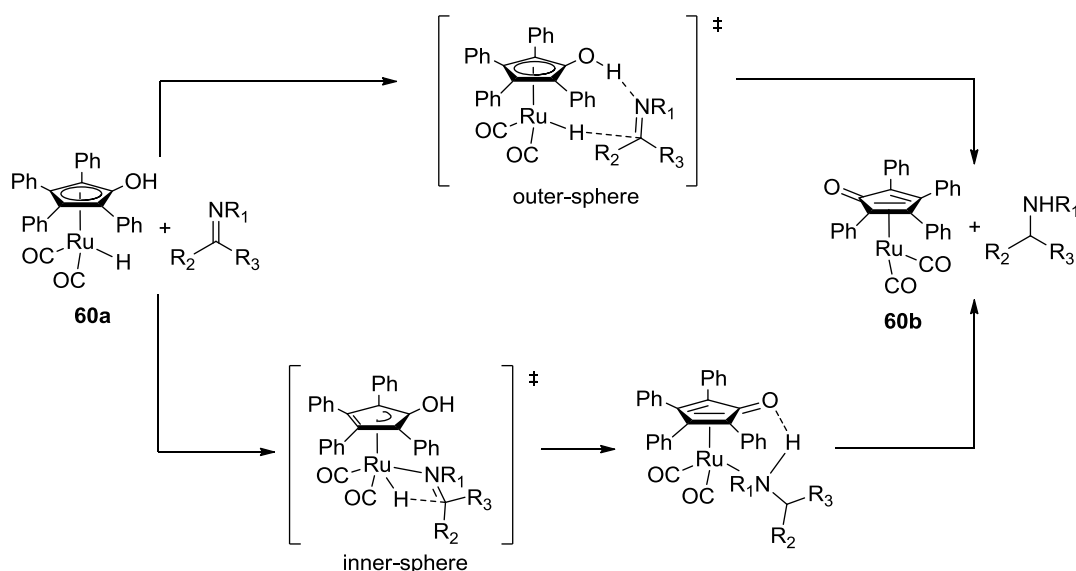
Scheme 1.37: Outer-sphere and inner-sphere mechanism proposed for imine reduction with Shvo's catalyst.

In recent years several reports have emerged describing the development of *N*-heterocyclic carbene (NHC) complexes for the reduction of imines in *i*PrOH.[30,104-108] Rh(III) complexes **10** and **61**, bearing chelating bis-carbene ligands were found to catalyse the reduction of aldimines to the corresponding amines in good yield (Scheme 1.38).[30] Interestingly, the analogous iridium catalyst **9c** (see page 8), which was more active for promoting the TH of ketones (*vide supra*), was only

active for the TH of aromatic aldimines but rather ineffective in the case of aldimines prepared by the condensation of benzaldehyde and aliphatic amine, even at higher catalyst loadings.[104] Both catalysts were sluggish, however, in the case of ketimine reduction. A Ru complex **62**, with a pincer type bis NHC ligand has been demonstrated to be capable of TH of both ketones and aldimine at a very low loading (0.015 mol%); however only one example was presented in the case of the latter (Scheme 1.38).[105] The high activity of the catalyst is probably due to the availability of two reactive sites and the stability provided by the chelating pincer type ligand.
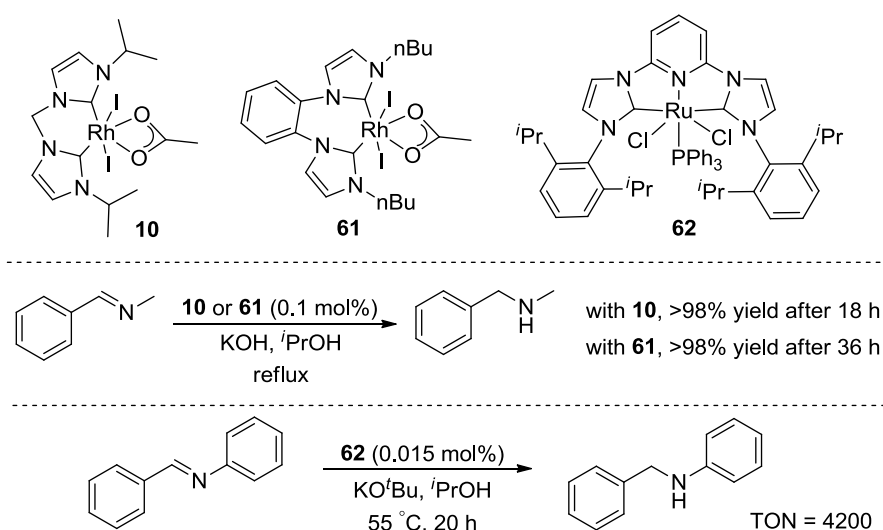
Scheme 1.38: Chelating bis-carbene complexes for TH of imines.

A mono NHC Ru(II) complex **63** has recently been demonstrated to be capable of both the hydrogenation and TH of aldimine in ^{i}PrOH, although higher catalyst loading was required for the latter (Scheme 1.39).[106] The Ir(III) complex **64** was found to be active under base free conditions; however a silver salt is necessary for the removal of the chlorides to activate the catalyst (3 equiv. AgOTf relative to **64**). Again only one example was described, where *N*-benzylideneaniline was reduced to its corresponding amine in ^{i}PrOH at S/C = 1000 (Scheme 1.39).[107] The combination of Ni(0) with NHC ligand also works effectively for the TH of imines, as

demonstrated by Schneider and co-workers.[108] A range of imines, including

ketimines were hydrogenated in the presence of Et_2CHONa as the hydrogen source.

Even though cyclic imines were also viable substrates, the reaction was not selective

for the substrates containing halogen groups, and heteroaromatic substrates were

found to poison the catalyst.
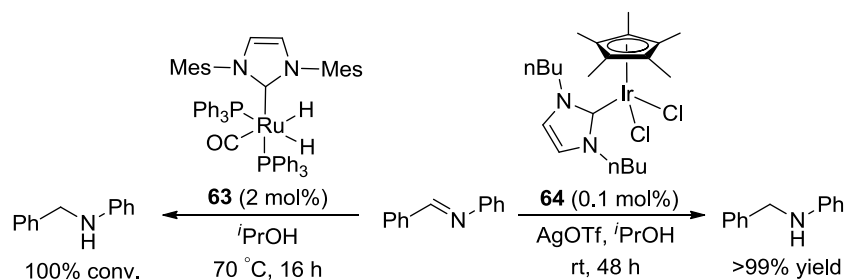
Scheme 1.39: Mono-carbene complexes for TH of imines.

1.8 ATH of imines

The first ATH of imines was reported by Noyori and co-workers using the half-

sandwich complex **34** as catalyst and their analogues **65-67**, some of which had been

previously reported for the enantioselective TH of ketones.[109] The reaction

proceeded at room temperature using F/T azeotrope as the hydrogen source. The TH

was found ineffective in ^{i}PrOH or other alcoholic media, unlike the analogous ketone

reductions. The use of aprotic polar co-solvents such as DMF, DMSO and MeCN

was beneficial for the reaction, as in the neat F/T the reduction preceded slowly.

Various imines, particularly the ones bearing alkyl and benzyl groups adjacent to the

C=N bond, were reduced with high yields and enantioselectivities (Scheme 1.40).

However, acyclic imines led to lower yields and enantioselectivities, possibly due to

their configurational instability (easy interconversion between E and Z isomers in

solution). Interestingly, under the conditions employed, the C=N bonds are reduced

more than 1000 times faster than the C=O bonds. Thus the chemoselectivity of this

reaction is superior to that observed with NaBH$_3$CN.[109] Later, Vedejs and co-workers applied this system for the reduction of aniline substituted 3,4-dihydroisoquinolines.[110] Even though moderate yields were obtained, the enantioselectivity was excellent.
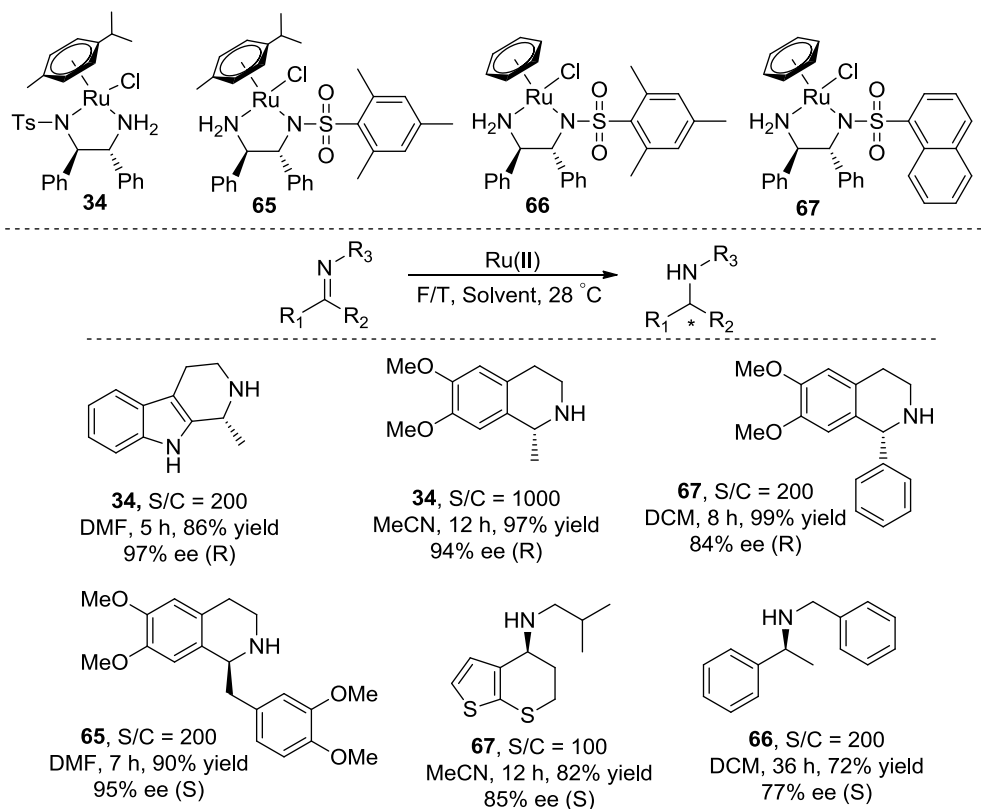
Scheme 1.40: ATH of imines using Ru(II) complexes.

Complex **34** is also effective for the TH of *N*-sulfonylimines to their corresponding sultams.[111] Ring-strained aziridines can be obtained from the ATH of arylazirines with the catalyst derived from the combination of [RuCl$_2$(*p*-cymene)]$_2$ and a chiral amino alcohol ligand, albeit with moderate enantioselectivities (Scheme 1.41).[112] The reaction was conducted in ^{i}PrOH, whereas the use of F/T led to the decomposition of azirine.
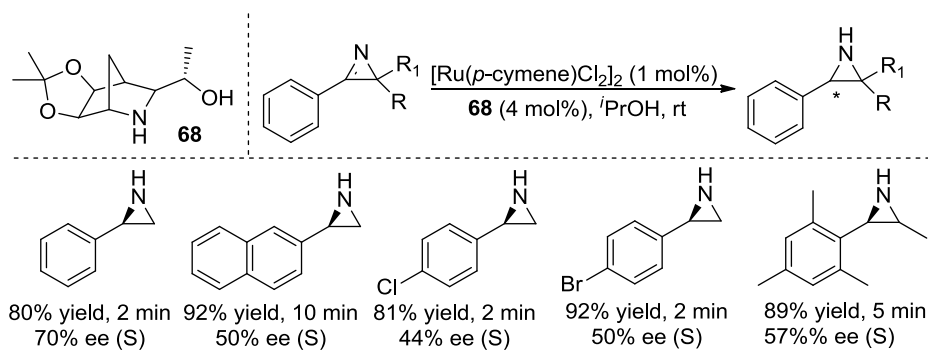
Scheme 1.41: ATH of aziridines.

Baker and co-workers demonstrated that complex **35**, which is isoelectronic with and analogous in structure to **34**, was more active for imine reduction with F/T azeotrope.[113] However, the enantioselectivities obtained are generally slightly lower than those observed with **34**, especially for acyclic imines derived from the condensation of acetophenone and benzylamine (Scheme 1.42). Blacker and co-workers have recently described that the ATH of acyclic imines bearing a sterically bulky *N*-diphenylphosphinoyl group led to the corresponding amines with a high degree of enantioselectivity (Scheme 1.42).[114] This superior enantiocontrol could be attributed to the bulkiness of the *N*-substituent, which may force the imine to exist predominantly in one geometrical isomer. In fact this transformation using **35** as catalyst has been accomplished on large scale too.[114] Still of further interest is that catalyst **35** has recently been applied to the reduction of *N*-sulfonyl ketimines and cyclic sulfamate imines, affording the corresponding amines with enantioselectivities up to 99% ee (Scheme 1.42).[115,116] The high selectivity observed could be attributed to the well defined E-geometry of *N*-sulfonyl imines.[115]
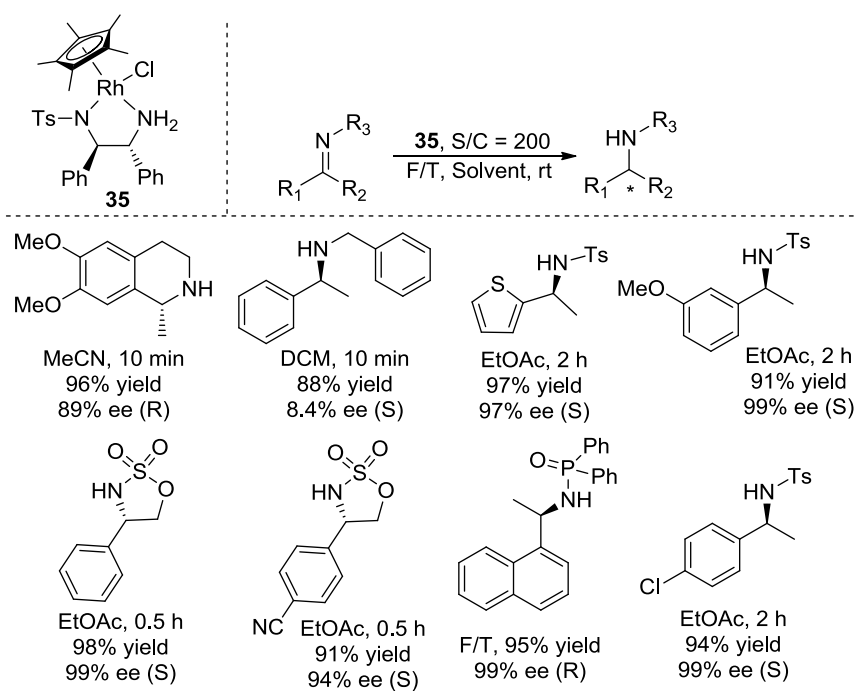
Scheme 1.42: ATH of imines using Rh(II) complex.

Compared with ketones, the mechanism for TH of imines with Noyori's Ru(II)-TsDPEN has been less explored. However, a few reports have suggested that the reaction with imines may proceed through a different pathway to that proposed for carbonyl reductions. For instance in a stoichiometric reaction conducted by Bäckvall and co-workers, complex **69**, derived from **34**, did not react with ketimines under neutral condition. However, the reaction took place rapidly in the presence of an acid.[117] Further studies conducted on 2-methylquinoline reduction also led to the same observations (Scheme 1.43).[118] These evidences are consistent with an ionic pathway, where the imine is activated by protonation prior to the hydride transfer and no coordination of the substrate to the metal is involved. Such hypothetical mechanism clearly differs from the well established concerted pathway followed by **34** for ketone reduction.[14]
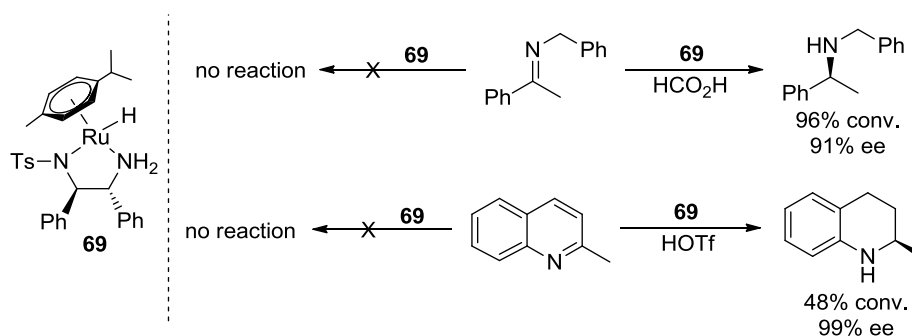
Scheme 1.43: Stoichiometric reduction with Ru-H.

ATH of imines can also be carried out in neat water. A range of cyclic imines were reduced with high yields and enantioselectivities with a catalyst prepared from [Ru(p-cymene)Cl$_2$]$_2$ and the water soluble diamine, **54**.[119] HCO$_2$Na was used as the hydrogen source and the presence of a surfactant, cetyltrimethylammonium bromide (CTAB), was found to be beneficial to the reaction, probably because it increased the solubility of the substrate in water. Interestingly, in some cases the enantioselectivities achieved were higher than those obtained in F/T (Scheme 1.44). Discouragingly, attempts to reduce acyclic imines in water resulted in complete decomposition of the starting imine. A simpler method using Noyori's catalyst **34** in the presence of CTAB and AgSbF$_6$ was also reported for cyclic imines reduction.[120] The protocol also permitted the reduction of polycyclic iminium salts, allowing an easy access to alkaloids such as harmicine and crispine. In addition, 3,4-dihydroisoquinolines bearing an aryl substituent at C1 position were also viable for reduction, albeit requiring a Lewis acid to activate the C=N bond towards the hydride attack (Scheme 1.45).
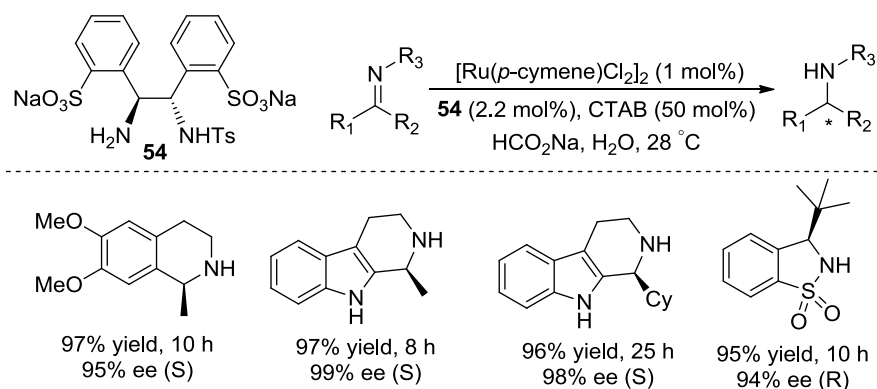
Scheme 1.44: ATH of imines in neat water.
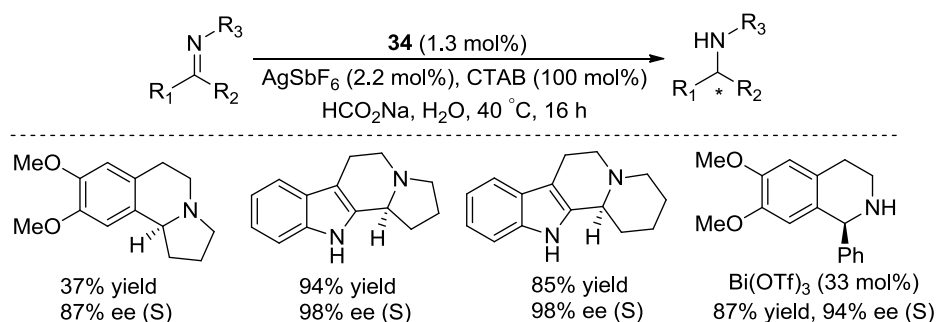
Scheme 1.45: ATH of cyclic and polycyclic iminium salts in water.

1.9 Immobilised catalysts

Catalyst separation is an important issue in homogeneous catalysis. Thus efforts have been made to immobilise these catalysts for recycling. Selected examples of immobilised ligands and catalysts are shown in Scheme 1.46. Besides being reusable, these ligands/catalysts have shown excellent activity and stereoinduction properties for ATH of ketones. The PEG-supported **70**, represents one of the most efficient catalyst for the ATH of ketones in water. A wide range of aromatic ketones including heteroaromatic examples can be reduced using HCO_2Na as the hydrogen source, with results comparable to those obtained with catalyst **34** (non-supported Ru-TsDPEN) under the same conditions. Remarkably, the catalyst could be recycled up to 14 times without compromising the enantioselectivity in the ATH of acetophenone in water (Scheme 1.47).[121]
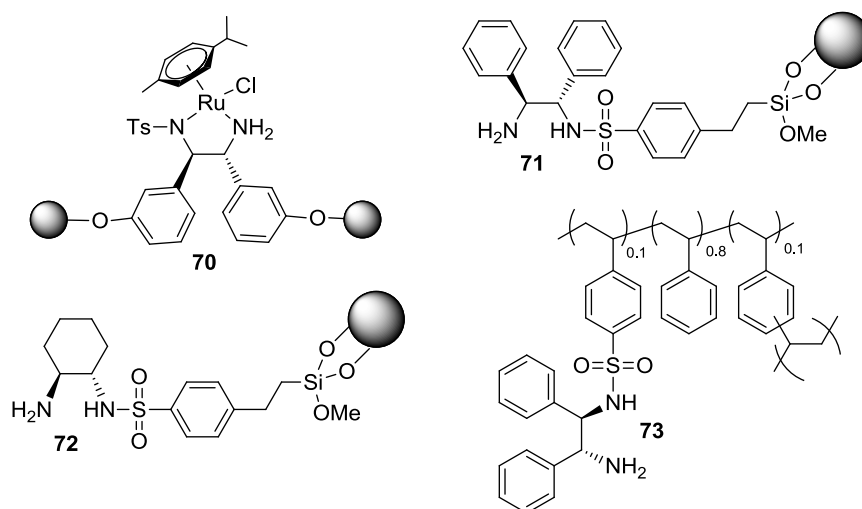
Scheme 1.46: Immobilised catalyst and ligands for ATH.
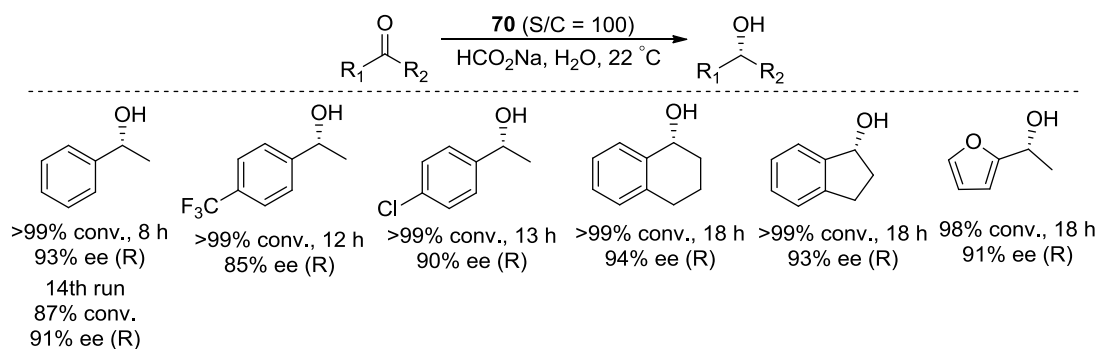
Scheme 1.47: ATH in water with supported Noyori-Ikariya catalyst.

Li and co-workers have recently reported magnetically recoverable catalysts based on chiral ligands such as TsDPEN and TsDAC attached to SiO_2 coated Fe_3O_4 nanoparticles (**71** and **72**, Scheme 1.46).[122] When such ligands were combined with [Cp*IrCl$_2$]$_2$ or [Cp*RhCl$_2$]$_2$, excellent activities and enantioselectivities (upto 99% ee) were obtained for the ATH of aromatic ketones in water. In addition to their high efficiency the main advantage of such catalysts is that they can be easily recovered by using a magnet. Thus neither filtration nor extraction is necessary. Moreover, the catalyst could be reused up to 10 times without losing its efficiency.

The crosslinked polystyrene immobilised ligand **73**, in combination with [Ru(*p*-cymene)Cl$_2$]$_2$, was effective in the ATH of *N*-benzyl imines in DCM using F/T as the

hydride source to give the corresponding amines in high yields and good enantioselectivities. The role of the metal was essential for achieving high efficiency as longer reaction times were required and lower enantioselectivities were obtained when [Ru(*p*-cymene)Cl$_2$]$_2$ was replaced with the isoelectronic [Cp*IrCl$_2$]$_2$ and [Cp*RhCl$_2$]$_2$ (Scheme 1.48).[123]

[Ru(*p*-cymene)Cl$_2$]$_2$	[Cp*RhCl$_2$]$_2$	[Cp*IrCl$_2$]$_2$
92% conv., 3h	>99% conv., 48 h	>99% conv., 24 h
88% ee (R)	29% ee (R)	77% ee (R)
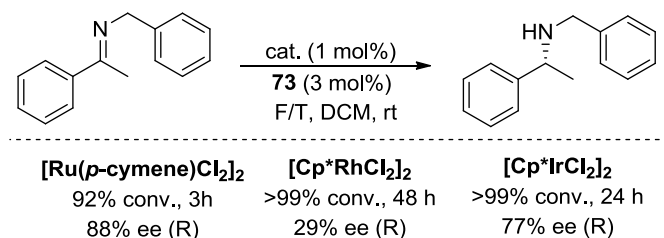
Scheme 1.48: ATH of *N*-benzyl imine with the crosslinked polystyrene immobilised catalysts.

1.10 Cheap metal-catalysed TH of carbonyls and imines

Parallel to the quest for more robust catalysts based on precious metals, chemists have also started to make progress with the use of cheaper metals, such as iron, cobalt and nickel.[108,124-126] Fe is cheaper, abundant and environmentally benign compared with other metals. However, the development of Fe based catalysts, in particular for TH, lags far behind.[2] Although, the potential of Fe in TH had been demonstrated as early as 1980's, significant progress has only been achieved in the past few years. Beller and co-workers reported a Fe/porphyrin system for the TH of ketones, using *i*PrOH as hydrogen source and Fe$_3$(CO)$_{12}$ as a suitable metal precursor. Both aromatic and aliphatic ketones were reduced with excellent yields; however the reduction of α-substituted aromatic ketones did not proceed under the reaction conditions (Scheme 1.49).[127]
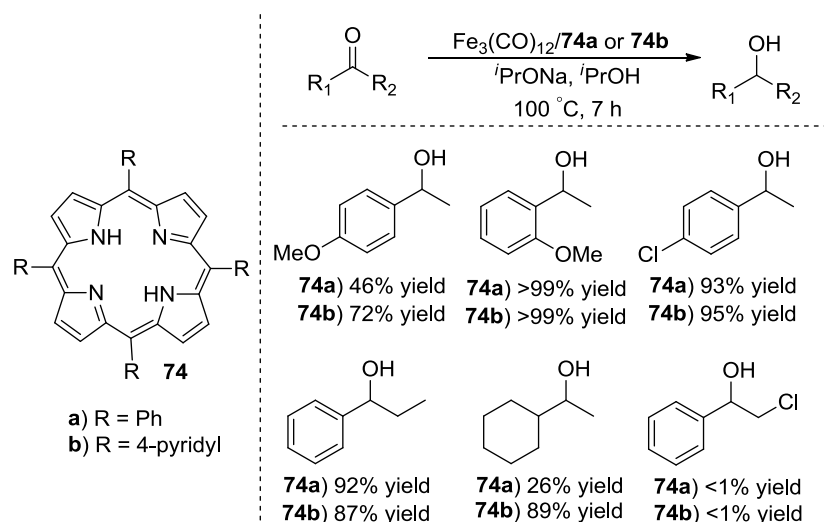
Scheme 1.49: Fe-prophyrin catalysed TH of ketones in ^{i}PrOH.

Casey and co-workers reported a bifunctional Fe complex **75**, which is analogous to the active Shvo's Ru catalyst (Scheme 1.50).[128] This catalyst displays high selectivity towards carbonyls and is active under both hydrogenation and TH conditions. It has been proposed that the hydrogenation of carbonyls with complex **75** proceeds by the concerted outer-sphere pathway in which both the hydride and the OH group contribute to the reduction (Scheme 1.50).[125]
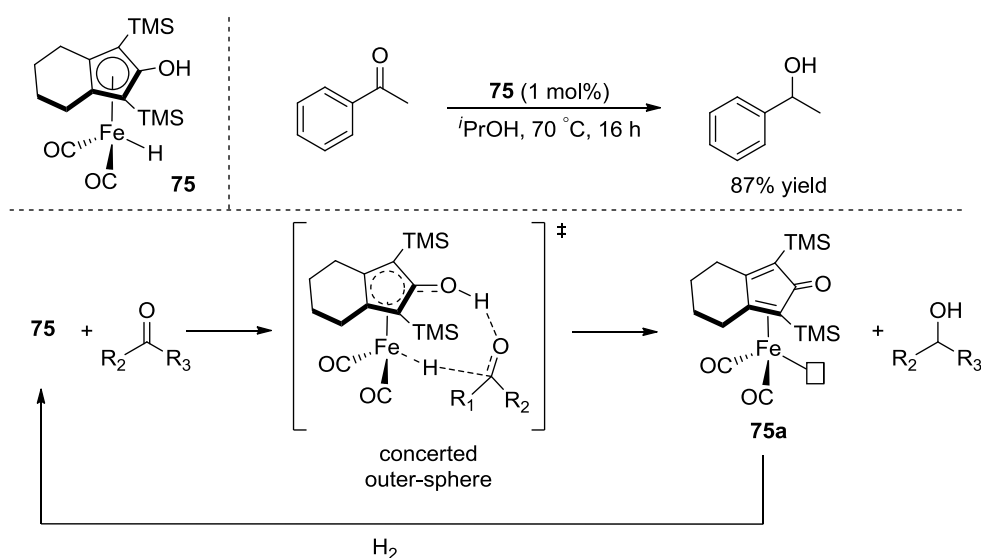
Scheme 1.50: Reduction of ketones with a bifunctional Fe complex and the proposed reaction pathway.

Morris and co-workers have developed a series of iron complexes with tetradentate PNNP ligands (Scheme 1.51).[129-131] Complex **76** represents the first well defined iron catalyst capable of ATH of aromatic ketones. Using only 0.5 mol% catalyst most of the aromatic ketones were fully reduced within half hour, although the enantioselectivities obtained were relatively low.[129] Complex **77**, prepared with a chiral diphenylethylenediamine backbone significantly improved the activity and selectivity, affording a TOF up to 4900 h^{-1} and enantioselectivities up to 99% for the TH of ketones.[130] The analogous **78** is highly enantioselective for the ATH of *N*-(diphenylphosphinoyl) and *N*-(p-tolylsulphonyl) ketimines (Scheme 1.51).[131] These iron complexes represent viable alternative to precious metal catalytic systems for TH; however they are still in their infancy. The catalytic activity and substrate scope have to be further improved in order to compete with the catalysts based on precious metals. In addition, their sensitivity to air and moisture makes them difficult for industrial applications.
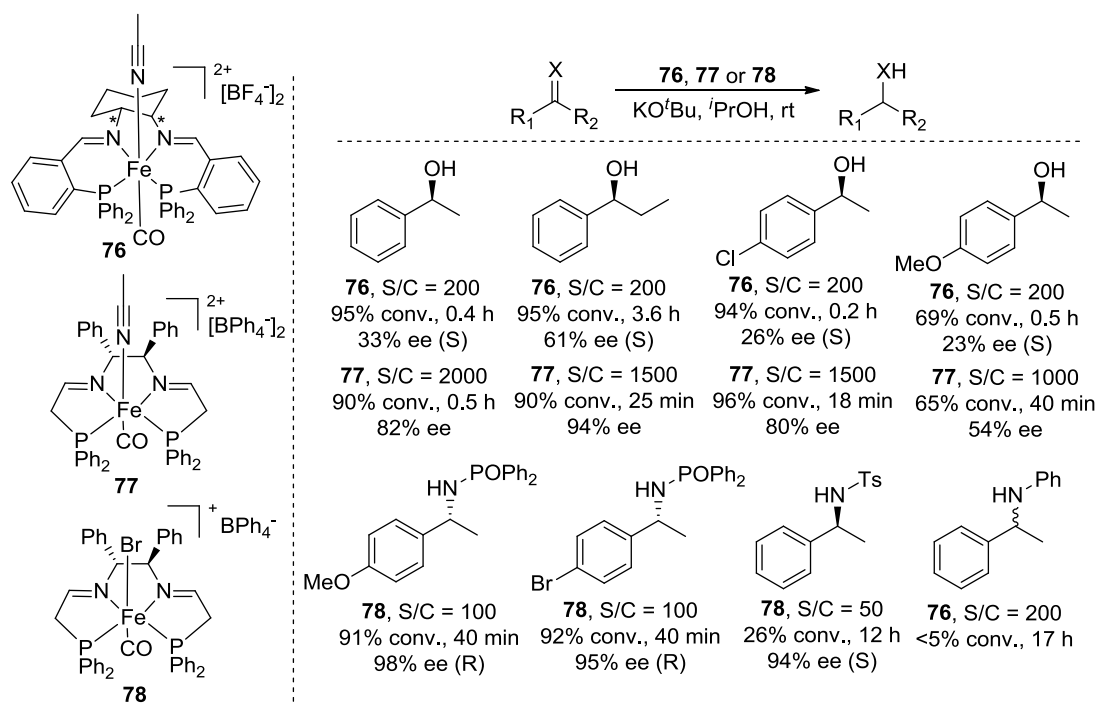
Scheme 1.51: Iron complexes for ATH.

1.11 Cyclometalated complexes

A complex containing a metal-carbon σ bond that is stabilised by at least one donor atom (such as N, O, C, P) is known as a cyclometalated complex (Scheme 1.52).[132] Cope and Siekman reported the first example of a cyclometalated reaction in 1965, when Pt and Pd dimer complexes were synthesised by reacting azobenzene with K_2PtCl_2 and $PdCl_2$, respectively, at room temperature in dioxane/water mixture (Scheme 1.53).[133]
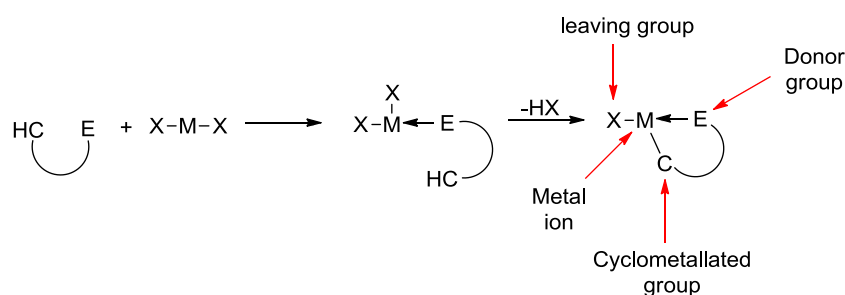
Scheme 1.52: General scheme for cyclometalation reaction.
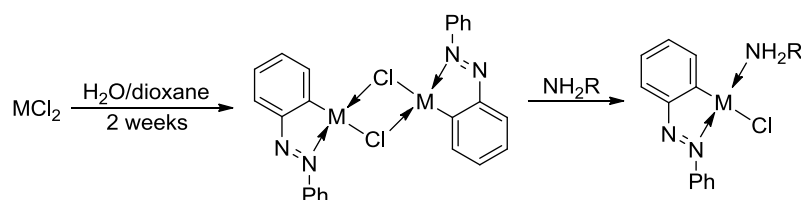
Scheme 1.53: First example of synthesis of a cyclometalated reaction.

Since then, a wide variety of organometallic complexes have been synthesised by cyclometalation. In particular, half-sandwich cyclometalated complexes based on Rh and Ir are probably two of the most popular classes of organometallic derivatives. Indeed, these metalacycles are particularly interesting because they are often encountered as intermediates in CH bond activation reactions promoted by $[Cp*MCl_2]_2$ (M = Rh, Ir) complexes.[132,134] These complexes have garnered much attention since the seminal reports of Davies[135] and Jones[136] on their reactivity

towards unsaturated organic molecules. Depending on the donor atom, metalacycles can be divided into four different classes: [Cp*M(C^C)Cl], [Cp*M(C^P)Cl], [Cp*M(C^O)Cl] and [Cp*M(C^N)Cl].

Recently, many catalytic applications have been found for half-sandwich cyclometalated complexes, such as racemisation of alcohols and amines,[137] hydroamination[138] and oxidation of water.[139] [Cp*Ir(C^N)Cl] complex **79**, reported by Feringa, de Vries and co-workers, is highly versatile for the racemisation of chiral alcohols, including aliphatic and β-halo alcohols in the presence of a base. Its analogous **80** is active in the racemisation of chiral amines. In the absence of a base, the racemisation of secondary and tertiary chiral amines was completed within few hours (Scheme 1.54).[137] The reaction was sluggish in the case of primary amines and led to the formation of dimers. Interestingly, complete racemisation of (S)-2-methyl-1,2,3,4-tetrahydroquinoline was also viable.
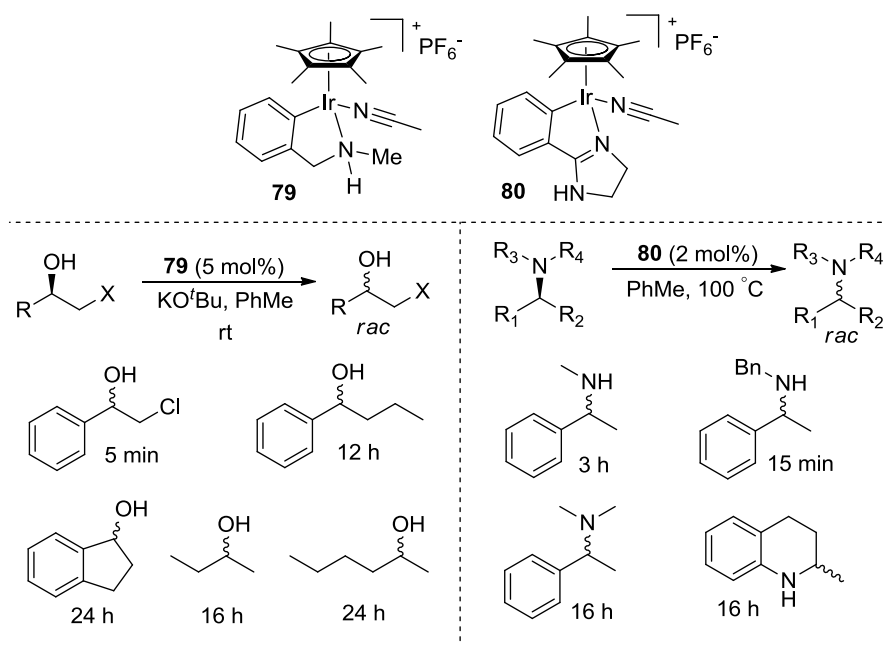
Scheme 1.54: Racemisation of alcohols and amines with complex **79** and **80**.

Jin and co-workers reported a new type of cyclometalated half-sandwich Ir and Rh complexes containing carboranylamidinate ligands. These complexes were prepared in a one pot reaction by in situ formation of a C-lithio-carboranylamidinate ligand, followed by the addition of [Cp*MCl$_2$]$_2$ (M = Rh, Ir) in THF at room temperature. Precatalyst **81** showed high activity for the polymerisation of norbornene in the presence of methylaluminoxane (MAO) as cocatalyst (Scheme 1.55).[140] Complexes **82-84**, synthesised by Crabtree and co-workers are active in number of reactions including *N*-alkylation of amines with alcohols and β-alkylation of secondary alcohols with primary alcohols (Scheme 1.55).[141]
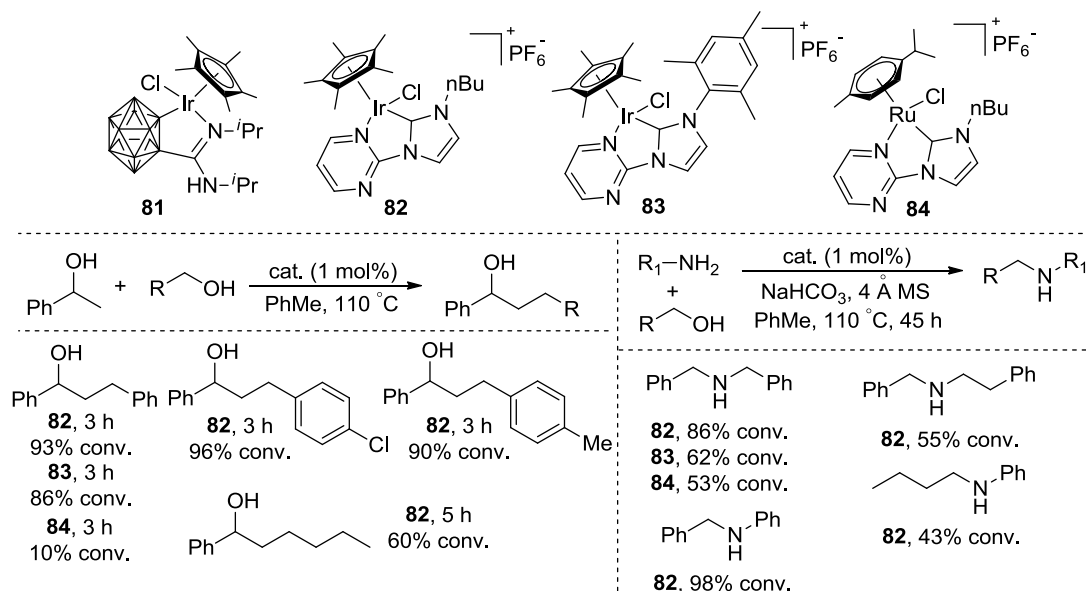
Scheme 1.55: Cyclometalated half-sandwich complexes and their application in catalysis.

Ikariya and co-workers have recently synthesised a new type of C-N chelate amido-Ir bifunctional complexes derived from benzylic amines (Scheme 1.56).[142] These complexes were subsequently explored as catalysts for the TH of acetophenone with *i*PrOH as the hydrogen source. Surprisingly, the activity of **88** was found to be much higher than that of **36** under the same conditions, clearly demonstrating the electronic properties that the C-N ligands impart on the metal/NH bifunctional

system. The enantioselectivities obtained with **88** were however moderate, compared with **36** (Scheme 1.56).[142]
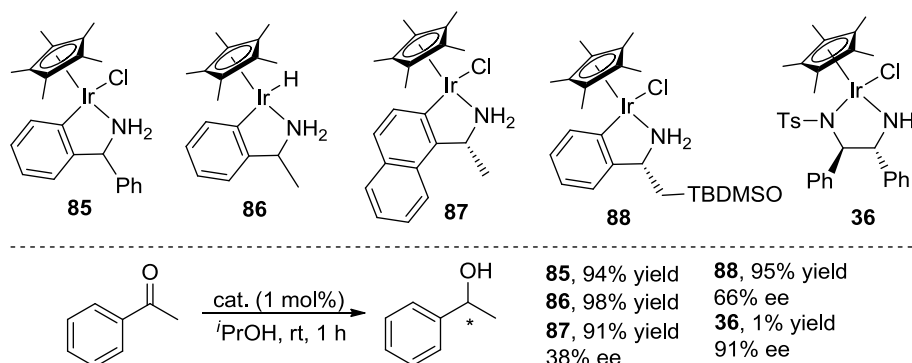
Scheme 1.56: Amino-Ir complexes and their reactivity towards the reduction of acetophenone.

Ikariya and co-workers also developed a β-NH based bifunctional catalyst **89**, bearing a C-N chelating protic pyrazole. Catalyst **89** promoted the intramolecular hydroamination of ω-alkenic primary amines to give the cyclisation product in the presence of KO^{t}Bu. A metal-ligand cooperating mechanism was proposed, where the reaction would involve the nucleophilic attack of the amine to the coordinated olefin which is assisted by the secondary interaction with the basic pyrazolato ligand. Subsequent proton transfer from the pyrazole nitrogen would cleave the Ir-C bond, releasing the cyclisation product and regenerating the catalyst (Scheme 1.57).[143]
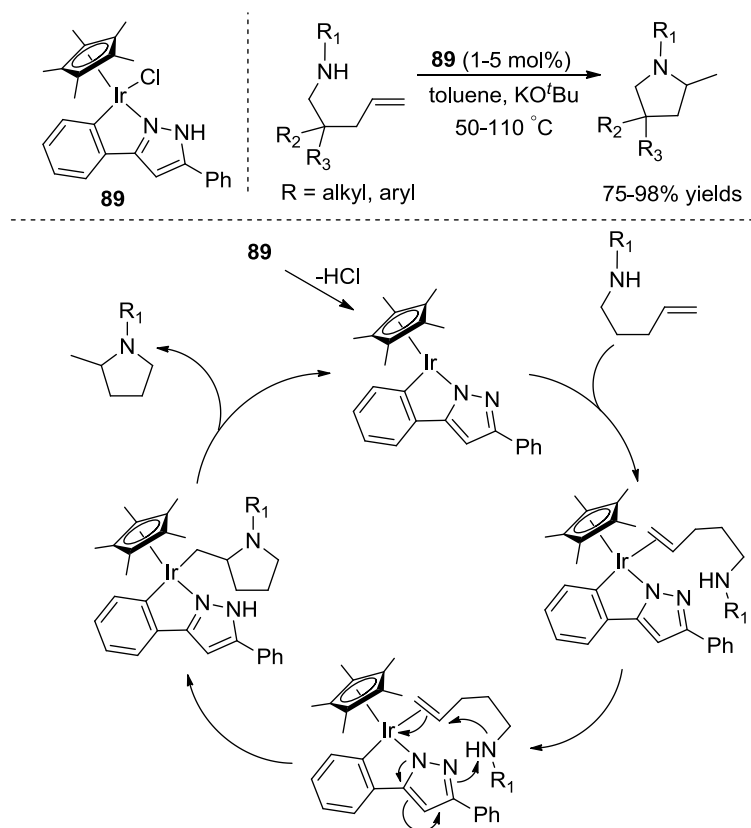
Scheme 1.57: Intramolecular hydroamination catalysed with **89**.

A recently reported Cr(CO)$_3$-bound iridacycle **90** can readily promote the tandem transformation of terminal alkynes into racemic *N*-phenylamines by hydroamination and hydrosilation-protodesilation reactions under mild conditions (Scheme 1.58).[144] Rh and Ir complexes, prepared with a pyrazolyl-NHC donor ligand and a [Cp*MCl$_2$]$_2$ (M = Rh, Ir) precursor, also promoted the hydroamination of internal alkynes to give indolyl and pyrolyl heterocycles in good yields. The Ir catalyst showed higher efficiency than its Rh counterpart and in both cases addition of the silver salt AgBF$_4$ was necessary to activate the catalysts (Scheme 1.59).[145]
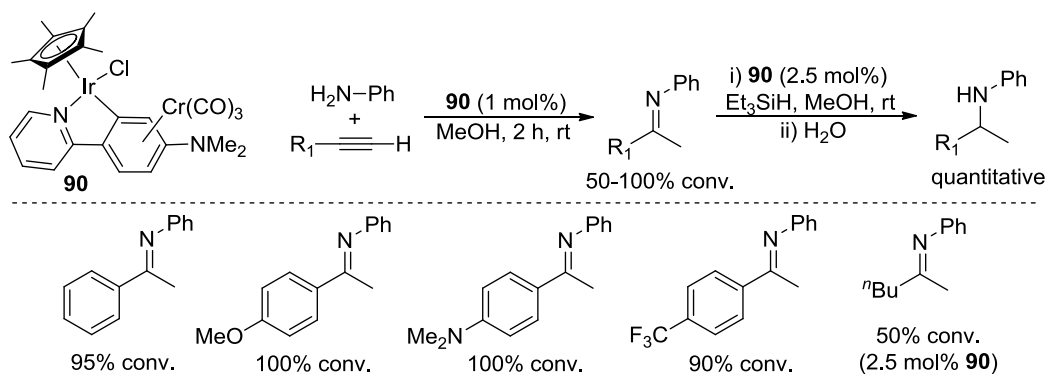
Scheme 1.58: Hydroamination and hydrosilation-protodesilation reactions.
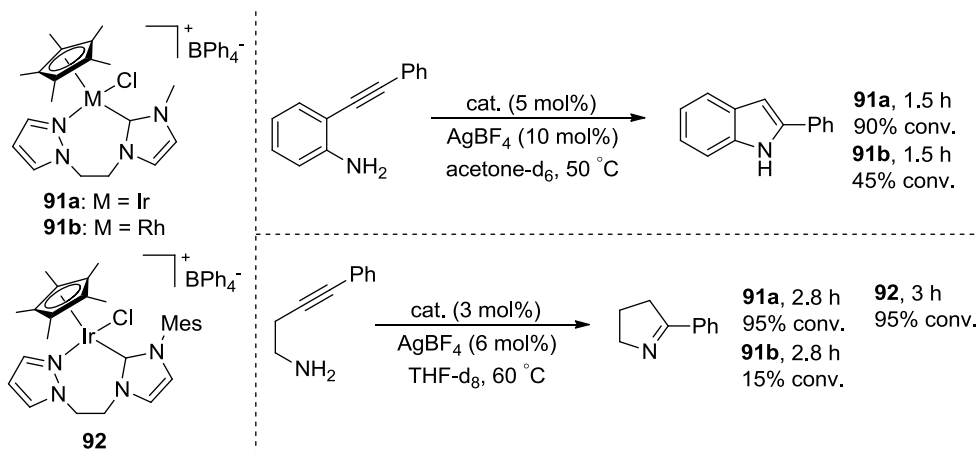
Scheme 1.59: Hydroamination of internal alkynes.

Recently Fujita, Yamaguchi and co-workers reported complex **93**, prepared by the NaOAc promoted cyclometalation of 6-phenyl-2-pyridone with $[Cp*IrCl_2]_2$. This complex exhibited high activity for the dehydrogenation of secondary alcohols. Under base free conditions, only a 0.1-0.5 mol% catalyst loading was sufficient for fully converting alcohols to their corresponding ketones. In comparison, a loading of 2 mol% was required for dehydrogenating primary alcohols. In the presence of a base moderate yields were achieved in most cases for their corresponding aldehydes. In both cases the reaction proceeded with the release of hydrogen gas (Scheme 1.60).[146]
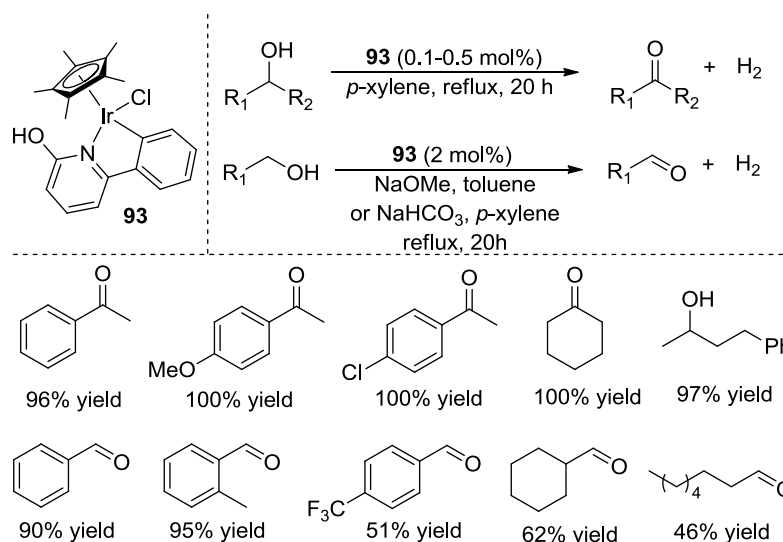
Scheme 1.60: Dehydrogenation of alcohols.

[Cp*M(C^C)Cl] and their role in catalysis have been mainly reported by the groups of Peris, Crabtree and Albrecht, where the C donor is usually a carbene (Scheme 1.61).[147-149] Albrecht and co-workers reported complexes **94** and **95**, prepared by the metalation of pyridinium functionalised triazolium salt with [Cp*IrCl$_2$]$_2$ in the presence of Ag$_2$O. These complexes were found to exhibit excellent activity in electrochemically induced water oxidation.[147] Later, Crabtree and co-workers synthesised Cp*Ir complex **96**, bearing a cyclometalated *N,N'*-diphenylimidazolyl ligand. This catalyst was also competent to serve as a precursor for water oxidation in the presence of ceric ammonium nitrate (CAN). The excellent activity observed with these catalysts may be due to the relative strong σ donating ability of the NHC ligand which probably stabilises the high valent form of Ir during the reaction.[148] Peris and co-workers have recently reported the six-membered iridacycle **97** that shown catalytic activity for the diboration of olefins providing high conversions (60-100%) for organodiboronate products.[149] In contrast, phosphorous and oxygen containing cyclometalated complexes of the formula [Cp*M(C^P)Cl] or [Cp*M(C^O)Cl] have mainly been investigated in CH activation studies.[132,150] It is

now evident that these half-sandwich cyclometalated complexes are emerging and beginning to realise their potential in catalysis. Although these catalysts have shown excellent activity in various reactions such as water oxidation and hydroamination, they are still relatively unexplored in TH or dehydrogenation reactions.
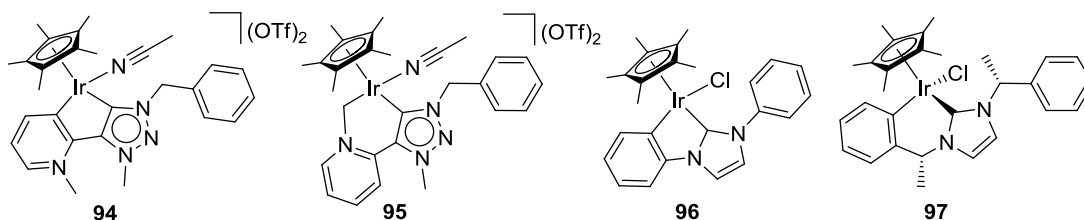
Scheme 1.61: Cyclometalated half-sandwich complexes with C donor atom.

1.12 Previous work within our group and the aim of this thesis

During study of TH of imines, our group serendipitously discovered the cyclometalated Cp*Ir(III) complexes bearing ketimine ligands (Iridicycles). These complexes show excellent chemoselectivity and activity for the TH of imines, achieving an initial TOF up to 1.9×10^4 h^{-1}. They are active for both aldimines and ketimines reduction, including aromatic and aliphatic ones. Moreover, these catalysts are also versatile in transfer hydrogenative reductive amination, capable of chemoselectively reducing a wide range of aromatic and aliphatic derivatives of ketones and amines (Scheme 1.62).[151] Analogous complexes bearing aldimine ligands have been reported by the groups of Davies and Jones; however they have not been reported for any catalytic reactions so far.
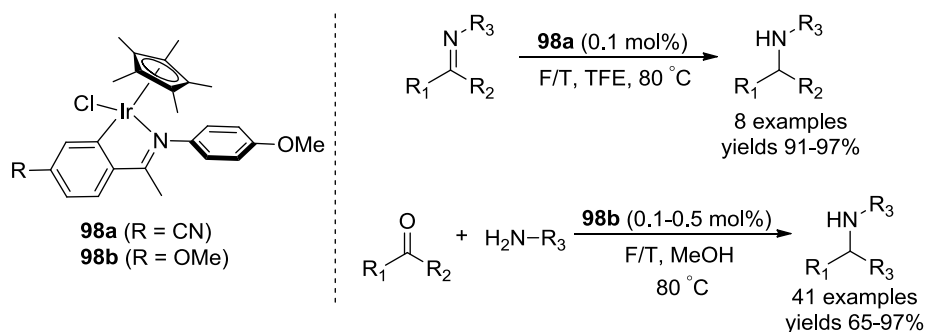
Scheme 1.62: Cyclometalated Cp*Ir(III) complexes bearing ketimine ligands.

The main aim of this thesis is to understand and explore the scope of these new types of cyclometalated ketimine complexes. In particular, they are easy to synthesise and their modular structure framework allows for the detailed and rational development of more active catalysts (Scheme 1.63). Our main target was the development of a single versatile catalyst that would be capable of transfer-hydrogenating various unsaturated bonds such as ketones, imines and *N*-heterocycles. Catalysts capable of selectively reducing multiple bonds under relatively mild conditions are rare, and their development would be of significant interest to the industry. Although transition metal catalysed TH of ketones and imines has been widely studied during the last 20 years, there is a continuous demand in developing new versatile catalysts that can achieve such reactions under greener conditions and using simple methodologies that can be easily scaled up. In particular, catalysts capable of chemoselectively reducing functionalised acyclic ketimines, α-substituted ketones and various *N*-heterocycles are highly desirable. Once a robust catalytic system has been established for hydrogenation, the next aim would be to explore such catalysts for dehydrogenation reactions. Catalytic acceptorless dehydrogenation (AD) of organic molecules has recently attracted great interest as it is clean, only liberating H_2, which is viewed as high energy clean fuel for the future. Therefore a single

catalyst capable of hydrogenate/dehydrogenate of organic molecules would be attractive and on demand.
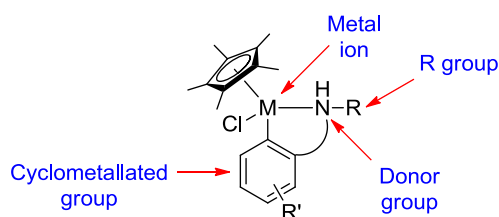
Scheme 1.63: Modular structure of cyclometalated Cp*MCl complexes.

During the course of my thesis, other members of our group have further expanded the scope of these cyclometalated Cp*Ir(III) complexes to numerous reactions. These include hydrogenation of imines[152] and *N*-heterocycles with H_2,[153] dehydrogenation of formic acid,[154] the TH of simple ketones and the RA of aldehydes, ketones and levulinic acid with various amines in water, which demonstrate the versatility of these catalysts (Scheme 1.64).[155-156]
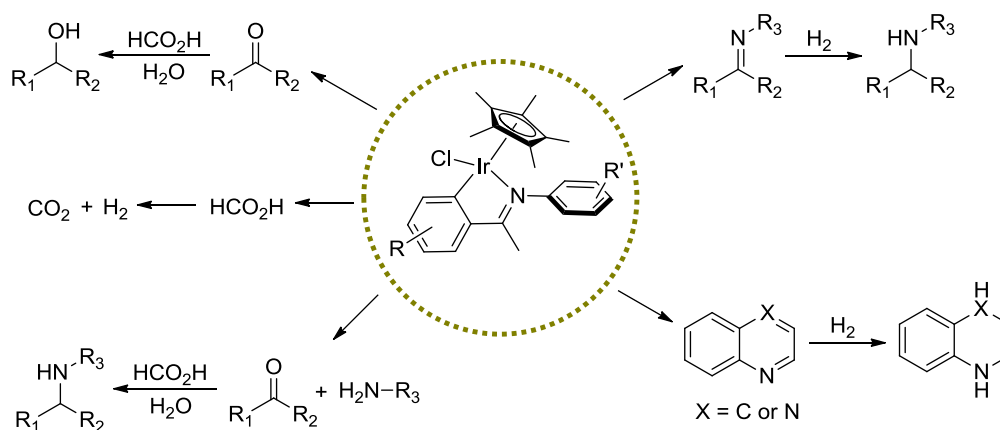
Scheme 1.64: Scope of cyclometalated Cp*Ir(III) complexes reported by our group.

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Chapter 2

Highly Efficient and Chemoselective Transfer Hydrogenation of Carbonyl Compounds in Water

2.1 Introduction

The reduction of α-substituted ketones to form β-functionalised secondary alcohols has drawn a lot of attention in the last two decades, due to the products being ubiquitous in naturally occurring and synthetic bioactive compounds.[1] For example, β-hydroxyethers have been used as biological probes and synthetic intermediates for molecular switches.[2,3] β-Aminoethers can be readily derived from β-hydroxyethers and are important precursors in the preparation of a wide variety of pharmaceutical compounds.[4] A further example is found in β-hydroxyamines, which have been demonstrated as building blocks in many synthetic methodologies, leading to various bioactive compounds, including, for example, medicines that affect the central nervous and respiratory systems (Scheme 2.1).[5] Of further interest are β-hydroxyhalo compounds, which have found use in the preparation of numerous compounds for pharmaceuticals, fine chemicals and functional materials.[2,6]

Propranolol
A sympathoplegic non-selective
β-blocker

Salbutamol
β₂-adrenergic receptor
agonist

Carvedilol
β₁,β₂-blocker and α₁ blocker
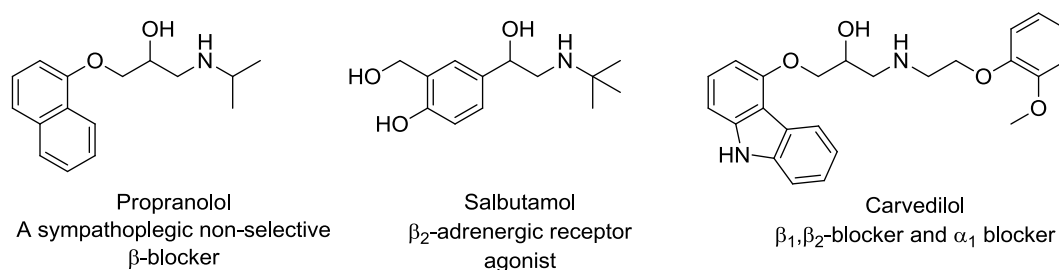
Scheme 2.1: Examples of drugs containing β-functionalised secondary alcohols.

Given the versatility of the α-substituted ketones, a number of reagents and methods have been developed for their selective reduction, especially the asymmetric version.[6-9] However, few catalysts are known that are capable of selective transfer hydrogenation (TH) of a wide range of α-substituted ketones.[7] In addition, most of the reactions are conducted in organic solvents, which generates unwanted waste. One way of minimising the environmental impact caused by the use of organic

solvents would be the use of water as the reaction medium. It is cheap, benign and readily available. However, the reduction of α-substituted ketones with TH in water is challenging, because the substrates are usually acid and/or base sensitive.[6] Thus, there is a need for a catalyst that is versatile, active and chemoselective for the TH of α-substituted ketones with diverse properties to form the corresponding secondary alcohols. Herein, we report that the cyclometalated iridium complexes are also highly efficient and chemoselective for the TH of various α-substituted ketones, keto esters and α,β-unsaturated aldehydes in water (Scheme 2.2).
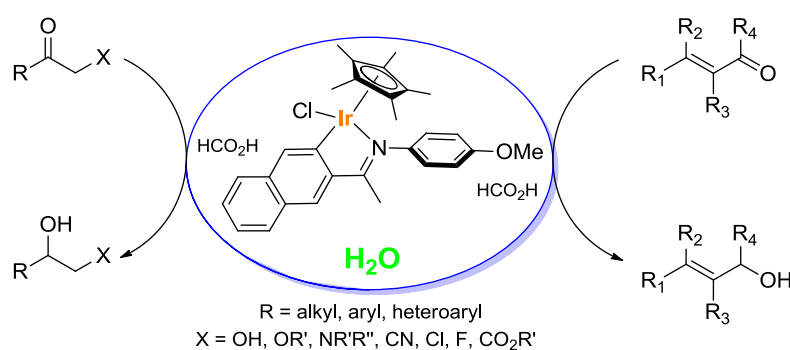
Scheme 2.2: Transfer hydrogenation of α-substituted ketones and α,β-unsaturated carbonyls under aqueous conditions.

2.2 Results and discussion

2.2.1 Optimisation of reaction conditions

A series of cyclometalated iridium complexes, iridicycles **C1-C6** (Scheme 2.3), were firstly synthesised according to the reported procedures.[10] To investigate the efficacy of the iridicycles in reducing α-substituted ketones, the synthesised complexes **C1-C6** were screened, by using 1-phenoxypropan-2-one as the benchmark substrate at a substrate/catalyst (S/C) ratio of 1000. As shown in Table 2.1, all of these six precatalysts afforded good to excellent conversions for the TH in water at pH 4.5 in a short reaction time of 0.5 h (Table 2.1, Entries 3-8). Without the

imino ligand, the [Cp*IrCl₂]₂ is inactive (Table 2.1, entry 2). As expected, no

reaction took place without a catalyst (Table 2.1, entry 1). It appears that the more

electronic donation of the imino ligand to the iridium, the faster the reduction in

water. This is seen by comparing the TH by using **C2** with those by using **C1** and

C3. The highly conjugated **C4** and **C6** gave even higher conversions, although the

anthracenyl-containing **C5** was surprisingly less active. In particular, the

phenanthrenyl-ligated **C6** afforded almost full conversion in 0.5 h (Table 2.1, entry

8), with higher S/C ratios being feasible. Thus, at an S/C of 10000, the TH was

approximately complete in 2 h (Table 2.1, entry 9), and the catalyst delivered a

conversion of 82% in 20 h at a much higher S/C of 50000 (Table 2.1, entry 11).
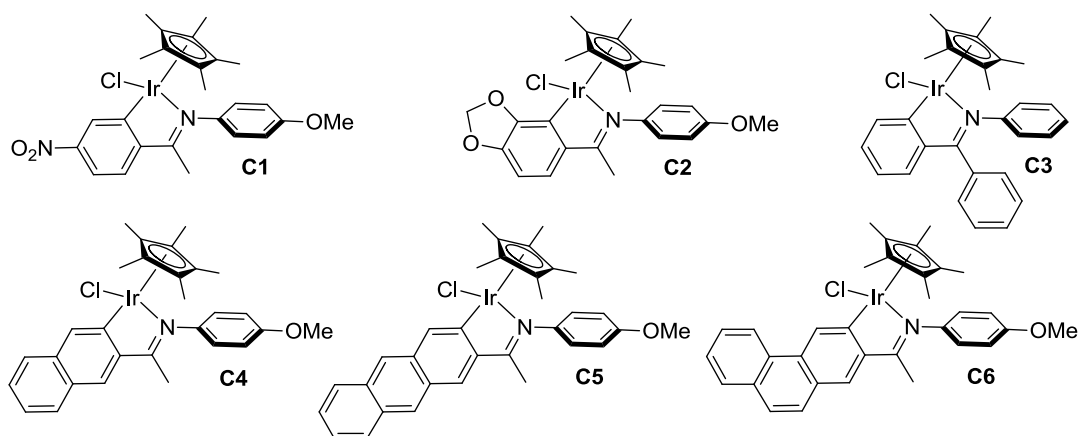
Scheme 2.3: Iridicycle catalysts examined for TH in water.

The TH reactions above were carried out at pH 4.5. Screening of the reaction

conditions with **C4** revealed that the solution pH value plays a critical role in the

reduction. Thus, the TH occurred only within a certain window of acidic conditions

(pH 3.0-5.0 for greater than 50% conversions), with the optimal pH value being 4.5

(Figure 2.1), which was adopted for subsequent studies.

Table 2.1: Screening of catalysts for the TH of 1-phenoxypropan-2-one in water
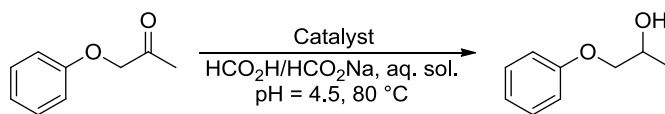
Entry[a]	Catalyst	S/C[b]	Time (h)	Conv. (%)[c]
1	-	-	0.5	n.r.
2	[Cp*IrCl$_2$]$_2$	1000	0.5	<2
3	**C1**	1000	0.5	88
4	**C2**	1000	0.5	96
5	**C3**	1000	0.5	59
6	**C4**	1000	0.5	98
7	**C5**	1000	0.5	75
8	**C6**	1000	0.5	>99
9	**C6**	10000	2	99
10	**C6**	20000	6	96
11	**C6**	50000	20	82

[a] Reaction conditions: ketone (2.5 mmol), catalyst (0.01 mol%), HCO$_2$H/HCO$_2$Na aqueous solution (pH = 4.5; 3mL; 14.0 mmol of HCO$_2$H and 29.4 mmol of HCO$_2$Na in 2.8 mL of H$_2$O), 80 °C, stirred in a carousel tube for 0.5 h. [b] S/C = substrate/catalyst molar ratio. [c] Conversion determined by ^{1}H-NMR spectroscopy; n.r. = no reaction.
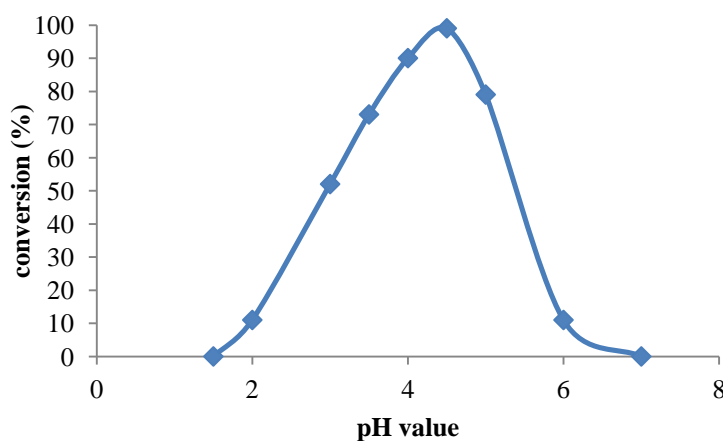
Figure 2.1: The effect of pH value on the TH of 1-phenoxypropan-2-one.

This value is higher than that required for the TH of acetophenone using an analogous catalyst (pH 3.5),[11] which presumably reflects the more electron-rich

ketone being reduced in this study. However, pH 4.5 is lower than that used with the Noyori-Ikariya M-TsDPEN catalysts (M = Ru, Rh or Ir), for which neutral to slightly basic reaction conditions were found to be optimal.[12,13] As explained before,[11,14] the iridicycle catalyst is not capable of activating the ketone through its ligands, which renders activation through an acidic medium necessary, whereas the Noyori-Ikariya type catalysts are able to readily hydrogenate a ketone by virtue of hydrogen bonding between the NH proton of the ligand and the substrate.[12,15]

2.2.2 TH of β-keto ethers in water
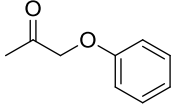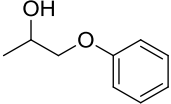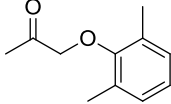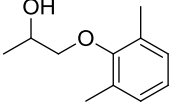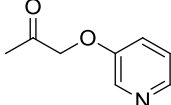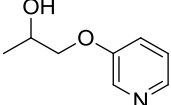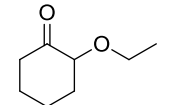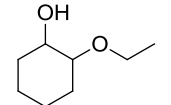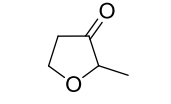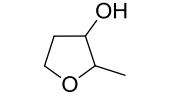
With the optimised reaction conditions in hand, the substrate scope of the reduction was explored. Firstly, a wide range of β-keto ethers were effectively and chemoselectively reduced to the desired β-hydroxy ethers. As shown in Table 2.2, the **C6** catalyst is capable of reducing all type of β-keto ethers. Keto ethers featuring either aromatic or aliphatic units and aromatic, aliphatic, heterocyclic and fluoronated ethers were all viable and furnishing excellent yields at the S/C ratio of 10000 and 2.5 mmol substrate scale. Furthermore, for β-aryl ketone aryl ethers, neither electron-withdrawing substituents nor electron-donating groups on the aryl ring of either ketones or ethers significantly affected the productivity and selectivity of the catalyst. Thus, TH of **1a** and **1b** afforded similar yields (Table 2.2, entry 1 versus 2) and the reductions of **1f**, **1g** and **1h** all provided excellent yields (Table 2.2, entries 6-8). The sterically bulky substituent on the aryl ether **1d** also has little effect (Table 2.2, entry 4). More importantly, substrates containing a hexafluoroisopropyl group (**1i**) and a heptafluorobutoxy group (**1j**) can be reduced smoothly with 87% and 86% yields to afford highly demanding intermediates for pharmaceuticals and fine chemicals.[16,17] To the best of our knowledge, there is no literature report for the TH of these substrates previously. The aliphatic substrates **1l-1o** can also be

translated into the desired products smoothly with good to excellent yields (Table 2.2, entries 12-15).

Table 2.2: TH of β-keto ethers with **C6** in water

Entry[a]	Substrate	Product		Yield (%)[b]
1			**2a**	93
2			**2b**	91
3			**2c**	97
4			**2d**	95
5			**2e**	89
6			**2f**	97
7			**2g**	97
8			**2h**	93
9			**2i**	87
10			**2j**	86

11			**2k**	98
12			**2l**	97
13			**2m**	91
14[c]			**2n**	90
15[d]			**2o**	87

[a] Reaction conditions: ketone (2.5 mmol), **C6** (0.01 mol%), HCO_2H/HCO_2Na aqueous solution (pH = 4.5; 3 mL; 14.0 mmol of HCO_2H and 29.4 mmol of HCO_2Na in 2.8 mL of H_2O), 80 °C, stirred in a carousel tube for 14 h. [b] Yield of isolated product. [c] 42:58 (*trans*:*cis*). [d] 52:48 (*trans*:*cis*)

2.2.3 TH of α-substituted ketones

α-Halo, hydroxy, nitrile-substituted ketones are more challenging to reduce due to the ease of dissociation of these α-functional groups under acidic and/or basic conditions.[18] However, the current reduction system overcomes these challenges. By modification of the reaction conditions, the desired products were obtained with excellent isolated yields for almost all of these problematic ketones. As shown in Table 2.3, with the cyclometalated complex **C4**, which is slightly more active than **C6**, α-hydroxyacetophenone (**3a**) was converted to a 1,3-diol with 93% yield at an S/C ratio of 1000 (Table 2.3, entry 1), and α-chloroacetophenone (**3b**) was reduced to the α-chlorophenylethanol with 94% isolated yield (Table 2.3, entry 2). For the substrates **3c** and **3d**, which bear an electron-donating and -withdrawing group, respectively, the reduction afforded almost identical yields (Table 2.3, entries 3 and 4). Moreover, α,α-dichloroacetophenone (**3e**) was successfully reduced to α,α-dichlorophenylethanol with 87% yield (Table 2.3, entry 5), albeit at a lower S/C ratio

of 200. The reduction of α-chloroketones is often problematic because they are vulnerable to dechlorination under TH conditions.[18,19] The α-fluoroketones were also viable for this reduction system. Thus, excellent yields were obtained for the TH of α-fluoro- and α,α,α-trifluoroacetophenone (**3f** and **3g**, respectively; Table 2.3, entries 6 and 7). Equally, the α-nitrile ketones (**3h**-**3l**) were converted into the corresponding secondary alcohols with excellent yields, including examples of heterocyclic ketones (Table 2.3, entries 8-12). Still further, the catalytic system was successfully applied to α-acyloxy, α-morpholino, and α-semialdehyde ketones (**3m**-**3p**; Table 2.3, entries 13-16), with the α-functional groups tolerated and high yields obtained for all of the desired products. Selective reduction of analogues of **3m** by TH is difficult, because the acyl group is prone to migration by hydrolysis.[20] Indeed, there are only a few literature reports describing the TH of this class of substrates; however, the catalyst loadings are high and the yields are relatively low due to the aforementioned problem.[21] To the best of our knowledge, this is the first time that a homogeneous catalyst has been reported for the TH of α-piperidyl and α-semialdehyde ketones.
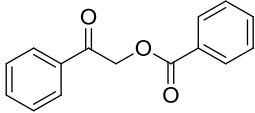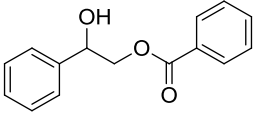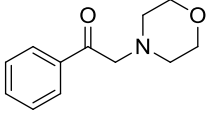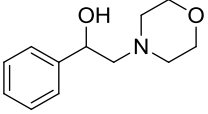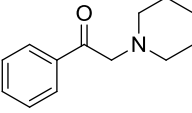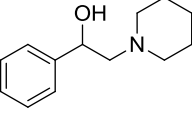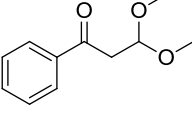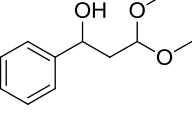
Unfortunately, the TH of α-bromoacetophenone is not selective under the present condition. The liability of α-bromo group meant that a range of products were obtained (Scheme 2.4). **3q** underwent debromonation to give **3r**, which in turn is further reduced to **4r**. Displacement of α-bromo group by formate ion gave **3s**, which was also further reduced to **4s** to some degree. However, despite the unwanted by-products, the desired **4q** was obtained in a moderate yield.

Table 2.3: TH of α-substituted ketones with **C4** in water

Entry[a]	Substrate	Product		Yield (%)[b]
1			**4a**	93
2			**4b**	94
3			**4c**	92
4			**4d**	93
5[c]			**4e**	87
6			**4f**	95
7			**4g**	96
8			**4h**	90
9			**4i**	92
10			**4j**	91
11			**4k**	89
12			**4l**	90

13			**4m**	96
14			**4n**	88
15[d]			**4o**	86
16			**4p**	94

[a] Reaction conditions: ketone (2.5 mmol), **C4** (0.1 mol%), HCO$_2$H/HCO$_2$Na aqueous solution (pH = 4.5; 3 mL; 14.0 mmol of HCO$_2$H and 29.4 mmol of HCO$_2$Na in 2.8 mL of H$_2$O, 80 °C, stirred in a carousel tube for 18 h. [b] Yield of isolated product. [c] S/C = 200. [d] Yield determined by ^{1}H-NMR spectroscopy.
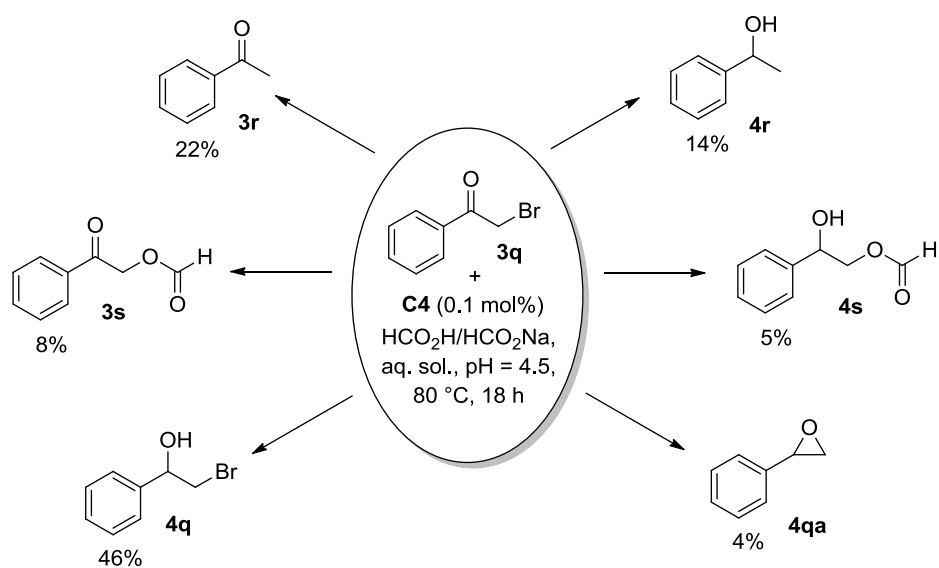
Scheme 2.4: TH of α-bromoacetophenone under present conditions.

2.2.4 TH of α- and β-keto esters

To showcase the broader utility of the catalytic system, **C4** was also applied to the reduction of keto esters.[22] Both aromatic and aliphatic β-keto esters were reduced to afford the corresponding alcohols with excellent yields under the catalysis of 0.1 mol% of **C4** (Table 2.4). Likewise, the analogous α-keto esters were also reduced with ease, which demonstrates the versatility of the cyclometalated iridium catalyst. Products **6e** and **8c** are known to be important intermediates for medicines and fine chemicals.[17,23] Again, there appears to be no correlation between the electron properties of the substituents on the phenyl ring and the yield obtained under the conditions employed (Table 2.4, entries 1-4).

Table 2.4: TH of α- and β-keto esters with **C4** in water

Reaction scheme: **5a-e** and **7a-c** → **6a-e** and **8a-c**

C4 (0.1 mol%)
HCO$_2$H/HCO$_2$Na, aq. sol.
pH = 4.5, 80 °C, 14 h
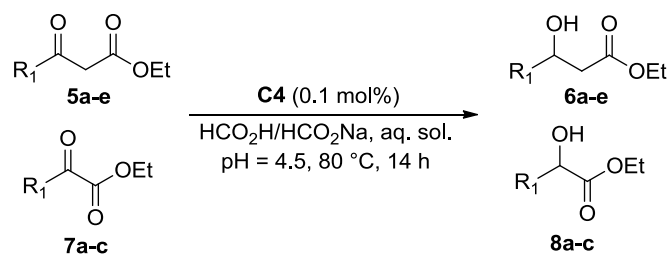
Entry[a]	Substrate	Product		Yield (%)[b]
1			**6a**	94
2			**6b**	91
3			**6c**	94
4			**6d**	92
5			**6e**	95
6			**8a**	96
7[c]			**8b**	91
8			**8c**	92

[a] Reaction conditions: keto ester (2.5 mmol), **C4** (0.1 mol%), HCO$_2$H/HCO$_2$Na aqueous solution (pH = 4.5; 3 mL; 14.0 mmol of HCO$_2$H and 29.4 mmol of HCO$_2$Na in 2.8 mL of H$_2$O), 80 °C, stirred in a carousel tube for 14 h. [b] Yield of isolated product. [c] Yield determined by ^{1}H-NMR spectroscopy.

2.2.5 TH of α,β-unsaturated aldehydes

The highly efficient and chemoselective reduction of α,β-unsaturated ketones and aldehydes has been a research topic in the last several decades.[24,25] Mixtures of products are frequently obtained, because many catalysts reduce both C=O and C=C bonds rather than exclusively either the C=O or C=C bond. Hence, selectivity is still an issue.[25] Therefore, we subsequently examined these substrates with the current reduction system. Disappointedly, **C4** was not chemoselective for the reduction of α,β-unsaturated ketones and catalysed the reduction of both the C=C and C=O bonds (Scheme 2.5).
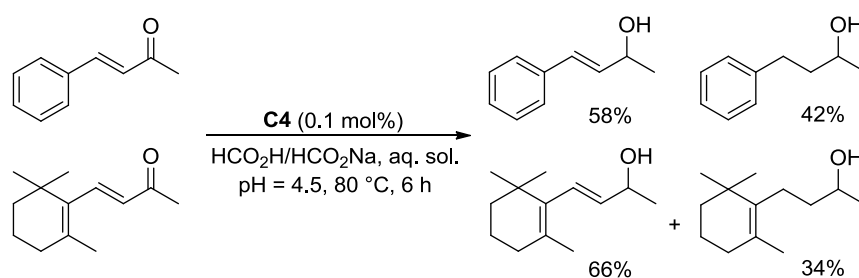
Scheme 2.5: Attempted chemoselective TH of α,β-unsaturated ketones in water.

Catalyst **C4** is, however, highly chemoselective in the reduction of α,β-unsaturated aldehydes to afford only unsaturated alcohols (Table 2.5). In the case of the aromatic α,β-unsaturated aldehydes, almost identical yields of allylic alcohols were obtained for those substrates that are relatively sterically demanding (**9b**, **9c** and **9f**; Table 2.5, entries 2, 3 and 6), or that bear electron-withdrawing or -donating groups substituted on the phenyl ring (**9d** versus **9e**; Table 2.5, entry 4 versus 5). Good yields were also achieved for the TH of aliphatic α,β-unsaturated aldehydes (Table 2.5, entries, 7-9). The chemoselectivity observed with the α,β-unsaturated aldehydes may stem from the aldehyde group being easier to reduce than a ketone. Once reduced, the C=C bond can no longer be hydrogenated by the catalyst.

Table 2.5: TH of α,β-unsaturated aldehydes with **C4** in water
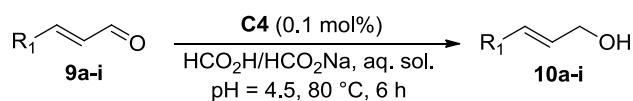
Entry[a]	Substrate	Product		Yield (%)[b]
1			**10a**	95
2			**10b**	91
3			**10c**	90
4			**10d**	88
5			**10e**	96
6			**10f**	94
7[c]			**10g**	92
8			**10h**	78
9			**10i**	85

[a] Reaction conditions: aldehyde (2.5 mmol), **C4** (0.1 mol%), HCO$_2$H/HCO$_2$Na aqueous solution (pH = 4.5; 3 mL; 14.0 mmol of HCO$_2$H and 29.4 mmol of HCO$_2$Na in 2.8 mL of H$_2$O), stirred in a carousel tube for 6 h. [b] Yield of isolated product. [c] *E/Z* = 52:48.

2.2.6 Mechanistic considerations

A plausible mechanism is proposed for the TH in question in Scheme 2.6. Catalyst **C** is first converted into the formate complex **I** in the presence of formate.[26] Decarboxylation of **I** leads to the active, but coordinatively saturated, hydride species **II**.[27] The ketone substrate, activated by the hydroxonium ion under the acidic conditions employed,[11] is then reduced through direct hydride transfer from **II** without ketone coordination to the metal centre, that is, by the ionic or outer-

sphere mechanism.[28] In previous studies, our group have shown that hydride can be easily generated from an iridicycle and formate and transferred to protonated imines.[27]
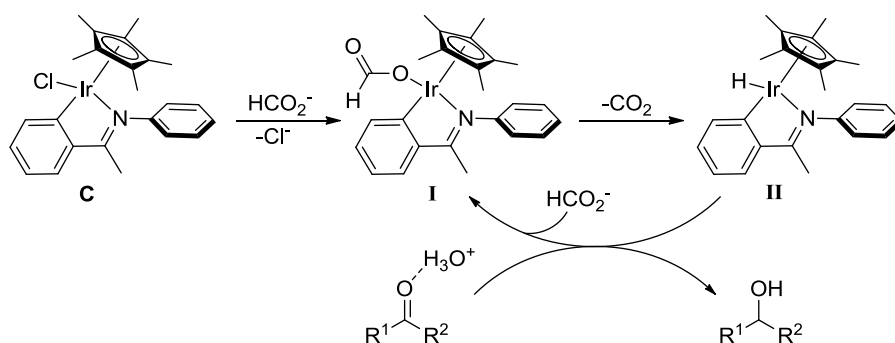
Scheme 2.6: Proposed mechanism for the TH by an iridicycle.

2.3 Conclusion

In summary, this chapter has demonstrated that cyclometalated iridium complexes, iridicycles, catalyse the highly efficient and chemoselective TH of a wide variety of carbonyl groups, including a series of α-substituted ketones, α- and β-ketoesters, and α,β-unsaturated aldehydes. With the reduction feasible in water at S/C ratios of 1000-50000, the current protocol provides a practical, easy and efficient synthesis of β-functionalised secondary alcohols, especially β-hydroxyethers, β-hydroxyamines and β-hydroxyhalo compounds, which are bioactive and/or of value for the synthesis of pharmaceuticals, fine chemicals, perfumes and agrochemicals.

2.4 Experimental

2.4.1 General information

Unless otherwise specified, all reagents were commercially purchased and used without further purification. Deionised water was used for the reactions. NMR spectra were recorded on a Bruker 400 MHz or 250 MHz NMR spectrometer with

TMS as the internal standard. HRMS were obtained by chemical ionisation (CI) at the Department of Chemistry, University of Liverpool or by (FAB) at the EPSRC National Mass Spectrometry Service Centre at Swansea University. Elemental analyses were performed by the Elemental Analysis Service of Department of Chemistry. β-keto ethers (**1a-j and 1l-m**) were prepared according to the literature.[29] Pentamethylcyclopentadienyliridium(III) chloride, dimer [Cp*IrCl$_2$]$_2$ was purchased from Strem Chemicals Inc. Solution of various pH value was prepared by a reported method and measured using a pH meter at 20 °C.[11] ^{1}H-NMR, ^{13}C-NMR and HRMS were collected for all the products, and the NMR data are consistent with the reported literature.

2.4.2 General procedure for the preparation of imine ligands

Ketone (5.0 mmol) and amine (5.5 mmol) were dissolved in toluene (80 mL). NaHCO$_3$ (420 mg, 5 mmol) and 4Å MS (1.2 g) were then added. The mixture was stirred under reflux for 24 h, then cooled to room temperature and filtered through celite. The solvent was removed under vacuum and the resulting crude mixture was crystallised using hexane/DCM to give the corresponding imine.[30]

2.4.3 General procedure for the preparation of cyclometalated iridium complexes

[Cp*IrCl$_2$]$_2$ (200 mg, 0.25 mmol), imine ligand (0.55 mmol), NaOAc (206 mg, 2.5 mmol) were placed in a carousel reaction tube. DCM (10 mL) was introduced and the resulting mixture was stirred for 24 h at room temperature. The reaction mixture was then filtered through celite and dried over Na$_2$SO$_4$. The solvent was evaporated under vacuum and the resulting solid was washed with a hexane/diethyl ether (2:1) mixture.[10]

2.4.4 Typical procedure for the TH of β-keto ethers in water

β-Keto ether (2.5 mmol) and **C6** (0.17 mg, 2.5 x 10^{-4} mmol) were placed in a carousel reaction tube. The tube was degassed and charged with nitrogen. HCO_2H/HCO_2Na aqueous solution of pH 4.5 (3 mL) was then introduced and the mixture was stirred at 80 °C for 14 h under nitrogen. The reaction mixture was cooled to room temperature and quenched with saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3 x 25 mL) and the combined organic layers were washed with brine (25 mL). The organic layer was collected and dried over anhydrous sodium sulphate. Filtration, followed by evaporation of the solvent under reduced pressure, gave the crude mixture. Flash column chromatography of the crude mixture afforded the desired β-hydroxy ether product.

2.4.5 Typical procedure for the TH of α-functionalised aromatic ketones in water

Ketone (2.5 mmol) and **C4** (1.6 mg, 2.5 x 10^{-3} mmol) were placed in a carousel reaction tube. The tube was degassed and charged with nitrogen. HCO_2Na/HCO_2H aqueous solution of pH 4.5 (3 mL) was then introduced and the mixture was stirred at 80 °C for 18 h under nitrogen. The reaction mixture was cooled to room temperature, quenched with saturated NaCl solution (20 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic layer was dried over anhydrous sodium sulphate. Filtration, followed by evaporation of the solvent under reduced pressure, gave the crude mixture. Flash column chromatography of the crude mixture afforded the desired product.

2.4.6 Typical procedure for the TH of α-keto and β-keto esters in water

Keto ester (2.5 mmol) and **C4** (1.6 mg, 2.5 x 10^{-3} mmol) were placed in a carousel reaction tube. The tube was degassed and charged with nitrogen. HCO_2Na/HCO_2H aqueous solution of pH 4.5 (3 mL) was then introduced and the mixture was stirred at 80 °C for 14 h under nitrogen. The reaction mixture was cooled to room temperature, quenched with saturated NaCl solution (20 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic layer was dried over anhydrous sodium sulphate. Filtration, followed by evaporation of the solvent under reduced pressure, gave the crude mixture. Flash column chromatography of the crude mixture afforded the desired hydroxy ester product.

2.4.7 Typical procedure for the TH of α,β-unsaturated aldehydes in water

α,β-Unsaturated aldehyde (2.5 mmol) and **C4** (1.6 mg, 2.5 x 10^{-3} mmol) were placed in a carousel reaction tube. The tube was degassed and charged with nitrogen. HCO_2Na/HCO_2H aqueous solution of pH 4.5 (3 mL) was then introduced and the mixture was stirred at 80 °C for 6 h under nitrogen. The reaction mixture was cooled to room temperature, quenched with saturated NaCl solution (20 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic layer was dried over anhydrous sodium sulphate. Filtration, followed by evaporation of the solvent under reduced pressure, gave the crude mixture. Flash column chromatography of the crude mixture afforded the desired alcohol product.

2.4.8 Data of the cyclometalated iridium complexes
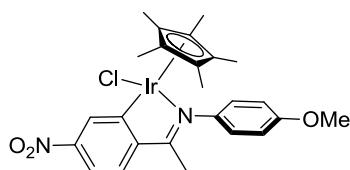
Complex C1:[14] Black solid; m.p. 170-174 °C: ^{1}H NMR (CDCl$_3$, 400 MHz, 253 K) δ (ppm): 8.62 (d, J = 2.3 Hz, 1H), 7.89 (dd, J = 8.4, 2.3 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 3.89 (s, 3H), 2.51 (s, 3H), 1.46 (s, 15H). ^{13}C NMR (CDCl$_3$, 100 MHz, 253 K) δ (ppm): 180.5, 168.4, 157.9, 153.6, 148.8, 143.6, 129.2, 128.7, 124.4, 123.1, 117.1, 115.1, 112.5, 90.1, 55.7, 17.8, 8.8. Anal. calc. for C$_{25}$H$_{28}$ClIrN$_2$O$_3$ (%): C, 47.50; H, 4.46; N, 4.43. Found: C, 47.56; H, 4.43; N, 4.42. HRMS (FAB) for C$_{25}$H$_{28}$Cl^{191}IrN$_2$O$_3$ [M]$^+$: m/z calc., 630.1389; found, 630.1383.
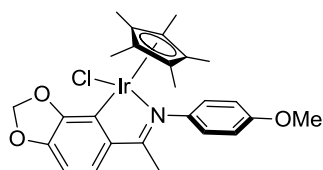
Complex C2: Yellow solid; m.p. 271-275 °C: ^{1}H NMR (CDCl$_3$, 400 MHz, 253 K) δ (ppm): 7.78 (d, J = 8.3 Hz, 1H), 7.21 (d, J = 8.1 Hz, 1H), 7.00-6.78 (m, 3H), 6.59 (d, J = 8.1 Hz, 1H), 6.12 (d, J = 1.2 Hz, 1H), 6.03 (d, J = 1.2 Hz, 1H), 3.87 (s, 3H), 2.38 (s, 3H), 1.49 (s, 15H). ^{13}C NMR (CDCl$_3$, 100 MHz, 253 K) δ (ppm): 180.5, 157.4, 150.5, 148.5, 144.3, 143.1, 142.2, 125.3, 125.1, 123.7, 114.9, 112.2, 102.9, 99.6, 89.6, 55.6, 17.6, 9.1. HRMS (FAB) for C$_{26}$H$_{29}$O$_3$N^{191}Ir [M-Cl]$^+$: m/z calc., 594.1748; found, 594.1747.
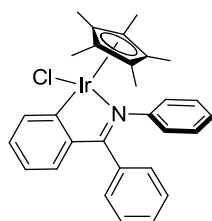
Complex C3: Yellow solid; m.p. 278-282 °C: ^{1}H NMR (CDCl$_3$, 400 MHz, 253 K) δ (ppm): 7.86 (d, J = 7.6 Hz, 1H), 7.47-7.41 (m, 2H), 7.35-7.05 (m, 7H), 7.04-6.99 (m, 1H), 6.96-6.89 (m, 1H), 6.84 (d, J = 7.7 Hz, 1H), 1.44 (s, 15H). ^{13}C NMR (CDCl$_3$, 100 MHz, 253 K) δ (ppm): 184.0, 169.9, 151.0, 148.3, 135.3, 134.3, 131.7, 131.3,

129.8, 129.7, 128.6, 128.1, 127.6, 125.6, 124.0 (br), 121.2, 89.7, 8.27. HRMS (ASAP) for $C_{29}H_{30}ClIrN$ [M+H]$^+$: m/z calc., 620.1696; found, 620.1699.
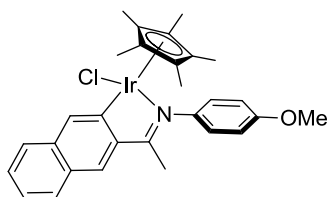
Complex C4:[14] Red solid; m.p. 276-280 °C: ^{1}H NMR (CDCl$_3$, 400 MHz, 293 K) δ (ppm): 8.16 (s, 1H), 8.05 (s, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.80 (dd, J = 8.3, 2.9 Hz, 2H), 7.48 (dd, J = 8.4, 7.4, 1H), 7.32 (dd, J = 8.4, 7.6 Hz, 1H), 7.08-6.82 (m, 3H), 3.90 (s, 3H), 2.58 (s, 3H), 1.47 (s, 15H). ^{13}C NMR (CDCl$_3$, 100 MHz, 253 K) δ (ppm): 181.3, 159.5, 157.6, 148.1, 144.2, 136.9, 132.2, 129.6, 129.2, 129.1, 127.4, 126.5, 125.1, 123.5, 123.4, 114.9, 112.3, 89.0, 55.7, 17.3, 8.8. Anal. calc. for $C_{29}H_{31}ClIrNO$ (%): C, 54.66; H, 4.90; N, 2.20. Found: C, 54.33; H, 4.90; N, 2.06. HRMS (FAB) for $C_{29}H_{31}Cl^{191}IrNO$ [M]$^+$: m/z calc., 635.1695; found, 635.1692.
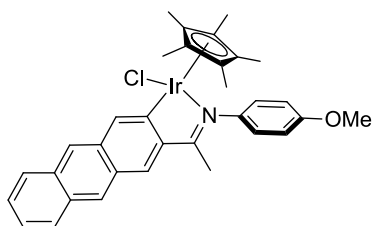
Complex C5: Deep Red solid; m.p. >300 °C: ^{1}H NMR (CDCl$_3$, 400 MHz, 253 K) δ (ppm): 8.42 (s, 1H), 8.35 (s, 1H), 8.27 (d, J = 13.1 Hz, 2H), 7.99 (dd, J = 16.4, 8.4 Hz, 2H), 7.94-7.87 (m, 1H), 7.48-7.36 (m, 2H), 7.09-6.84 (m, 3H), 3.90 (s, 3H), 2.59 (s, 3H), 1.49 (s, 15H). ^{13}C NMR (CDCl$_3$, 100 MHz, 253 K) δ (ppm): 180.8, 157.7, 156.9, 148.8, 144.2, 135.0, 133.0, 131.2, 130.1, 129.9, 129.0, 128.6, 128.4, 128.3, 128.2, 125.9, 125.3, 124.2, 123.4, 114.9, 112.3, 89.0, 55.7, 17.3, 8.8. HRMS (FAB) for $C_{33}H_{33}NO^{191}Ir$ [M-Cl]$^+$: m/z calc., 650.2163; found, 650.2156.
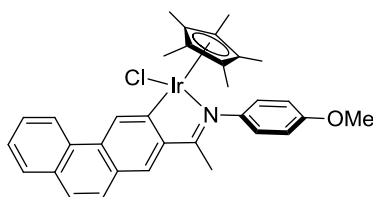
Complex C6: Deep Red solid; m.p. >300 °C: ^{1}H NMR (CDCl$_3$, 400 MHz, 253 K) δ (ppm): 9.10 (s, 1H), 8.84 (d, J = 8.1 Hz, 1H), 8.05 (s, 1H), 7.96-7.84 (m, 2H), 7.76-

7.57 (m, 4H), 7.12-6.84 (m, 3H), 3.90 (s, 3H), 2.62 (s, 3H), 1.52 (s, 15H). ^{13}C NMR (CDCl$_3$, 100 MHz, 253 K) δ (ppm): 181.4, 162.9, 157.6, 147.8, 144.1, 133.5, 133.2, 129.4, 129.0, 128.6, 128.5, 128.0, 127.5, 127.0, 126.1, 125.0, 124.6, 123.6, 123.5, 115.0, 112.3, 89.2, 55.7, 17.3, 9.0. Anal. calc. for C$_{33}$H$_{33}$ClIrNO (%):C, 57.67; H, 4.84; N, 2.04. Found: C, 57.88; H, 4.80; N, 1.91. HRMS (FAB) for C$_{33}$H$_{33}$NO^{191}Ir [M-Cl]$^+$: m/z calc., 650.2163; found, 650.2160.

2.4.9 Data of the β-hydroxy ethers
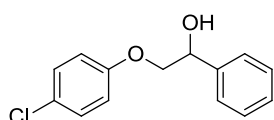
2-(4-Chlorophenoxy)-1-phenylethanol, 2a:[31] ^{1}H NMR (CDCl$_3$, 250 MHz, 300 K) δ (ppm): 7.48-7.33 (m, 5H), 7.27-7.20 (m, 2H), 6.90-6.82 (m, 2H), 5.12 (dt, J = 8.5, 2.7 Hz, 1H), 4.13-3.93 (m, 2H), 2.73 (bs, OH). ^{13}C NMR (CDCl$_3$, 63 MHz, 300 K) δ (ppm): 157.0, 139.4, 129.4, 128.6, 128.3, 126.2 (2), 115.9, 73.6, 72.5. HRMS for C$_{14}$H$_{12}$ClO [(M-H$_2$O) + H]$^+$: m/z calc., 231.0571; found, 231.0579.
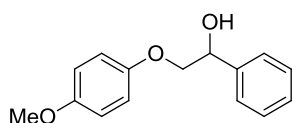
2-(4-Methoxyphenoxy)-1-phenylethanol, 2b:[32] ^{1}H NMR (CDCl$_3$, 250 MHz, 300 K) δ (ppm): 7.47-7.28 (m, 5H), 6.88-6.79 (m, 4H), 5.09 (dd, J = 8.8, 3.2 Hz, 1H), 4.05 (dd, J = 9.6, 3.2 Hz, 1H), 3.94 (dd, J = 9.7, 8.8 Hz, 1H), 3.76 (s, 3H), 2.87 (bs, OH). ^{13}C NMR (CDCl$_3$, 63 MHz, 300 K) δ (ppm): 154.2, 152.5, 139.7, 128.5, 128.1, 126.3, 115.7, 114.7, 74.1, 72.6, 55.7. HRMS for C$_{15}$H$_{20}$NO$_3$ [M+NH$_4$]$^+$: m/z calc., 262.1443; found, 262.1435.
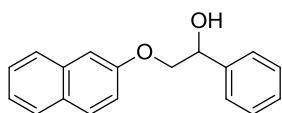
2-(Naphthalen-2-yloxy)-1-phenylethanol, 2c:[33] ^{1}H NMR (CDCl$_3$, 250 MHz, 300 K) δ (ppm): 7.75-7.56 (m, 3H), 7.43-7.24 (m, 7H), 7.13 (dd, J = 9.0, 2.5 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 5.09 (dd, J = 8.4, 3.4 Hz, 1H), 4.14-4.01 (m, 2H), 3.13 (bs, OH). ^{13}C NMR (CDCl$_3$, 63 MHz, 300 K) δ (ppm): 156.4, 139.9, 134.6, 129.7, 129.3,

128.7, 128.3, 127.8, 126.9, 126.6, 126.5, 124.0, 118.8, 107.2, 73.4, 72.6. HRMS for $C_{18}H_{15}O$ [(M-H_2O) + H]$^+$: m/z calc., 247.1123; found, 247.1117.

OH
O
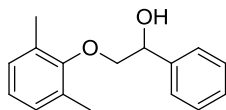
2-(2,6-Dimethylphenoxy)-1-phenylethanol, 2d:[4] ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K) δ (ppm): 7.45-7.40 (m, 2H), 7.38-7.32 (m, 2H), 7.32-7.26 (m, 1H), 6.99 (d, J = 7.5 Hz, 2H), 6.91 (dd, J = 8.3, 6.5 Hz, 1H), 5.16-5.09 (m, 1H), 3.89-3.84 (m, 2H), 3.06 (bs, OH), 2.27 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz, 300 K) δ (ppm): 155.6, 140.2, 131.1, 129.4, 128.9, 128.5, 126.7, 124.6, 77.3, 73.8, 16.8. HRMS for $C_{16}H_{22}NO_2$ [M+NH_4]$^+$: m/z calc., 260.1651; found, 260.1646.

OH
O
N
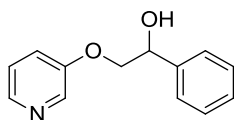
1-Phenyl-2-(pyridin-3-yloxy)ethanol, 2e:[4] ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K) δ (ppm): 8.18 (t, J = 1.7 Hz, 1H), 8.14-8.10 (m, 1H), 7.48-7.42 (m, 2H), 7.40-7.34 (m, 2H), 7.32-7.28 (m, 1H), 7.19-7.14 (m, 2H), 5.11 (dd, J = 6.8, 5.5 Hz, 1H), 4.50 (bs, OH), 4.08-4.03 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, 300 K) δ (ppm): 154.9, 142.1, 140.1, 137.7, 128.6, 128.2, 126.3, 124.0, 121.5, 73.7, 72.3. HRMS for $C_{13}H_{14}NO_2$ [M+H]$^+$: m/z calc., 216.1025; found, 216.1029.

OH
O
Cl
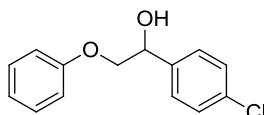
1-(4-Chlorophenyl)-2-phenoxyethanol, 2f:[33] ^{1}H NMR ($CDCl_3$, 400 MHz, 300 K) δ (ppm): 7.41-7.35 (m, 4H), 7.31-7.27 (m, 2H), 7.00-6.97 (m, 1H), 6.92-6.89 (m, 2H), 5.10 (dd, J = 8.7, 3.2 Hz, 1H), 4.08 (dd, J = 9.6, 3.3 Hz, 1H), 3.96 (dd, J = 9.6, 8.7 Hz, 1H), 2.83 (bs, OH). ^{13}C NMR ($CDCl_3$, 100 MHz, 300 K) δ (ppm): 158.2, 138.1, 133.9, 129.6, 128.8, 127.7, 121.5, 114.6, 73.1, 72.0. HRMS for $C_{14}H_{17}ClNO_2$ [M+NH_4]$^+$: m/z calc., 266.0942; found, 266.0932.
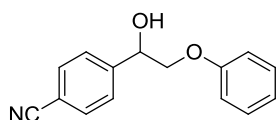
4-(1-Hydroxy-2-phenoxyethyl)benzonitrile, 2g:[31] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.60-7.56 (m, 2H), 7.47-7.36 (m, 5H), 6.99-6.96 (m, 2H), 5.16 (dd, J = 8.4, 3.4 Hz, 1H), 4.15-4.06 (m, 2H), 2.42 (bs, OH). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 161.7, 139.2, 134.1, 128.7, 128.5, 126.2, 119.0, 115.3, 104.6, 73.4, 72.4. HRMS for C$_{15}$H$_{17}$N$_2$O$_2$ [M+NH$_4$]$^+$: m/z calc., 257.1285; found, 257.1283.
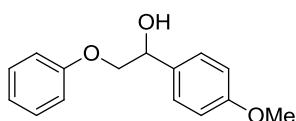
1-(4-Methoxyphenyl)-2-phenoxyethanol, 2h:[33] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.40-7.35 (m, 2H), 7.31-7.24 (m, 2H), 6.99-6.89 (m, 5H), 5.08-5.04 (m, 1H), 4.06 (dd, J = 9.6, 3.3 Hz, 1H), 3.99 (dd, J = 9.6, 8.8 Hz, 1H), 3.81 (s, 3H), 2.79 (d, J = 2.1 Hz, OH). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 160.0, 158.8, 132.2, 130.0, 128.0, 121.7, 115.1, 114.4, 73.7, 72.6, 55.7. HRMS for C$_{15}$H$_{15}$O$_2$ [(M-H$_2$O) + H]$^+$: m/z calc., 227.1072; found, 227.1066.
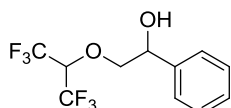
2-((1,1,1,3,3,3-Hexafluoropropan-2-yl)oxy)-1-phenylethanol, 2i: ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.40-7.32 (m, 5H), 5.01 (dt, J = 8.8, 2.8 Hz, 1H), 4.32 (sep, J = 5.9 Hz, 1H), 4.00 (dd, J = 10.3, 2.8 Hz, 1H), 3.86 (dd, J = 10.3, 9.1 Hz, 1H), 2.53 (d, J = 2.7 Hz, OH). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 138.8, 128.7, 128.4, 126.1, 121.4 (ddq, J = 3.1, 14.3, 285.7 Hz), 79.7, 76.5 (sep, J = 32.4 Hz), 73.2. ^{19}F NMR (CDCl$_3$, 375 MHz, 300 K) δ (ppm): -73.9. HRMS for C$_{11}$H$_{14}$F$_6$NO$_2$ [M+NH$_4$]$^+$: m/z calc., 306.0923; found, 306.0927.
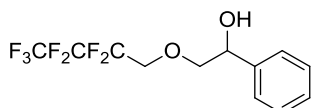
2-(2,2,3,3,3-Pentafluoropropoxy)-1-phenylethanol, 2j: ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.40-7.28 (m, 5H), 4.92 (dt, J = 8.7, 2.8 Hz, 1H), 4.14-3.94 (m, 2H), 3.78 (dd, J = 9.9, 3.1 Hz, 1H), 3.64 (dd, J = 9.9, 9.0 Hz, 1H), 2.69 (d, J = 2.6 Hz,

OH). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 139.4, 128.6, 128.2, 126.2, 116.2 (qt, J = 288.3, 33.7 Hz), 114.8 (tq, J = 257.1, 31.9 Hz), 109.0 (tq, J = 264.8, 38.7 Hz), 78.3, 72.9, 68.0 (t, J = 25.6 Hz). ^{19}F NMR (CDCl$_3$, 375 MHz, 300 K) δ (ppm): -137.9 (m), -131.1 (m), -91.2 (m). HRMS for C$_{12}$H$_{15}$F$_7$NO$_2$ [M+NH$_4$]$^+$: m/z calc., 338.0986; found, 338.0987.
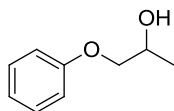
1-Phenoxypropan-2-ol, 2k:[34] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.26 (dd, J = 8.8, 7.4 Hz, 2H), 6.94 (t, J = 7.4 Hz, 1H), 6.89 (dd, J = 8.8, 0.91 Hz, 2H), 4.21-4.13 (m, 1H), 3.88 (dd, J = 9.4, 3.3 Hz, 1H), 3.77 (dd, J = 9.4, 7.6 Hz, 1H), 2.83 (d, J = 3.4 Hz, OH), 1.26 (d, J = 6.5 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 158.6, 129.6, 121.1, 114.6, 73.2, 66.3, 18.9. HRMS for C$_9$H$_{16}$NO$_2$ [M+NH$_4$]$^+$: m/z calc., 170.1176; found, 170.1171.
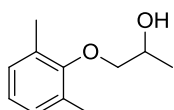
1-(2,6-Dimethylphenoxy)propan-2-ol, 2l:[35] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.01 (d, J = 7.5 Hz, 2H), 6.92 (dd, J = 8.4, 6.6 Hz, 1H), 4.26-4.20 (m, 1H), 3.72 (dd, J = 9.4, 3.3 Hz, 1H), 3.64 (dd, J = 9.4, 7.7 Hz, 1H), 2.65 (bs, OH), 2.28 (s, 6H), 1.26 (d, J = 6.4 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 155.6, 131.2, 129.4, 124.5, 77.4, 67.5, 19.0, 16.7. HRMS for C$_{11}$H$_{20}$NO$_2$ [M+NH$_4$]$^+$: m/z calc., 198.1494; found, 198.1490.
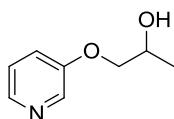
1-(Pyridin-3-yloxy)propan-2-ol, 2m:[36] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.19 (t, J = 1.8 Hz, 1H), 8.11 (t, J = 3.0 Hz, 1H), 7.15-7.11 (m, 2H), 4.18-4.09 (m, 1H), 3.86 (dd, J = 9.4, 3.7 Hz, 1H), 3.80 (dd, J = 9.4, 7.1 Hz, 1H), 1.22 (d, J = 6.4 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 154.0, 140.9, 136.8, 123.0, 120.3, 72.7, 64.8, 18.2. HRMS for C$_8$H$_{12}$NO$_2$ [M+H]$^+$: m/z calc., 154.0868; found, 154.0863.
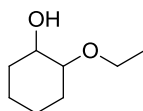
2-Ethoxycyclohexanol, 2n:[37] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): (42:58, *trans:cis*): *trans isomer*: 3.83-3.81 (m, 1H), 3.62-3.35 (m, 3H), 2.76 (bs, OH), 2.09-1.99 (m, 1H), 1.79-1.68 (m, 2H), 1.63-1.49 (m, 2H), 1.29-1.19 (m, 6H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 83.4, 73.5, 63.9, 32.0, 29.2, 24.2, 22.2, 15.6.; *cis isomer*: 3.75-3.67 (m, 1H), 3.62-3.35 (m, 2H), 3.05-2.99 (m, 1H), 2.70 (bs, OH), 2.09-1.99 (m, 1H), 1.79-1.68 (m, 2H), 1.63-1.49 (m, 3H), 1.29-1.19 (m, 5H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 78.3, 68.4, 63.5, 30.4, 26.6, 23.9, 21.1, 15.5. HRMS for C$_8$H$_{17}$O$_2$ [M+H]$^+$: m/z calc., 145.1223; found, 145.1228.
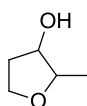
2-Methyltetrahydrofuran-3-ol, 2o:[38] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): (52:48, *trans:cis*): *trans isomer*: 4.13-4.05 (m, 1H), 4.00-3.81 (m, 2H), 3.72-3.62 (m, 1H), 2.28 (bs, OH), 2.20-2.05 (m, 1H), 1.83-1.71 (m, 1H), 1.13 (d, J = 6.4 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 77.6, 72.1, 64.6, 33.6, 12.9; *cis isomer*: 4.00-3.81 (m, 2H), 3.77 (qd, J = 6.4, 3.3 Hz, 1H), 3.72-3.62 (m, 1H), 2.70 (bs, OH), 2.20-2.05 (m, 1H), 1.93-1.83 (m, 1H), 1.20 (d, J = 6.4 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 81.0, 76.2, 65.1, 34.7, 17.9. HRMS for C$_5$H$_{14}$NO$_2$ [M+NH$_4$]$^+$: m/z calc., 120.1019; found, 120.1020.

2.4.10 Data of the α-functionalised alcohols
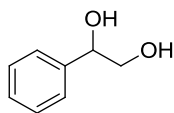
1-Phenylethane-1,2-diol, 4a:[39] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.38-7.28 (m, 5H), 4.78 (dd, J = 8.4, 3.4 Hz, 1H), 3.71 (dd, J = 11.5, 3.4 Hz, 1H), 3.62 (dd, J = 11.5, 8.4 Hz, 1H), 3.30 (bs, 2 OH's). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 140.5, 128.6, 128.0, 126.1, 74.7, 68.1. HRMS for C$_8$H$_{14}$NO$_2$ [M+NH$_4$]$^+$: m/z calc., 156.1019; found, 156.1020.
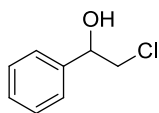
2-Chloro-1-phenylethanol, 4b:[40] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.37-7.29 (m, 5H), 4.86 (dt, J = 8.7, 3.3 Hz, 1H), 3.71 (dd, J = 11.3, 3.5 Hz, 1H), 3.62 (dd, J = 11.4, 8.7 Hz, 1H), 2.87 (d, J = 3.0 Hz, OH). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 140.0, 128.7, 128.5, 126.1, 74.1, 50.9. HRMS for C$_8$H$_{13}$ClNO [M+NH$_4$]$^+$: m/z calc., 174.0686; found, 174.0681.
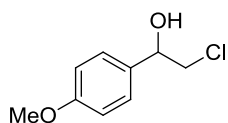
2-Chloro-1-(4-methoxyphenyl)ethanol, 4c:[41] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.30 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 4.84 (dd, J = 8.6, 3.3 Hz, 1H), 3.80 (s, 3H), 3.71-3.60 (m, 2H), 2.69 (bs, OH). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 159.7, 132.1, 127.3, 114.1, 73.7, 55.3, 50.9. HRMS for C$_9$H$_{12}$ClO$_2$ [M+H]$^+$: m/z calc., 187.0520; found, 187.0522.
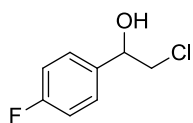
2-Chloro-1-(4-fluorophenyl)ethanol, 4d:[41] ^{1}H NMR (CDCl$_3$, 250 MHz, 300 K) δ (ppm): 7.40-7.29 (m, 2H), 7.11-7.00 (m, 2H), 4.86 (dt, J = 8.4, 3.8 Hz, 1H), 3.72-3.55 (m, 2H), 2.93 (d, J = 3.2 Hz, OH). ^{13}C NMR (CDCl$_3$, 63 MHz, 300 K) δ (ppm): 162.6 (d, J = 246.7 Hz), 135.7 (d, J = 3.2 Hz), 127.8 (d, J = 8.2 Hz), 115.5 (d, J = 21.6 Hz), 73.4, 50.7 (d, J = 1.1 Hz). ^{19}F NMR (CDCl$_3$, 235 MHz, 300 K) δ (ppm): -113.5. HRMS for C$_8$H$_7$ClF [(M-H$_2$O) + H]$^+$: m/z calc., 157.0215; found, 157.0214.
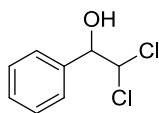
2,2-Dichloro-1-phenylethanol, 4e:[42] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.45-7.35 (m, 5H), 5.82 (d, J = 5.4 Hz, 1H), 4.98 (dd, J = 5.5, 4.2 Hz, 1H), 2.90 (d, J = 4.0 Hz, OH). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 137.3, 129.1, 128.5, 127.1, 78.9, 76.4. HRMS for C$_8$H$_7$Cl$_2$ [(M-H$_2$O) + H]$^+$: m/z calc., 172.9919; found, 172.9923.
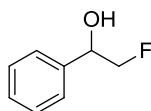
2-Fluoro-1-phenylethanol, 4f:[43] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.40-7.29 (m, 5H), 5.01-4.94 (m, 1H), 4.55-4.31 (m, 2H), 2.83 (d, J = 2.0 Hz, OH). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 139.1 (d, J = 8.2 Hz), 129.5, 129.3, 127.2, 88.0 (d, J = 174.7 Hz), 73.8 (d, J = 19.8 Hz). HRMS for C$_8$H$_8$F [(M-H$_2$O) + H]$^+$: m/z calc., 123.0605; found, 123.0606.
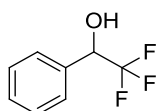
2,2,2-Trifluoro-1-phenylethanol, 4g:[44] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.46-7.32 (m, 5H), 4.94 (q, J = 6.7 Hz, 1H), 3.02 (bs, OH). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 133.9, 129.6, 128.7, 127.5, 124.3 (q, J = 281.5 Hz), 72.8 (q, J = 31.8 Hz). ^{19}F NMR (CDCl$_3$, 375 MHz, 300 K) δ (ppm): -78.3 (d, J = 6.7 Hz). HRMS for C$_8$H$_6$F$_3$ [(M-H$_2$O) + H]$^+$: m/z calc., 159.0416; found, 159.0414.
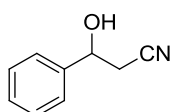
3-Hydroxy-3-phenylpropanenitrile, 4h:[45] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.41-7.28 (m, 5H), 4.95 (t, J = 6.1 Hz, 1H), 3.26 (bs, OH), 2.68 (d, J = 6.2 Hz, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 141.1, 128.9, 128.7, 125.6, 117.6, 69.8, 27.9. HRMS for C$_9$H$_{10}$NO [M+H]$^+$: m/z calc., 148.0757; found, 148.0758.
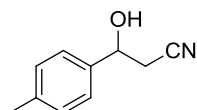
3-Hydroxy-3-(p-tolyl)propanenitrile, 4i:[46] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.27 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 4.99-4.95 (m, 1H), 2.74-2.70, 3.26 (m, 2H), 2.60 (d, J = 3.4 Hz, OH), 2.35 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 138.7, 138.1, 129.6, 125.5, 117.4, 70.0, 27.9, 21.1. HRMS for C$_{10}$H$_{15}$N$_2$O [M+NH$_4$]$^+$: m/z calc., 179.1179; found, 179.1183.
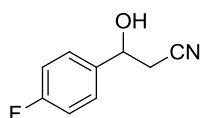
3-(4-Fluorophenyl)-3-hydroxypropanenitrile, 4j:[47] ^{1}H NMR (CDCl$_3$, 250 MHz, 300 K) δ (ppm): 7.42-7.29 (m, 2H), 7.14-7.01 (m, 2H), 5.08-4.92 (m, 1H), 3.32 (d, J = 3.9 Hz, OH), 2.71 (d, J = 6.1 Hz, 2H). ^{13}C NMR (CDCl$_3$, 63 MHz, 300 K) δ (ppm): 162.6 (d, J = 247.2 Hz), 136.9 (d, J = 3.2 Hz), 127.4 (d, J = 8.3 Hz), 117.4, 115.7 (d, J = 21.7 Hz), 69.2, 28.0. ^{19}F NMR (CDCl$_3$, 235 MHz, 300 K) δ (ppm): -113.1. HRMS for C$_9$H$_9$FNO [M+H]$^+$: m/z calc., 166.0663; found, 166.0666.
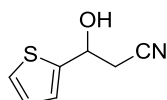
3-Hydroxy-3-(thiophen-2-yl)propanenitrile, 4k:[47] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.31 (dd, J = 5.1, 1.0 Hz, 1H), 7.08 (d, J = 3.5 Hz, 1H), 7.03 (dd, J = 5.1, 3.7, 1H), 5.32-5.24 (m, 1H), 2.93 (d, J = 3.2 Hz, OH), 2.89-2.83 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 144.4, 127.1, 125.8, 124.8, 117.0, 66.3, 28.2. HRMS for C$_7$H$_8$NOS [M+H]$^+$: m/z calc., 154.0321; found, 154.0326.
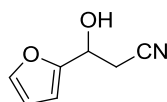
3-(Furan-2-yl)-3-hydroxypropanenitrile, 4l:[47] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.43-7.39 (m, 1H), 6.42-6.35 (m, 2H), 5.07-5.00 (m, 1H), 2.90 (d, J = 6.3 Hz, 2H), 2.87 (d, J = 5.0 Hz, OH). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 152.9, 142.9, 116.9, 110.6, 107.5, 63.8, 24.9. HRMS for C$_7$H$_{11}$N$_2$O$_2$ [M+NH$_4$]$^+$: m/z calc. 155.0815; found, 155.0817.
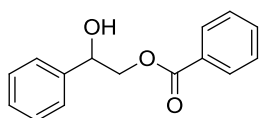
2-Hydroxy-2-phenylethyl benzoate, 4m:[48] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.06 (d, J = 7.7 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.50-7.30 (m, 7H), 5.16-5.07 (m, 1H), 4.53 (dd, J = 11.6, 3.4 Hz, 1H), 4.43 (dd, J = 11.6, 8.2 Hz, 1H), 2.66 (bs, OH). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 166.8, 139.9, 133.3, 129.8, 129.7, 128.7, 128.5, 128.3, 126.2, 72.6, 69.8. HRMS for C$_{15}$H$_{13}$O$_2$ [(M-H$_2$O) + H]$^+$: m/z calc., 225.0910; found, 225.0910.
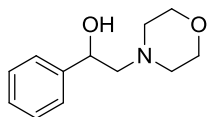
2-Morpholino-1-phenylethanol, 4n:[49] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.41-7.28 (m, 5H), 4.75 (dd, J = 10.4, 3.6 Hz, 1H), 3.80-3.69 (m, 4H), 2.80-2.69 (m, 2H), 2.58-2.40 (m, 4H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 141.9, 128.4, 127.6, 125.9, 68.6, 67.1, 66.7, 53.5. HRMS for C$_{12}$H$_{18}$NO$_2$ [M+H]$^+$: m/z calc., 208.1332; found, 208.1334.
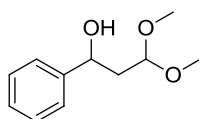
3,3-Dimethoxy-1-phenylpropan-1-ol, 4p:[50] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.37-7.31 (m, 4H), 7.28-7.23 (m, 1H), 4.86 (dd, J = 9.1, 3.4 Hz, 1H), 4.55 (t, J = 5.6 Hz, 1H), 3.37 (s, 3H), 3.34 (s, 3H), 2.10-2.02 (m, 1H), 1.99-1.94 (m, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 144.2, 128.4, 127.4, 125.7, 103.4, 70.8, 53.7, 53.0, 41.6. HRMS for C$_{11}$H$_{20}$NO$_3$ [M+NH$_4$]$^+$: m/z calc., 214.1438; found, 214.1442.

2.4.11 Data of the α-hydroxy and β-hydroxy esters
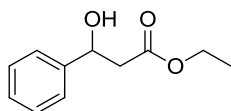
Ethyl 3-hydroxy-3-phenylpropanoate, 6a:[51] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.40-7.25 (m, 5H), 5.11 (dt, J = 8.9, 4.1 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.45 (d, J = 3.6 Hz, OH), 2.77-2.64 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 172.4, 142.6, 128.5, 127.8, 125.7, 70.3, 60.9, 43.4, 14.2. HRMS for C$_{11}$H$_{16}$NO$_2$ [(M-H$_2$O) + NH$_4$]$^+$: m/z calc., 194.1176; found, 194.1169.
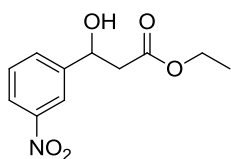
Ethyl 3-hydroxy-3-(3-nitrophenyl)propanoate, 6b:[51] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.27 (s, 1H), 8.15 (dd, J = 8.1, 1.3 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H),

7.54 (t, J = 8.1 Hz, 1H), 5.28-5.18 (m, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.78 (d, J = 3.5 Hz, OH), 2.80-2.72 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 172.0, 148.4, 144.7, 131.9, 129.5, 122.7, 120.8, 69.3, 61.2, 43.0, 14.1. HRMS for C$_{11}$H$_{17}$N$_2$O$_5$ [M+NH$_4$]$^+$: m/z calc., 257.1132; found, 257.1126.
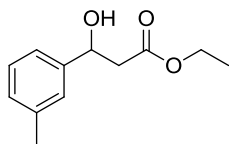
Ethyl 3-hydroxy-3-(m-tolyl)propanoate, 6c:[52] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.24 (dd, J = 7.5, 6.9 Hz, 1H), 7.20 (s, 1H), 7.16 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 7.4 Hz, 1H), 5.11 (dt, J = 8.9, 3.8 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.27 (d, J = 3.4 Hz, OH), 2.78-2.66 (m, 2H), 2.35 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 172.5, 142.5, 138.2, 128.6, 128.5, 126.4, 122.7, 70.3, 60.9, 43.3, 21.5, 14.2. HRMS for C$_{12}$H$_{15}$O$_2$ [(M-H$_2$O) + H]$^+$: m/z calc., 191.1067; found, 191.1070.
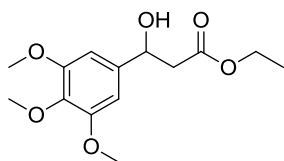
Ethyl 3-hydroxy-3-(3,4,5-trimethoxyphenyl)propanoate, 6d:[53] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 6.60 (s, 2H), 5.06 (dt, J = 9.0, 3.4 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 3.50 (d, J = 3.3 Hz, OH), 2.78-2.65 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 172.3, 153.2, 138.5, 137.2, 102.5, 70.5, 60.9, 60.8, 56.0, 43.6, 14.2. HRMS for C$_{14}$H$_{19}$O$_5$ [(M-H$_2$O) + H]$^+$: m/z calc., 267.1227; found, 267.1230.
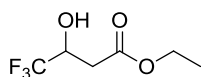
Ethyl 4,4,4-trifluoro-3-hydroxybutanoate, 6e:[54] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 4.51-4.41 (m, 1H), 4.36 (bs, OH), 4.21 (q, J = 7.2 Hz, 2H), 2.75-2.63 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 170.8, 124.5 (q, J = 281.2 Hz), 67.0 (q, J = 32.4 Hz), 61.6, 34.9, 13.9. ^{19}F NMR (CDCl$_3$, 375 MHz, 300 K) δ (ppm): -80.0. HRMS for C$_6$H$_{13}$F$_3$NO$_3$ [M+NH$_4$]$^+$: m/z calc., 204.0842; found, 204.0843.
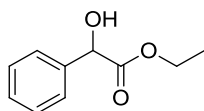
Ethyl 2-hydroxy-2-phenylacetate, 8a:[55] ^{1}H NMR (CDCl$_3$, 250 MHz, 300 K) δ (ppm): 7.45-7.25 (m, 5H), 5.15 (d, J = 5.7 Hz, 1H), 4.30-4.10 (m, 2H), 3.51 (d, J = 5.7 Hz, OH), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (CDCl$_3$, 63 MHz, 300 K) δ (ppm): 173.7, 138.4, 128.5, 128.4, 126.5, 72.9, 62.2, 14.0. HRMS for C$_{10}$H$_{11}$O$_2$ [(M-H$_2$O) + H]$^+$: m/z calc., 163.0754; found, 163.0751.
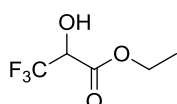
Ethyl 3,3,3-trifluoro-2-hydroxypropanoate, 8c:[56] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 4.42-4.38 (m, 1H), 4.36-4.25 (m, 2H), 3.43 (bs, OH), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 167.9 (d, J = 2.2 Hz), 122.6 (q, J = 283.2 Hz), 70.3 (q, J = 33.1 Hz), 64.1, 14.3. ^{19}F NMR (CDCl$_3$, 375 MHz, 300 K) δ (ppm): -76.6. HRMS for C$_5$H$_8$F$_3$O$_3$ [M+H]$^+$: m/z calc., 173.0420; found, 173.0418.

2.4.12 Data of the α,β-unsaturated alcohols
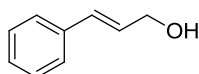
3-Phenylprop-2-en-1-ol, 10a:[57] ^{1}H NMR (CDCl$_3$, 250 MHz, 300 K) δ (ppm): 7.39-7.20 (m, 5H), 6.59 (d, J = 15.9 Hz, 1H), 6.34 (dt, J = 15.9, 5.6 Hz, 1H), 4.29 (dd, J = 5.6, 1.3 Hz, 2H), 2.07 (bs, OH). ^{13}C NMR (CDCl$_3$, 63 MHz, 300 K) δ (ppm): 136.7, 131.1, 128.6, 128.5, 127.7, 126.5, 63.6. HRMS for C$_9$H$_9$ [(M-H$_2$O) + H]$^+$: m/z calc., 117.0699; found, 117.0695.
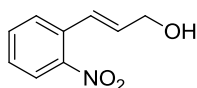
3-(2-Nitrophenyl)prop-2-en-1-ol, 10b:[58] ^{1}H NMR (CDCl$_3$, 250 MHz, 300 K) δ (ppm): 8.00-7.85 (m, 1H), 7.65-7.52 (m, 2H), 7.46-7.33 (m, 1H), 7.09 (dt, J = 15.7, 1.6 Hz, 1H), 6.35 (dt, J = 15.7, 5.3 Hz, 1H), 4.49-4.30 (m, 2H), 2.10 (bs, OH). ^{13}C NMR (CDCl$_3$, 63 MHz, 300 K) δ (ppm): 147.8, 134.1, 133.1, 132.5, 128.8, 128.1, 125.8, 124.5, 63.3. HRMS for C$_9$H$_{13}$N$_2$O$_3$ [M+NH$_4$]$^+$: m/z calc., 197.0921; found, 197.0919.
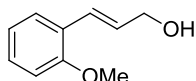
3-(2-Methoxyphenyl)prop-2-en-1-ol, 10c:[59] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.41 (d, J = 7.5 Hz, 1H), 7.21 (t, J = 7.9 Hz, 1H), 6.93-6.84 (m, 3H), 6.35 (dt, J = 16.1, 5.9 Hz, 1H), 4.29 (d, J = 5.5 Hz, 2H), 3.81 (s, 3H), 2.12 (bs, OH). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 156.7, 129.4, 128.8, 127.0, 126.1, 125.8, 120.7, 110.9, 64.1, 55.4. HRMS for C$_{10}$H$_{13}$O$_2$ [M+H]$^+$: m/z calc., 165.0916; found, 165.0913.
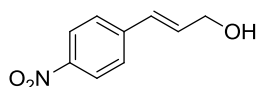
3-(4-Nitrophenyl)prop-2-en-1-ol, 10d:[60] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.18 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 16.0 Hz, 1H), 6.55 (dt, J = 15.9, 5.0 Hz, 1H), 4.41 (td, J = 5.4, 1.5 Hz, 2H), 1.87 (t, J = 5.7 Hz, OH). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 146.9, 143.3, 133.6, 128.2, 126.9, 124.0, 63.1. HRMS for C$_9$H$_{13}$N$_2$O$_3$ [M+NH$_4$]$^+$: m/z calc., 197.0921; found, 197.0918.
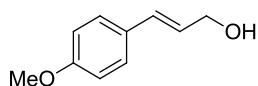
3-(4-Methoxyphenyl)prop-2-en-1-ol, 10e:[61] ^{1}H NMR (CDCl$_3$, 250 MHz, 300 K) δ (ppm): 7.25 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 6.49 (d, J = 15.9 Hz, 1H), 6.17 (dt, J = 15.9, 5.8 Hz, 1H), 4.23 (d, J = 5.8 Hz, 2H), 3.76 (s, 3H), 2.97 (bs, OH). ^{13}C NMR (CDCl$_3$, 63 MHz, 300 K) δ (ppm): 159.2, 130.6, 129.5, 127.7, 126.4, 114.0, 63.6, 55.2. HRMS for C$_{10}$H$_{13}$O$_2$ [M+H]$^+$: m/z calc., 165.0916; found, 165.0915.
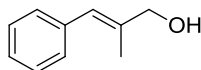
2-Methyl-3-phenylprop-2-en-1-ol, 10f:[57] ^{1}H NMR (CDCl$_3$, 250 MHz, 300 K) δ (ppm): 7.36-7.18 (m, 5H), 6.52 (s, 1H), 4.17 (s, 2H), 1.96 (bs, OH), 1.89 (s, 3H). ^{13}C NMR (CDCl$_3$, 63 MHz, 300 K) δ (ppm): 137.7, 137.6, 128.9, 128.1, 126.4, 125.0, 68.9, 15.3. HRMS for C$_{10}$H$_{11}$ [(M-H$_2$O) + H]$^+$: m/z calc., 131.0855; found, 131.0858.
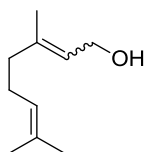
3,7-Dimethylocta-2,6-dien-1-ol, 10g:[57] mixture of *E/Z* isomers (52:48): ^{1}H NMR (CDCl₃, 400 MHz, 300 K) δ (ppm): 5.49-5.37 (m, 1H), 5.14-5.04 (m, 1H), 4.15-4.08 ((m, 2H): 4.14 (d, J = 6.9 Hz, 1H, CH₂OH, *E* isomer), 4.09 (d, J = 7.2 Hz, 1H, CH₂OH, *Z* isomer)), 2.12-2.01 (m, 4H), 1.75-1.60 (m, 10H). ^{13}C NMR (CDCl₃, 100 MHz, 300 K) δ (ppm): *Z* isomer: 139.8, 132.4, 124.5, 123.8, 58.9, 32.0, 26.5, 26.66, 23.4, 17.7. *E* isomer: 139.6, 131.7, 123.9, 123.4, 59.3, 39.5, 26.4, 26.65, 17.6, 16.2. HRMS for C₁₀H₁₇ [(M-H₂O) + H]⁺: m/z calc., 137.1325; found, 137.1322.
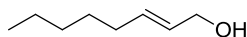
Oct-2-en-1-ol, 10h:[62] ^{1}H NMR (CDCl₃, 250 MHz, 300 K) δ (ppm): 5.76-5.57 (m, 2H), 4.08 (d, J = 4.7 Hz, 2H), 2.12-1.95 (m, 2H), 1.56 (bs, OH), 1.44-1.21 (m, 6H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (CDCl₃, 63 MHz, 300 K) δ (ppm): 133.5, 128.8, 63.8, 32.2, 31.4, 28.8, 22.5, 14.0. HRMS for C₈H₁₅ [(M-H₂O) + H]⁺: m/z calc., 111.1168; found, 111.1169.
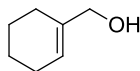
Cyclohex-1-en-1-ylmethanol, 10i:[63] ^{1}H NMR (CDCl₃, 250 MHz, 300 K) δ (ppm): 5.79-5.57 (m, 1H), 3.96 (s, 2H), 2.14-1.92 (m, 5H), 1.75-1.50 (m, 4H). ^{13}C NMR (CDCl₃, 63 MHz, 300 K) δ (ppm): 137.5, 122.9, 67.5, 25.5, 24.9, 22.5, 22.4. HRMS for C₇H₁₁ [(M-H₂O) + H]⁺: m/z calc., 95.0855; found, 95.0855.

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Chapter 3

A Simple and Environmentally Friendly Approach for the Transfer Hydrogenation of *N*-Heterocycles in Water

3.1 Introduction

Saturated nitrogen heterocycles are frequently found in drug and biologically active molecules, such as oxamniquine, a schistosomicide,[1] paroxetine, a CCRI type anti-depressant,[2] salsolinol, an endogenous monoamine oxidase inhibitor,[3] and CEPC a serotonin 5-HT$_{2C}$ antagonist,[4] (Scheme 3.1). The most obvious route to access these types of molecules is via the reduction of the corresponding unsaturated parent heterocycles, which can be efficiently synthesised by cross-coupling and classic heterocyclic chemistry. Nonetheless, this method only has 0.8% occurrence rate among the medical chemist's toolbox, despite the fact that 42.9% of the total pharmaceutical compounds contain aliphatic amines.[5] This must be a reflection of either limited supply of the building blocks from commercial sources or significant challenges at the late stage reduction step.
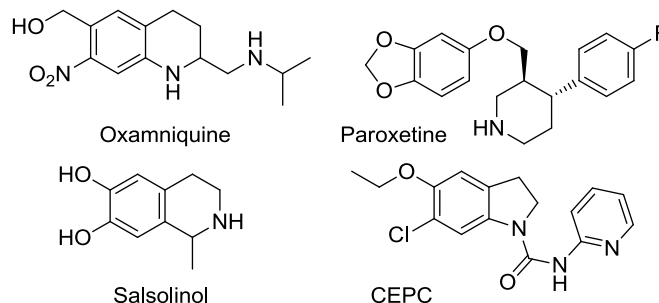
Scheme 3.1: Bioactive molecules that contain a saturated nitrogen heterocycle core.

Reduction of nitrogen heterocycles has traditionally been done by heterogeneous hydrogenation (i.e. Pd/C, Rh/C, Adams's catalyst, Raney nickel),[6] electrolytic reduction,[7] Birch reduction[8] and more recently with homogenous hydrogenation.[9] Despite the fact that there are many examples in the literature, one or more significant limitations are always found under those reaction conditions. For example, Birch and metal hydride reduction require stoichiometric amount of

metallic reductants and have very limited functional group compatibility. Whilst heterogeneous catalysts containing Pd, Pt, Ni or Rh on supported materials can reduce a range of heterocycles even under atmospheric pressure of hydrogen, they often have limited selectivity and the potential of over reduction. Homogeneous catalysis has attracted much attention, due to the easily controllable selectivities and reactivities through ligand modification. Nevertheless, there are still significant challenges in this area, including the improvement in turnover number (TON) and turnover frequency (TOF), reduction in cost, and the expansion of the reaction scope.

Transfer hydrogenation (TH) of heterocycles is a reaction of great interest due to its operational simplicity. In contrast to ketones, the TH of heterocycles has been much less explored. Yamaguchi demonstrated that by using [IrCp*Cl$_2$]$_2$ in a mixture of ^{i}PrOH and H$_2$O under refluxing conditions, a series of quinolines can be fully reduced to tetrahydroquinolines (Scheme 3.2).[10] The presence of an acid considerably enhanced the reduction, presumably by activating the quinoline through the protonation to form a quinolinium salt, which is easier to reduce.
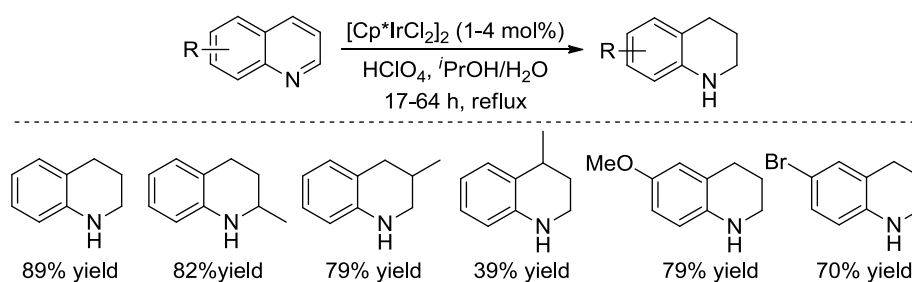
Scheme 3.2: Ir catalysed TH of quinolines with ^{i}PrOH.

Frediani and co-workers reported a Rh-bipyridine catalyst that can reduce quinoline and pyridines with a moderate conversion by using ^{i}PrOH as the hydride source (Scheme 3.3).[11] The same catalyst could also be applied to the reduction of other unsaturated bonds, including C=C and C=O bonds in reasonable conversions.

Crabtree identified a cationic Ir(I)-NHC catalyst (**1a**) that can reduce quinolines to tetrahydroquinolines in *i*PrOH with moderate yields. Pyrazine showed complete conversion to piperazine under the reaction condition (Scheme 3.4).[12] Other *N*-heterocycles, for instance, isoquinolines, pyridines and indoles, were found to be inactive in this system.
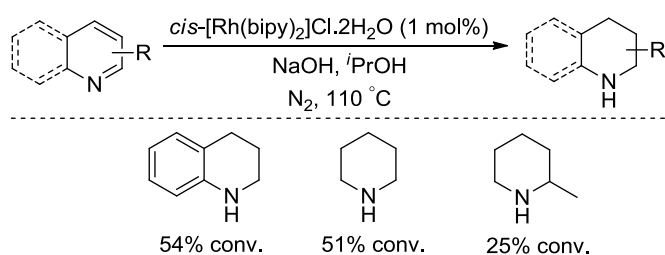
Scheme 3.3: Rh catalysed TH of quinolines with *i*PrOH.
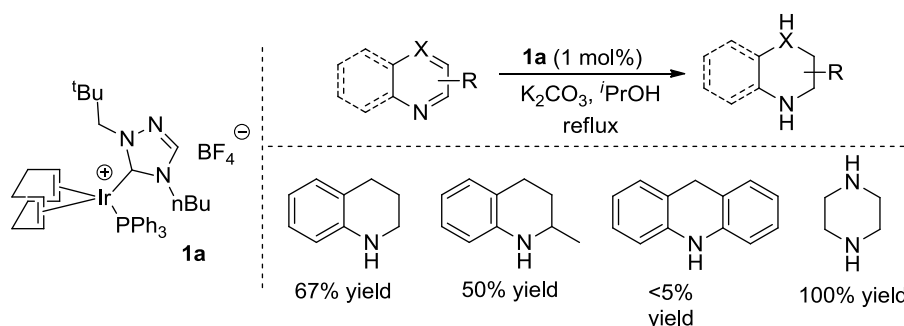
Scheme 3.4: **1a** catalysed TH of *N*-heterocycles.

The most versatile, simple and yet highly active system was recently reported by Xiao and co-workers. By using $[Cp*RhCl_2]_2$ with KI as an additive, a range of *N*-heterocycles, including quinolines, isoquinolines, quinoxalines and pyridinium salts, can be reduced in the HCO_2H-NEt_3 azeotrope.[13,14] As shown in Scheme 3.5, *N*-heterocycles were reduced in high yields using just 0.01-0.2 mol% catalyst under mild condition. TH of indoles did not proceed under the protocol, however, and the reduction of 4-subtituted quinoline was rather sluggish. For example at higher catalyst loading of 2 mol% and 50% KI, only 23% conversion of 4-methyl quinoline was obtained after 24 h.[13] Interestingly, the TH of pyridinium salts affords two

different products, depending on the substitution pattern at the pyridinium ring. For instance, 2- or 3-substitued pyridines are fully reduced to piperdines, while 4-substitued pyridines exclusively gives 1,2,3,6-tetrahydropyridines (Scheme 3.6). This is because the hydride addition preferentially takes place at the 4 position for 2- or 3-substituted pyridines (i.e. 1,4-addition), whereas in the case of 4-substituted pyridines 1,4-addition is disfavoured possibly due to the steric reasons and instead 1,2-addition takes place (Scheme 3.7).[14]
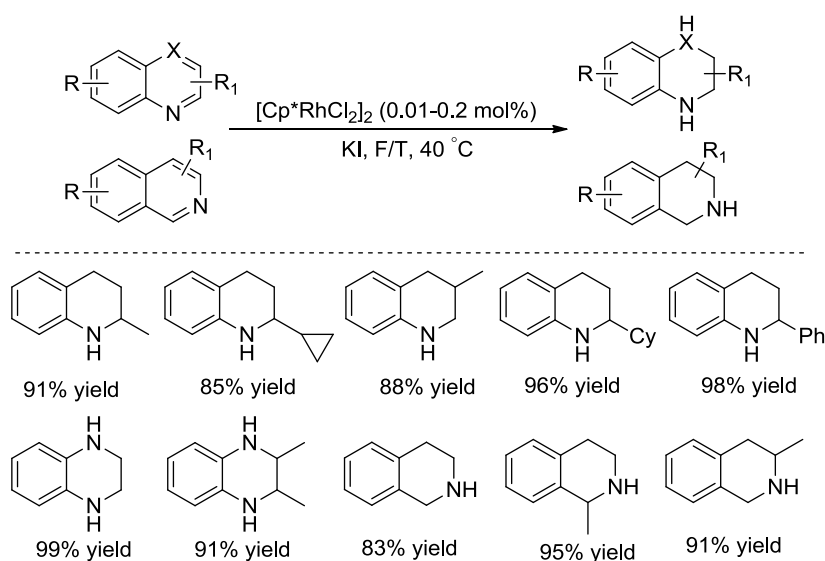
Scheme 3.5: [Cp*RhCl$_2$]$_2$ catalysed TH of *N*-heterocycles.
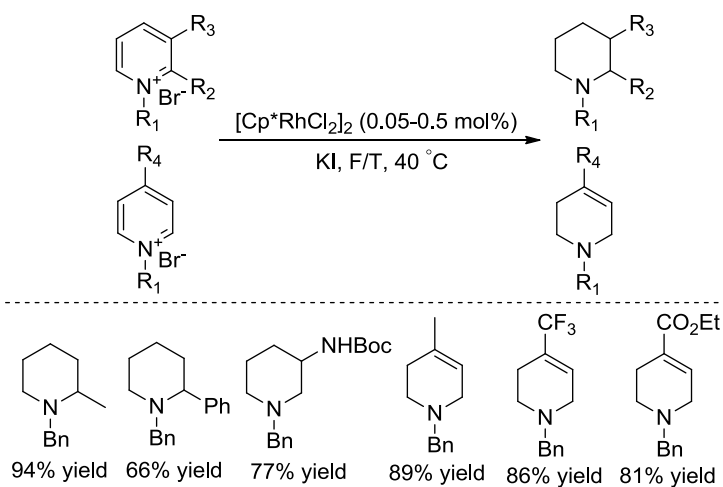
Scheme 3.6: [Cp*RhCl$_2$]$_2$ catalysed TH of pyridinium salts.
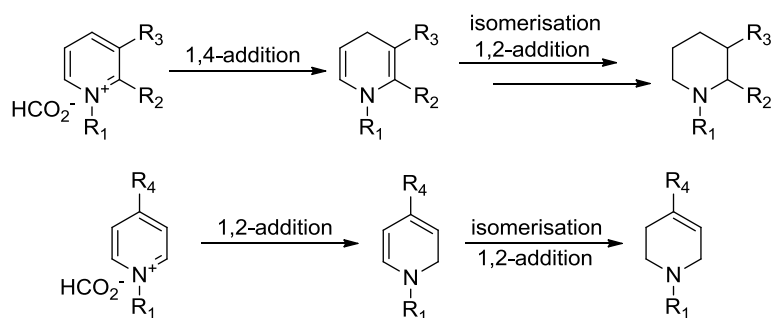
Scheme 3.7: 1,4-Addition versus 1,2-addition.

Asymmetric transfer hydrogenation (ATH) of *N*-heterocycles has also been investigated, mainly with organocatalysts[15] and to a lesser degree with homogeneous catalysts.[16] However, Hantzsch esters are predominantly used, which are expensive hydrogen donors compared with others that are commercially available (*t*Bu-HEH - £70.5/gram versus HCO_2H - £30/L).

The conditions for both TH and ATH of *N*-heterocycles reactions are not yet ideal, as high catalyst loadings, high reaction temperature and/or a limited substrate scope are limitations often encountered. Moreover, organic solvents are normally used that impose an environmental impact. In addition, an active, versatile catalyst capable of either hydrogenation or TH of various *N*-heterocycles, for example quinolines, isoquinolines, quinoxalines, indoles and pyridines, remain to be seen. Following the success of iridicycles in the TH of a range of α-substituted ketones in water described in Chapter 2, we report in this chapter our efforts to test whether the same catalysts are capable of reducing these more inert *N*-heterocycles in water.

3.2 Results and discussion

3.2.1 Optimisation of the reaction conditions

In Chapter 2 it was discussed that the complex **C4** exhibits the highest activity at pH 4.5 for the TH of α-substituted ketones in water; hence the same conditions were adopted for the optimisation study. 2-Methylquinoline (**2a**) was chosen as a model substrate. TH of **2a** gave full conversion within 3 h with only 0.1 mol% loading of **C4** at both 80 °C and 60 °C, in an aqueous formate solution of pH 4.5 (Table 3.1, entries 1 and 2). Gratifyingly, lowering the temperature to 30 °C also led to a 70% conversion within 3 h (Table 3.1, entry 3). Screening of the solution pH with **C4** revealed that the reaction occurs only within a certain window of acidic condition. pH 4.5 was adopted for subsequent studies. This finding is also consistent with the TH of α-substituted ketones (*vide supra*). In contrast, the analogous Rh complex **D4** only gave a 12% conversion (Table 3.1, entry 6). Other catalysts, which are known to be active for the TH of quinolines (Scheme 3.8), showed much lower activities under the reaction conditions employed (Table 3.1, entries 7-11). Although the dimeric [Cp*IrCl$_2$]$_2$ also led to a moderate conversion (38% in 3 h, Table 3.1, entry 11), further testing showed that it exhibited very limited substrate scope (Table 3.2). For instance, TH of 3-methylquinoline led to its tetrahydro variant only in 4% conversion after 20 h (Table 3.2, entry 2).
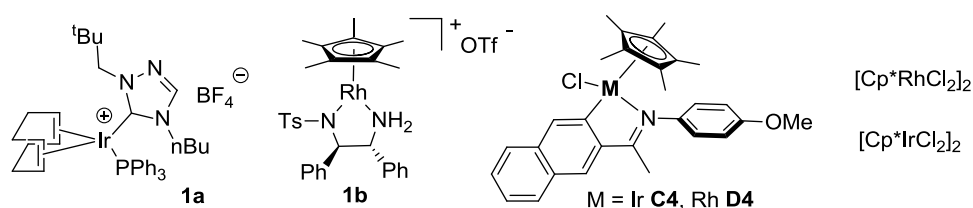
Scheme 3.8: List of TH catalysts examined for quinoline reduction.

Table 3.1: Screening of catalysts for the TH of 2-methylquinoline in water
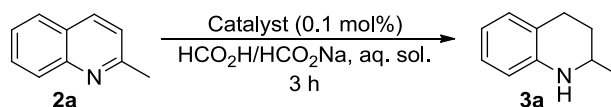
Entry[a]	Catalyst	pH	Temp. (°C)	Conv. (%)[b]
1	**C4**	4.5	80	>99
2	**C4**	4.5	60	>99
3	**C4**	4.5	30	70
4	**C4**	2.5	30	20
5	**C4**	6.5	30	<5
6	**D4**	4.5	30	12
7	**1a**	4.5	30	n.r.
8	**1b**	4.5	30	8
9	[Cp*RhCl$_2$]$_2$	4.5	30	5
10[c]	[Cp*RhCl$_2$]$_2$	4.5	30	4
11	[Cp*IrCl$_2$]$_2$	4.5	30	38

[a] Reaction conditions: 2-methylquinoline (2.5 mmol), catalyst (0.1 mol%), HCO$_2$H/HCO$_2$Na aqueous solution (pH = 4.5; 3mL; 14.0 mmol of HCO$_2$H and 29.4 mmol of HCO$_2$Na in 2.8 mL of H$_2$O), stirred in a carousel tube for the time indicated. [b] Conversion determined by ^{1}H-NMR spectroscopy [c] With 10 mol% KI; n.r. = no reaction.

Table 3.2: Substrate scope with [Cp*IrCl$_2$]$_2$

Entry[a]	Substrate	Time (h)	Temp. (°C)	Conv. (%)[b]
1	Quinoline	20	30	8
2	3-Methylquinoline	20	30	4
3	6-Bromoquinoline	3	30	n.r.
4	Indole	20	30	n.r.

[a] Reaction conditions: substrate (0.5 mmol), [Cp*IrCl$_2$]$_2$ (1 mol%), HCO$_2$H/HCO$_2$Na aqueous solution (pH = 4.5; 3mL; 14.0 mmol of HCO$_2$H and 29.4 mmol of HCO$_2$Na in 2.8 mL of H$_2$O), stirred in a carousel tube for the time indicated. [b] Conversion determined by ^{1}H-NMR spectroscopy; n.r. = no reaction.

In order to establish that aqueous conditions are the optimum, other hydride sources and solvents were also tested using **C4** for the TH of 2-methylquinoline. As seen in Table 3.3, apart from water, the TH also worked in MeOH and TFE with F/T as the hydrogen source, but with lower conversions (65% and 68%, respectively). Much lower conversions were recorded in non-protic solvents, such as THF or DMF (<5% conversion in 3 h). Other commonly used hydride sources such as ^{i}PrOH and Et$_3$SiH were sluggish under the reaction conditions (Table 3.3, entries 7 and 8).

Table 3.3: Screening of hydride sources and solvents
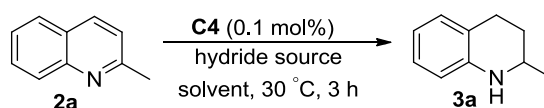
Entry[a]	Hydride source	Solvent	Conv. (%)[b]
1	F/T	MeOH	64
2	F/T	TFE	68
3	F/T	THF	1
4	F/T	toluene	3
5	F/T	DCM	13
6	F/T	DMF	4
7	0.1M KOH/^{i}PrOH	^{i}PrOH	15
8	Et$_3$SiH	H$_2$O	n.r.

[a] Reaction conditions: 2-methylquinoline (2.5 mmol), **C4** (0.1 mol%), hydride source (20 equiv.), solvent, stirred in a carousel tube for the 3 h. [b] Conversion determined by ^{1}H-NMR spectroscopy; n.r. = no reaction.

3.2.2 TH of quinolines

Once the optimal TH condition for 2-methylquinoline had been established, an array of 26 diversely substituted quinolines (**2a**-**2z**) was hydrogenated in the aqueous formate solution of pH 4.5, as summarised in Table 3.4. The iridium based catalyst **C4** exhibited high reactivity for all of the quinoline substrates examined. Thus,
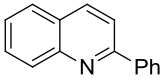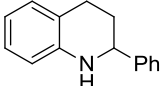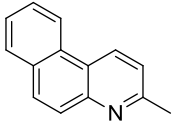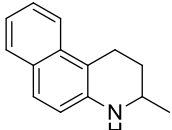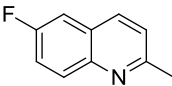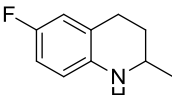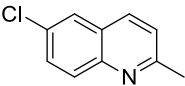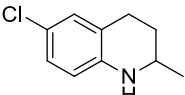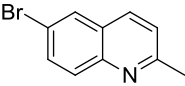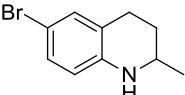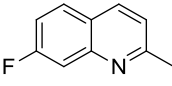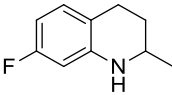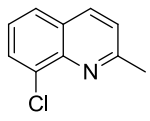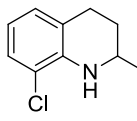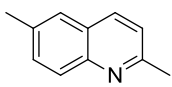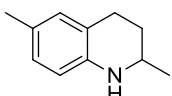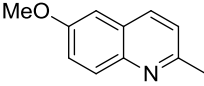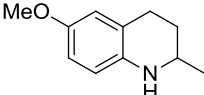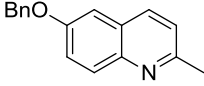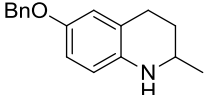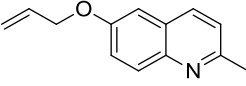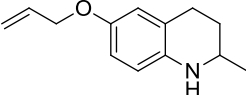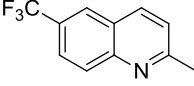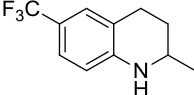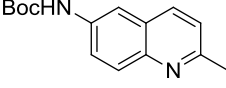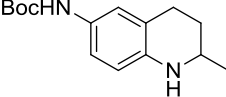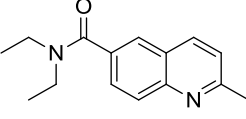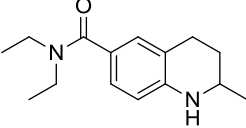
unsubstituted quinoline **2d**, 2-substituted quinoline **2a** and 3-substitued quinoline **2b** were all effectively reduced at 30 °C with excellent yields (Table 3.4, entries 1, 2 and 4). Increasing the steric bulkiness at the 2-postion led to a decrease in conversion, which could be compensated by increasing the reaction temperature to reflux (**3e**, 84% yield; Table 3.4, entry 5). Challenging 4-substitued quinolines **2c** and **2z** were also reduced in high yields, albeit with high temperature (Table 3.4, entries 3 and 26). Other functional groups, including halogen (**2g-2k**), ether (**2m-2o**), protected amine (**2q**), amide (**2r**), ester (**2s**), carboxylic acid (**2t**), heterocycles (**2v-2x**) and a trifluoromethyl group (**2p**) were all tolerated under the reaction condition, exhibiting insignificant effect on the yields with products isolated in average yield of >90% (Table 3.4, entries 7-20 and 22-24). Even with a highly sensitive functional group, such as boronic acid pinacol ester, **3u** was isolated in 62% (Table 3.4, entry 21), together with 30% of the deboronated product **3a**.

Table 3.4: TH of quinolines
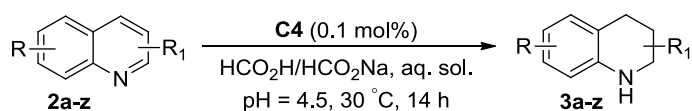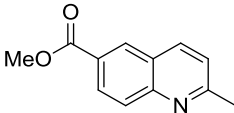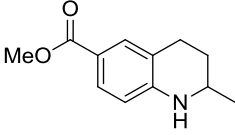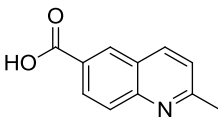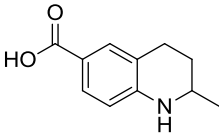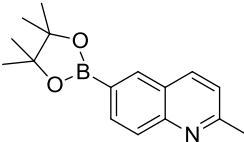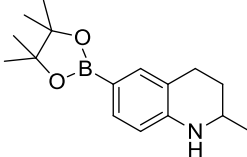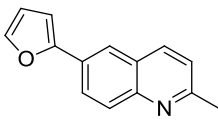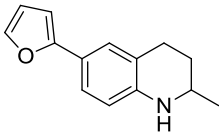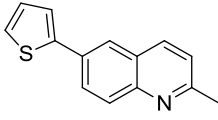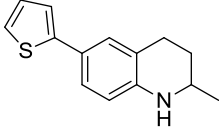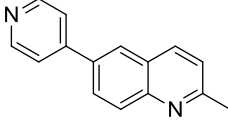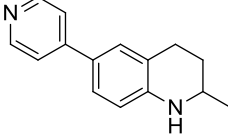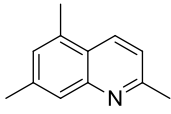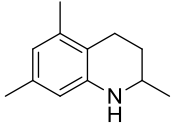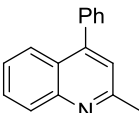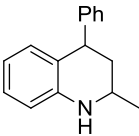
Entry[a]	Substrate	Product		Yield (%)[b]
1			**3a**	96
2			**3b**	93
3[c]			**3c**	90
4			**3d**	90

5[c]			**3e**	84
6			**3f**	94
7			**3g**	97
8			**3h**	97
9			**3i**	95
10			**3j**	98
11			**3k**	92
12			**3l**	95
13			**3m**	96
14			**3n**	94
15			**3o**	93
16			**3p**	98
17[c,d]			**3q**	90
18[c]			**3r**	91

19			**3s**	92
20			**3t**	82
21[c]			**3u**	62
22			**3v**	95
23			**3w**	96
24[c]			**3x**	82
25			**3y**	95
26[c,e]			**3z**	84

[a] Reaction conditions: quinoline (2.5 mmol), **C4** (0.1 mol%), HCO$_2$H/HCO$_2$Na aqueous solution (pH = 4.5; 3mL; 14.0 mmol of HCO$_2$H and 29.4 mmol of HCO$_2$Na in 2.8 mL of H$_2$O), 30 °C stirred in a carousel tube for 14 h. [b] Yield of isolated product. [c] Reaction was carried out at reflux. [d] Yield determined by ^{1}H-NMR spectroscopy. [e] 0.5 mol% **C4** used.

In order to demonstrate the potential usefulness of this method in process chemistry, **2a** was used as the model substrate for a larger scale reduction. As shown in Scheme 3.9, 35.8g (0.25 mol) of **2a** was effectively reduced with just 0.01 mol% **C4** at 30 °C (75% conversion in 24 h; TON = 7500). The product was separated from the reaction mixture by a simple phase separation and purified by fractional distillation.

Moreover, the aqueous layer could be reused by adjusting the pH back to 4.5 by the addition of fresh formic acid. No special equipment was required for this reaction, nor was an inert atmosphere necessary. In addition, no organic solvent was required for the entire operation, and only minimum waste was generated, showing the protocol to be greener than the traditional methods, which often involves the use of $NaBH_3CN$ in acetic acid or Pd/C or Pd/Al_2O_3 under high pressure of H_2.[17,18]
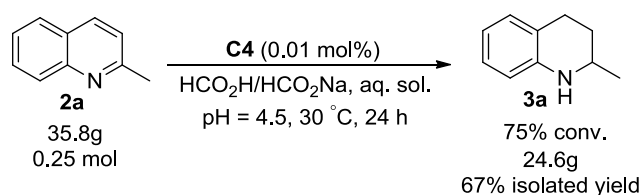
Scheme 3.9: Large scale TH of 2-methylquinoline.

3.2.3 TH of isoquinolines and pyridines

Based on the successful results obtained for the TH of quinolines with **C4**, the substrate scope was expanded to more challenging isoquinolines and pyridines. Reduction of isoquinoline and 2-phenylpyridine led to the recovery of the starting material under the reaction conditions used in Table 3.4, presumably due to their high aromatic stability. It was thought that activating the substrate by quaternizing the nitrogen atom would lead to a higher activity.[14] This is indeed the case, and the optimisation results for isoquinoline and pyridine are shown in Table 3.5 and 3.6, respectively.

Table 3.5: Reaction optimisation for the TH of isoquinoline
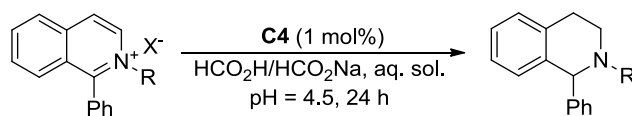
Entry[a]	R	X⁻	Temp. (°C)	Conv. (%)[b]
1	-	-	30	n.r.
2	-	-	reflux	n.r.
3	H	OTf	reflux	47
4	Me	I	reflux	n.r.
5	Et	I	reflux	89
6	Bn	Br	reflux	90
7	Bn	Br	30	n.r.

[a] Reaction conditions: isoquinoline (0.5 mmol), **C4** (1 mol%), HCO_2H/HCO_2Na aqueous solution (pH = 4.5; 3mL; 14.0 mmol of HCO_2H and 29.4 mmol of HCO_2Na in 2.8 mL of H_2O), stirred in a carousel tube for 24 h. [b] Conversion determined by ${}^1H$-NMR spectroscopy; n.r. = no reaction.

Table 3.6: Reaction optimisation for the TH of pyridine
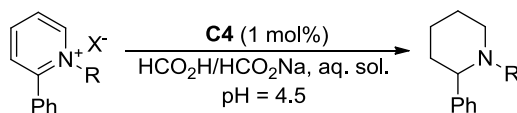
Entry[a]	R	X⁻	Temp. (°C)	Time (h)	Conv. (%)[b]
1	-	-	30	24	n.r.
2	-	-	reflux	24	n.r.
3	H	OTf	reflux	24	n.r.
4	Me	I	reflux	24	n.r.
5	Et	I	reflux	24	63
6	Et	I	reflux	36	93
7	Bn	Br	reflux	36	92

[a] Reaction conditions: pyridine (0.5 mmol), **C4** (1 mol%), HCO_2H/HCO_2Na aqueous solution (pH = 4.5; 3mL; 14.0 mmol of HCO_2H and 29.4 mmol of HCO_2Na in 2.8 mL of H_2O), stirred in a carousel tube for the time indicated. [b] Conversion determined by ${}^1H$-NMR spectroscopy; n.r. = no reaction.

After the optimised conditions had been established, an array of 6 isoquinolinium (**4a**-**4f**) and 10 pyridinium (**6a**-**6j**) salts were reduced (Table 3.7). Unsubstitued isoquinolinium, 1-methyl, 3-methyl and 6-methyl isoquinolinium salts gave the highest yields (>95%; Table 3.7, entries 2-5). Increasing the steric bulk at the 1-position by replacing the methyl group with a phenyl did not affect the yield (Table 3.7, entry 1). A functional group, such as bromine, was well tolerated under the reaction condition (Table 3.7, entry 6). Likewise, 2-substituted pyridinium salts (**6a**-**6e**) were all reduced with good yields, regardless of the nature of the functional groups (Table 3.7, entries 7-11). Interestingly, substrates bearing an electron withdrawing group at the 4-position gave exclusively the fully reduced piperidines, whilst those having an electron donating group led to the partially reduced 3,4-unsaturated piperidines (Table 3.7, entries 13 and 14 versus 15 and 16). This phenomenon could be explained by a competitive 1,2-hydride addition versus 1,4-hydride addition (*vide supra*). Having an electron withdrawing substituent probably renders the 4-position more electrophilic, favouring the 1,4-addition.

Table 3.7: TH of isoquinolinium and pyridinium salts
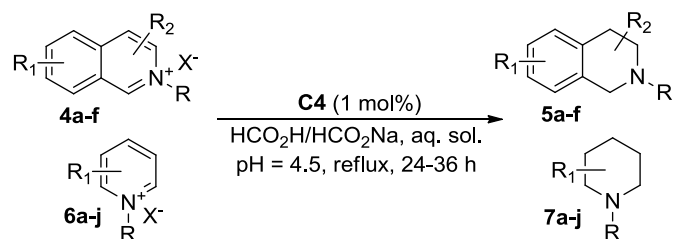
Entry[a]	Substrate	Product		Yield (%)[b]
1			**5a**	90
2			**5b**	95
3[c]			**5c**	98
4[c]			**5d**	97
5			**5e**	99
6			**5f**	91
7			**7a**	90
8[d]			**7b**	72
9			**7c**	90
10			**7d**	94
11			**7e**	81

Entry	Substrate	Product		Yield
12[c]	ethyl 1-benzylpyridinium-3-carboxylate bromide (CO₂Et)	ethyl 1-benzylpiperidine-3-carboxylate (CO₂Et, Bn)	7f	82
13[c]	1-benzyl-3,4-dimethylpyridinium bromide	1-benzyl-3,4-dimethyl-2-phenyl-tetrahydropyridine	7g	95
14	1,4-dibenzylpyridinium bromide (Bn)	1,4-dibenzyl-tetrahydropyridine (Bn)	7h	92
15	1-benzyl-4-(trifluoromethyl)pyridinium bromide (CF₃)	1-benzyl-4-(trifluoromethyl)piperidine (CF₃, Bn)	7i	82
16	ethyl 1-benzylpyridinium-4-carboxylate bromide (CO₂Et)	ethyl 1-benzylpiperidine-4-carboxylate (CO₂Et, Bn)	7j	80

[a] Reaction conditions: isoquinolinium or pyridinium salts (2.5 mmol), **C4** (1 mol%), HCO_2H/HCO_2Na aqueous solution (pH = 4.5; 3mL; 14.0 mmol of HCO_2H and 29.4 mmol of HCO_2Na in 2.8 mL of H_2O), reflux, stirred in a carousel tube for 24 h (isoquinolinium) or 36 h (pyridinium). [b] Yield of isolated product. [c] Yield determined by ^{1}H-NMR spectroscopy. [d] Isolated as debenzylated product after the column.

3.2.4 TH of indoles

Substrate scope of indoles was examined next with **C4** under the condition of Table 3.4. A range of indoles with both electron-donating and electron-withdrawing groups were reduced to the corresponding indolines in good yields (Table 3.8). However, TH of 5-bromoindole gave a lower yield (Table 3.8, entry 3). For 5-bromoindole **8c**, a thick layer of coating was always observed on the reaction vessel above the solvent level, even at reflux and with the addition of MeOH as a co-solvent. This reflects that the solubility of **8c** was an issue under the reaction conditions employed and this may have led to the lower conversion. Disappointedly, TH of sterically hindered 2-phenylindole failed to proceed under the present reaction conditions, and 3-

methylindole gave a low yield (Table 3.8, entries 6 and 7). One of the explanations

could be the unfavourable tautomerization of **8f** or difficulty in its protonation at the

3-position due to sterics, following which 1,2-hydride addition can occur.

Table 3.8: TH of indoles
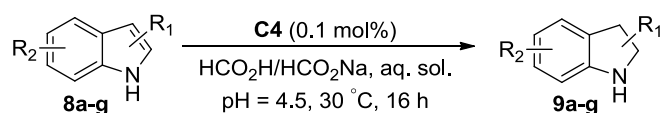
Entry[a]	Substrate	Product		Yield (%)[b]
1			**9a**	96
2			**9b**	94
3[c,d]			**9c**	30
4			**9d**	92
5[c]			**9e**	78
6[c,d]			**9f**	33
7			**9g**	n.r.

[a] Reaction conditions: indole (2.5 mmol), **C4** (0.1 mol%), HCO$_2$H/HCO$_2$Na aqueous solution (pH = 4.5; 3mL; 14.0 mmol of HCO$_2$H and 29.4 mmol of HCO$_2$Na in 2.8 mL of H$_2$O), 30 °C, stirred in a carousel tube for 16 h. [b] Yield of isolated product. [c] Using 0.5 mol% **C4**, at reflux and with the addition of MeOH (1 mL). [d] Yield determined by ^{1}H-NMR spectroscopy; n.r. = no reaction.

3.2.5 TH of other *N*-heterocycles and imines

In order to further demonstrate the potential of **C4** as a versatile catalyst for the TH of a range of heterocycles, rather than a specialised catalyst for a particular class of substrates, a range of diverse substrates, including cyclic and acyclic imines and other fused heterocycles, were examined. Acridine (**10b**), neocuproine (**10c**) and quinoxaline (**10a**) were all reduced to their corresponding products in excellent yields, although the latter was exclusively isolated as a mono *N*-formyl derivative (Table 3.9, entries 1-3). Interestingly, 1*H*-cyclopenta[*b*]pyridine **10d** was reduced at the carbocycle ring to give the pyridine **11d** (Table 3.9, entry 4). Both the cyclic and acyclic imines were fully reduced to give the corresponding amines **11f** and **11g**, respectively, with good yields (Table 3.9, entries 6 and 7). Salsolidine (**11f**) is naturally isolated from the plants of the genus *salsola* and is a stereoselective competitive inhibitor of the enzyme monoamine oxidase.[19] Under the present reaction condition pyrazine also resisted the TH with **C4** (Table 3.9, entry 5).

Table 3.9: TH of other *N*-heterocycles and imines
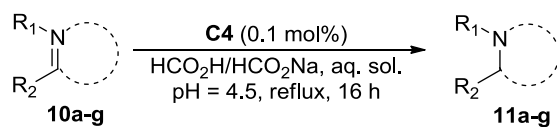
Entry[a]	Substrate	Product		Yield (%)[b]
1			**11a**	90
2			**11b**	82
3			**11c**	96
4			**11d**	99
5			**11e**	n.r.
6[c]			**11f**	98
7[d,e]			**11g**	90

[a] Reaction conditions: *N*-heterocycle or imine (2.5 mmol), **C4** (0.1 mol%), HCO$_2$H/HCO$_2$Na aqueous solution (pH = 4.5; 3mL; 14.0 mmol of HCO$_2$H and 29.4 mmol of HCO$_2$Na in 2.8 mL of H$_2$O), reflux, stirred in a carousel tube for 16 h. [b] Yield of isolated product. [c] Reaction conducted at 30 °C. [d] Yield determined by ^{1}H-NMR spectroscopy. [e] Obtained as a mixture of 60% and 30% **11g** and its *N*-formyl derivative, respectively; n.r. = no reaction

3.2.6 Mechanistic investigations

The TH of quinolines in an acidic medium has been suggested to proceed by an ionic pathway.[13] The initial hydride delivery to the protonated quinoline may occur via the 1,4-addition fashion; isomerisation and further reduction via 1,2-addition would afford the product (Scheme 3.10). If the reaction is initiated by 1,2-hydride addition, the resulting 1,2-dihydroquinoline may not be further reduced; but it may undergo dehydrogenation to go back to the starting material or disproportionate.[20] In order to gain more insight into the reaction mechanism, a combination of intermediate reactions, isotope labelling and stoichiometric reactions were explored.
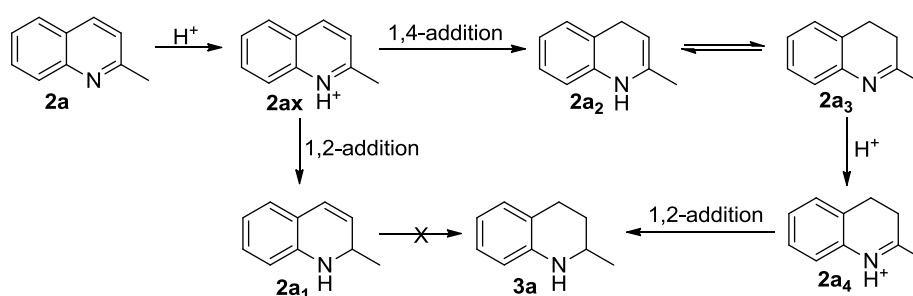
Scheme 3.10: Suggested possible reaction pathways for the TH of quinolines.

3.2.6.1 Deuterium labelling

Deuterium labelling reactions were carried out on the model substrate **2a** with **C4** at 30 $^{\circ}$C in water. Using fully deuterated reagents and solvent, 87%, 94% and 100% deuterium incorporation onto the 2, 3 and 4-position of the product was observed, respectively (Scheme 3.11, eq. 1). When HCO_2Na and HCO_2H were used together with D_2O, 52%, 49%, and 55% deuterium were incorporated onto the 2, 3 and 4-position of the product, respectively (Scheme 3.11, eq. 2). On the other hand, when DCO_2D, DCO_2Na were used in H_2O, only 18%, 0%, and 14% deuterium were incorporated onto these positions, respectively (Scheme 3.11, eq. 3). One possible

explanation for deuterium (Eq. 2) and hydrogen (Eq. 3) incorporation is that following the formation of the iridium hydride/deuteride takes place, the transfer of the hydride/deuteride to the substrate is the rate limiting step. This would allow the iridium hydride/deuteride to be scrambled with the solvent (Scheme 3.11, eq. 4 and 5), producing a mixture of iridium hydride and deuteride and consequently the partial incorporation of deuterium into the product.[21] The reaction shown in Eq. 3 also reveals that when H_2O was used as the solvent, no deuterium was incorporated onto the 3-position. This is consistent with the assumption that there is an acid-mediated isomerisation reaction between the hydride addition steps (Scheme 3.10).
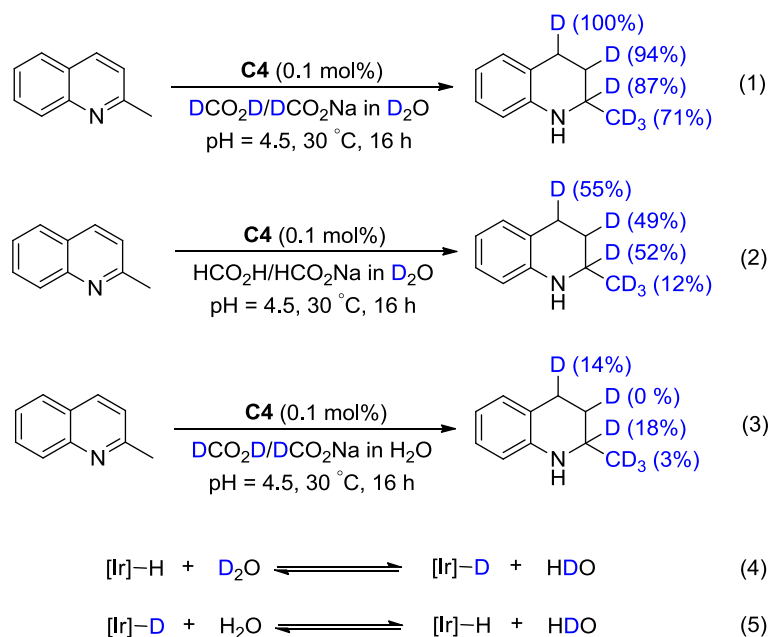
Scheme 3.11: Deuterium labelling experiments.

3.2.6.2 Monitoring the reaction by ^{1}H-NMR in situ

Further support to the hydride transfer being the rate limiting was gained by monitoring the reduction of the protonated **2a** with **C4** in situ using ^{1}H-NMR spectroscopy (Figure 3.1). As noted before, neutral **2a** was not reduced with an isolated closely-related Ir-H.[22] The reaction was carried out in a NMR tube

equipped with a Young's tap, containing 1 equiv. of **C4** and 5 equiv. of **2a**·HBF$_4$ in

d^4-MeCN (Figure 3.1, spectrum 1). After the addition of 5 equiv. of the F/T, a

hydride signal was immediately observed at δ -15.8 (Spectrum 2). While the signal

of the product tetrahydroquinoline gradually increased in intensity over time (Spectra

3 and 4), signals corresponding to the potential intermediates **2a$_1$**, **2a$_2$** and **2a$_3$**

(Scheme 3.10) were not observed. Nonetheless the hydride signal remained, which,

together with the rapid hydride formation, is consistent with the assumption that the

transfer hydrogenation in question is turnover-limited by the step of hydride transfer.
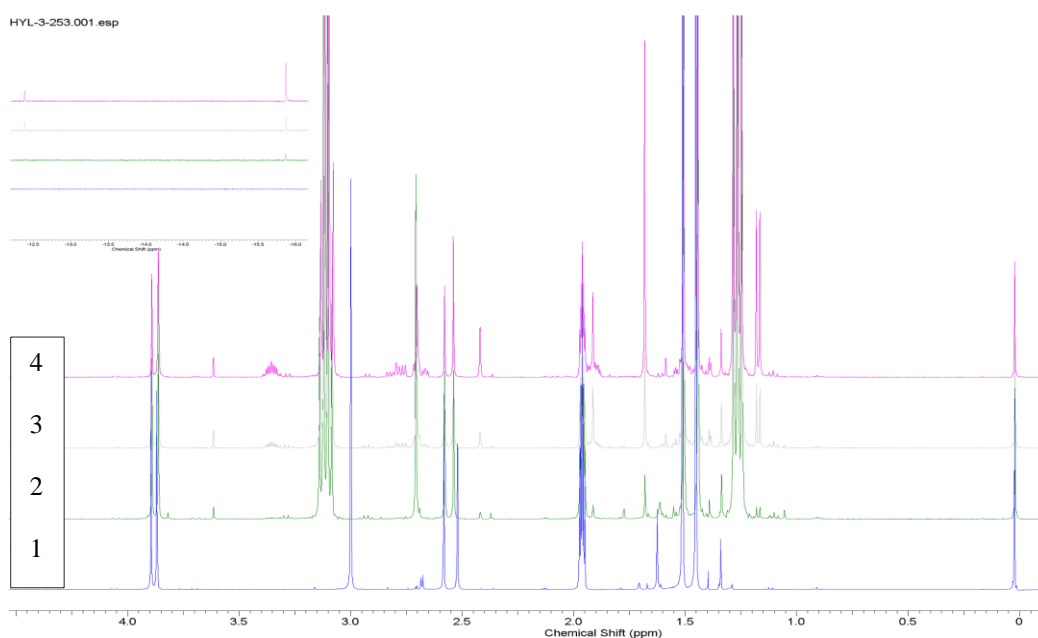
Figure 3.1: In situ ^{1}H-NMR; spectrum 1: **C4** and **2a**·HBF$_4$ (5 equiv.) in d^4-MeCN; spectrum 2: after the addition of F/T (5 equiv.); spectrum 3: after 5 min; spectrum 4: after 30 min.

3.2.6.3 Reactions of proposed intermediates

The TH of **2a** may yield two distinct intermediates, namely 1,2-dihydroquinoline

(via 1,2-addition) and 3,4-dihydroquinoline (via 1,4-addition) (Scheme 3.10). To

gain evidence into their possible involvement in the reduction, a 1:1 mixture of

dihydroquinoline **2l$_1$** and quinoline **2l** was subjected to the standard reaction

conditions (Scheme 3.12, eq 6). In the presence of **C4**, only the fully reduced

tetrahydroquinoline **3l** (100%) was obtained after the reaction. However, in the absence of **C4**, 23% of **3l** and 77% of **2l** were obtained. And in both cases, no starting dihydroquinoline **2l$_1$** was observed after the reaction. These results supports the hypothesis that the 1,2-addition product (e.g. **2l$_1$**) is consumed via a disproportionation mechanism instead of being reduced by the catalysis of **C4**. Further evidence to this hypothesis comes from the observation that when **2l$_2$** was used as a substrate, no reaction occurred (Scheme 3.12, eq 7).
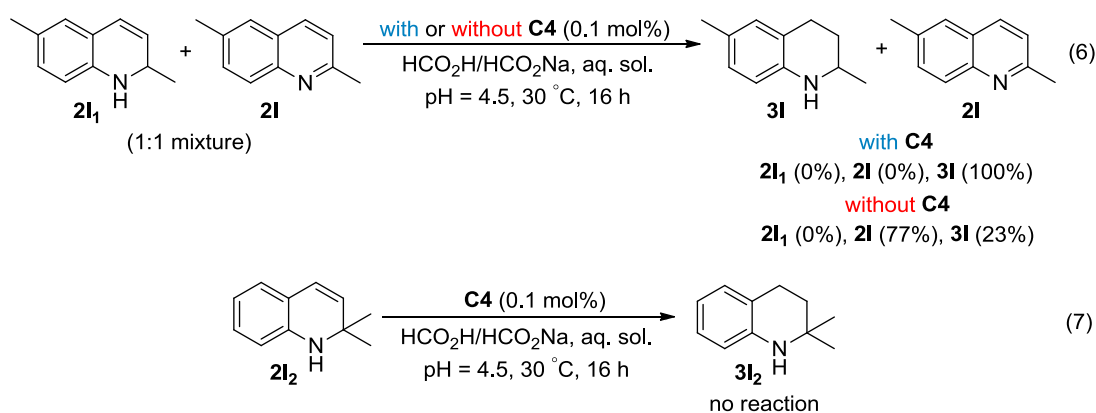
Scheme 3.12: Control experiments.

To probe whether the 1,4-addition precedes the 1,2-addition in the TH or vice versa, a model substrate *N*-cinnamylidene aniline **12a** was subjected to the **C4** catalysed reduction. Under the standard reaction conditions, a mixture of **13a** and **13b** (43:57) was obtained (Scheme 3.13), indicating that both 1,2- and 1,4-hydride additions are likely to happen for quinoline type substrates.
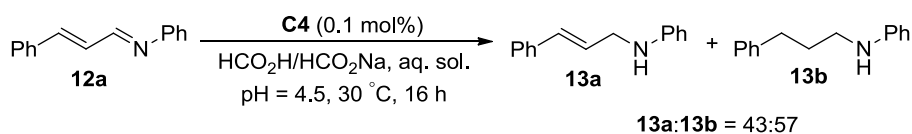
Scheme 3.13: Reaction of *N*-cinnamylidene aniline with **C4** in water.

3.2.6.4 Proposed reaction mechanism

On the basis of the experimental results presented above, a plausible mechanism is proposed for the TH of quinolines (Scheme 3.14). **C4** reacts with formate to generate the active Ir-H species that can react with the **2ax** (2-methylquinoline, pKa 5.4) in two different pathways. In Pathway 1, **2ax** undergoes 1,4-addition to give the 1,4-dihydroquinoline **2a$_2$**, which then isomerises to **2a$_3$**. Protonation of **2a$_3$** followed by 1,2-addition then yields **3a**. Pathway 2 involves the 1,2-hydride addition as the first step to give 1,2-dihydroquinoline **2a$_1$**, which then reduces **2ax** to **2a$_2$**. Isomerisation of the latter affords **2a$_3$**, which is finally reduced by 1,2-addition after protonation to yield **3a**. Whilst the pathway 1 and 2 are both competitive, the rate of each is likely to be affected by both steric and electronic effects.
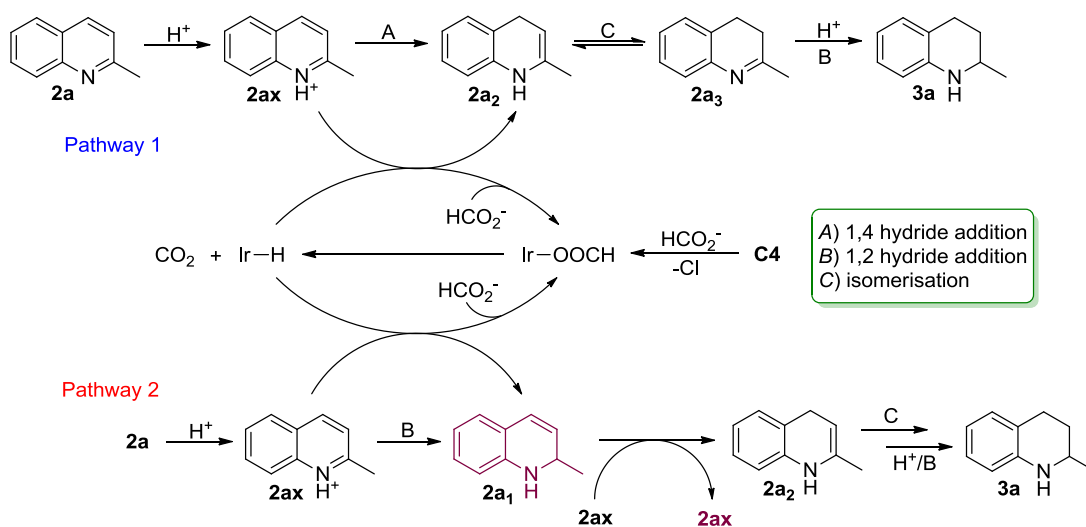
Scheme 3.14: Plausible reaction mechanism for the TH of quinolines catalysed by **C4**.

3.3 Conclusion

In summary, this chapter demonstrates that a wide variety of *N*-heterocycles, including but not limited to quinolines, isoquinolines, indoles, quinoxalines and pyridinium salts, can be effectively reduced using an iridicycle in water. This reaction is applicable to large scale synthesis with no need for specialised equipment. The use of environmentally benign solvent, renewable hydride donor and easy work-up and purification provides a significant advantage for industrial applications. To the best of our knowledge, this work constitutes the first example of a highly versatile homogenous catalyst that can reduce a range of *N*-heterocycles in water under the TH conditions. In addition, iridicycle exhibits great functional group tolerance, including highly sensitive boronic acid pinacol ester.

3.4 Experimental

3.4.1 General information

Unless otherwise specified, all reagents were commercially purchased and used without further purification. Deionised water was used for the reactions. NMR spectra were recorded on a Bruker 400 MHz or 250 MHz NMR spectrometer with TMS as the internal standard. Elemental Analysis and Mass Spectrometry Analysis were carried out at the Microanalysis Centre of the University of Liverpool. Quinolines **2n-t**, **2v-x** and **2z** were prepared according to the reported literature procedures.[23] All the data collected for the products were consistent with the literature. Compounds **3f**, **3n**, **3o**, **3r-y**, **5e**, **5f**, **7e**, **7i** and **11a** are unknown.

3.4.2 Typical reaction procedure for the TH of quinolines

Quinoline (2.5 mmol) and **C4** (1.6 mg, 2.5×10^{-3} mmol) were placed in a carousel reaction tube. HCO_2H/HCO_2Na aqueous solution of pH 4.5 (3 mL) was then introduced and the mixture was stirred at 30 °C for 14 h. The reaction mixture was quenched with saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were washed with brine (20 mL). The organic layer was collected and dried over anhydrous sodium sulphate. Filtration, followed by evaporation of the solvent under reduced pressure, gave the crude mixture that was purified with flash column chromatography to afford the desired 1,2,3,4-tetrahydroquinoline.

3.4.3 Typical reaction procedure for the TH of isoquinolinium and pyridinium salts

Isoquinolinium or pyridinium (2.5 mmol) and **C4** (16 mg, 2.5×10^{-2} mmol) were placed in a carousel reaction tube. HCO_2H/HCO_2Na aqueous solution of pH 4.5 (3 mL) was then introduced and the mixture was stirred at reflux temperature for 24 h (36 h for pyridinium). The reaction mixture was quenched with saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were washed with brine (20 mL). The organic layer was collected and dried over anhydrous sodium sulphate. Filtration, followed by evaporation of the solvent under reduced pressure, gave the crude mixture that was purified with flash column chromatography to afford the desired 1,2,3,4-tetrahydroisoquinoline or piperidine.

3.4.4 Typical reaction procedure for the TH of indoles, imines and other *N*-heterocycles

Imine/*N*-heterocycle (2.5 mmol) and **C4** (1.6 mg, 2.5 x 10^{-3} mmol) were placed in a carousel reaction tube. HCO_2H/HCO_2Na aqueous solution of pH 4.5 (3 mL) was then introduced (for substrate **8c, 8e** and **8f**, 1 mL of MeOH was added) and the mixture was stirred at 30 °C (or at reflux, refer to the Tables 3.8 and 3.9 for the reaction temperature) for 16 h. The reaction mixture was quenched with saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were washed with brine (20 mL). The organic layer was collected and dried over anhydrous sodium sulphate. Filtration, followed by evaporation of the solvent under reduced pressure, gave the crude mixture that was purified with flash column chromatography to afford the desired product.

3.4.5 Data of the cyclometalated rhodium complex D4
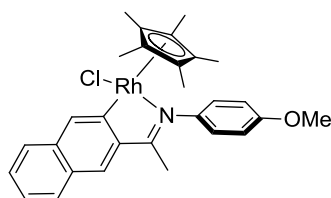
Complex D4: Red solid; ^1H NMR (CD_2Cl_2, 400 MHz, 293 K) δ (ppm): 8.11 (s, 1H), 8.02 (s, 1H), 7.83 (d, J = 8.3 Hz, 2H), 7.52-7.33 (m, 4H), 7.00 (d, J = 8.5 Hz, 2H), 3.86 (s, 3H), 2.43 (s, 3H), 1.40 (s, 15H). ^{13}C NMR (CD_2Cl_2, 100 MHz, 293 K) δ (ppm): 178.8, 175.5, 175.2, 157.9, 147.5, 143.5, 135.7, 133.5, 130.1, 128.9, 127.6, 127.2, 126.1, 124.0, 123.8, 113.8, 96.2, 96.1, 55.5, 16.9, 8.5. Anal. calc. for $C_{29}H_{31}ClRhNO + H_2O$ (%): C, 61.55; H, 5.88; N, 2.47. Found: C, 61.70; H, 5.46; N, 2.37.

3.4.6 Data of 1,2,3,4-tetrahydroquinolines (3a-z)
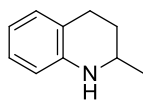
2-Methyl-1,2,3,4-tetrahydroquinoline, 3a:[13] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 6.95-6.94 (m, 2H), 6.61-6.58 (m, 1H), 6.47-6.45 (m, 1H), 3.66 (bs, 1H), 3.42-3.35 (m, 1H), 2.87-2.70 (m, 2H), 1.95-1.88 (m, 1H), 1.63-1.53 (m, 1H), 1.20 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 144.8, 129.3, 126.7, 121.1, 117.0, 114.0, 47.2, 30.2, 26.6, 22.6. HRMS for C$_{10}$H$_{14}$N [M+H]$^+$: m/z calc., 148.1121; found, 148.1124.
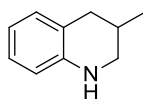
3-Methyl-1,2,3,4-tetrahydroquinoline, 3b:[13] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 6.98-6.92 (m, 2H), 6.60 (td, J = 7.3, 1.1 Hz, 1H), 6.47 (d, J = 7.9 Hz, 1H), 3.82 (bs, 1H), 3.28-3.24 (m, 1H), 2.89 (dd, J = 10.6, 9.7 Hz, 1H), 2.77 (ddd, J = 16.0, 4.8, 1.8 Hz, 1H), 2.42 (dd, J = 16.0, 10.3 Hz, 1H), 2.11-1.99 (m, 1H), 1.04 (d, J = 6.7 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 144.2, 129.5, 126.7, 121.2, 117.0, 113.9, 48.9, 35.5, 27.2, 19.0. HRMS for C$_{10}$H$_{14}$N [M+H]$^+$: m/z calc., 148.1121; found, 148.1125.
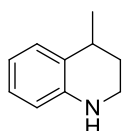
4-Methyl-1,2,3,4-tetrahydroquinoline, 3c:[22] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.05 (d, J = 7.5 Hz, 1H), 6.97-6.93 (m, 1H), 6.62 (td, J = 7.4, 1.0 Hz, 1H), 6.46 (dd, J = 8.0, 0.9 Hz, 1H), 3.79 (bs, 1H), 3.35-3.23 (m, 2H), 2.95-2.86 (m, 1H), 2.01-1.94 (m, 1H), 1.71-1.63 (m, 1H), 1.28 (d, J = 7.0 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 144.3, 128.5, 126.7, 126.6, 117.0, 114.2, 39.0, 30.3, 29.9, 22.7. HRMS for C$_{10}$H$_{14}$N [M+H]$^+$: m/z calc., 148.1121; found, 148.1126.
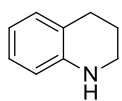
1,2,3,4-Tetrahydroquinoline, 3d:[22] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 6.97-6.93 (m, 2H), 6.59 (t, J = 7.4 Hz, 1H), 6.46 (d, J = 7.8 Hz, 1H), 3.79 (bs, 1H),

3.29 (t, J = 5.4 Hz, 2H), 2.75 (t, J = 6.4 Hz, 2H), 1.96-1.90 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 144.8, 129.5, 126.7, 121.5, 116.9, 114.2, 42.0, 27.0, 22.2. HRMS for C$_9$H$_{12}$N [M+H]$^+$: m/z calc., 134.0970; found, 134.0974.
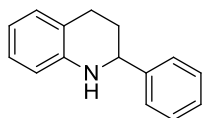
2-Phenyl-1,2,3,4-tetrahydroquinoline, 3e:[13] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.40-7.33 (m, 4H), 7.30-7.26 (m, 1H), 7.02-6.99 (m, 2H), 6.65 (td, J = 7.4, 0.8 Hz, 1H), 6.54 (d, J = 7.7 Hz, 1H), 4.44 (dd, J = 9.4, 3.3 Hz, 1H), 4.05 (bs, 1H), 2.96-2.88 (m, 1H), 2.73 (dt, J = 16.3, 4.7 Hz, 1H), 2.15-2.09 (m, 1H), 2.04-1.94 (m, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 144.8, 144.7, 129.3, 128.6, 127.4, 126.9, 126.6, 120.9, 117.2, 114.0, 56.3, 31.0, 26.4.
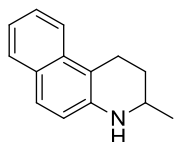
3-Methyl-1,2,3,4-tetrahydrobenzo[f]quinoline, 3f: ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.72 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.43-7.38 (m, 1H), 7.22-7.18 (m, 1H), 6.76 (d, J = 8.8 Hz, 1H), 3.86 (bs, 1H), 3.48-3.40 (m, 1H), 3.15-3.08 (m, 1H), 3.02-2.94 (m, 1H), 2.15-2.08 (m, 1H), 1.77-1.67 (m, 1H), 1.27 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 141.9, 133.4, 128.4, 127.8, 127.2, 126.3, 121.6, 121.3, 118.2, 111.5, 46.9, 30.1, 22.6, 22.2. HRMS for C$_{14}$H$_{16}$N [M+H]$^+$: m/z calc., 198.1280; found, 198.1283.
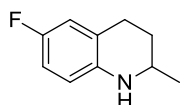
6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline, 3g:[13] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 6.69-6.64 (m, 2H), 6.41-6.37 (m, 1H), 3.57 (bs, 1H), 3.38-3.30 (m, 1H), 2.86-2.77 (m, 1H), 2.72-2.66 (m, 1H), 1.94-1.88 (m, 1H), 1.60-1.50 (m, 1H), 1.20 (d, J = 6.2 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 155.5 (d, J = 234.7 Hz), 141.0 (d, J = 1.7 Hz), 122.5 (d, J = 6.8 Hz), 115.4 (d, J = 21.5 Hz), 114.7 (d, J = 7.7 Hz), 113.2 (d, J = 22.4 Hz), 47.3, 29.9, 26.7, 22.5. HRMS for C$_{10}$H$_{13}$FN [M+H]$^+$: m/z calc., 166.1027; found, 166.1031.
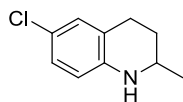
***6-Chloro-2-methyl-1,2,3,4-tetrahydroquinoline, 3h*:**[13] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 6.92-6.88 (m, 2H), 6.38 (d, J = 8.3 Hz, 1H), 3.69 (bs, 1H), 3.41-3.33 (m, 1H), 2.83-2.65 (m, 2H), 1.94-1.88 (m, 1H), 1.60-1.50 (m, 1H), 1.20 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 143.3, 128.8, 126.5, 122.6, 121.3, 114.9, 47.1, 29.7, 26.5, 22.5.
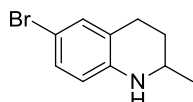
***6-Bromo-2-methyl-1,2,3,4-tetrahydroquinoline, 3i*:**[13] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.06-7.01 (m, 2H), 6.33 (d, J = 8.5 Hz, 1H), 3.72 (bs, 1H), 3.41-3.33 (m, 1H), 2.83-2.65 (m, 2H), 1.94-1.88 (m, 1H), 1.59-1.49 (m, 1H), 1.20 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 143.7, 131.7, 129.3, 123.1, 115.4, 108.3, 47.1, 29.6, 26.4, 22.5. HRMS for C$_{10}$H$_{13}$BrN [M+H]$^+$: m/z calc., 226.0226; found, 226.0230.
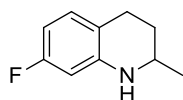
***7-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline, 3j*:**[13] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 6.85 (t, J = 7.4 Hz, 1H), 6.27 (td, J = 8.5, 2.5 Hz, 1H), 6.15 (dd, J = 10.8, 2.5 Hz, 1H), 3.76 (bs, 1H), 3.43-3.35 (m, 1H), 2.80-2.64 (m, 2H), 1.95-1.88 (m, 1H), 1.60-1.50 (m, 1H), 1.20 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 162.1 (d, J = 240.3 Hz), 145.9 (d, J = 10.5 Hz), 130.0 (d, J = 9.9 Hz), 116.4 (d, J = 2.4 Hz), 103.3 (d, J = 21.5 Hz), 100.1 (d, J = 24.4 Hz), 47.0, 30.0, 26.0, 22.5. HRMS for C$_{10}$H$_{13}$FN [M+H]$^+$: m/z calc., 166.1027; found, 166.1030.
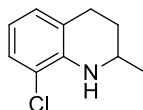
***8-Chloro-2-methyl-1,2,3,4-tetrahydroquinoline, 3k*:**[24] ^{1}H NMR (CDCl$_3$, 250 MHz, 298 K) δ (ppm): 7.06 (d, J = 7.9 Hz, 1H), 6.86 (d, J = 7.4 Hz, 1H), 6.51 (t, J = 7.7 Hz, 1H), 4.26 (bs, 1H), 3.53-3.40 (m, 1H), 2.91-2.69 (m, 2H), 1.99-1.89 (m, 1H), 1.66-1.50 (m, 1H), 1.27 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 63 MHz, 298 K) δ (ppm): 140.7, 127.4, 126.7, 122.4, 117.8, 116.3, 47.2, 29.6, 26.7, 22.5.
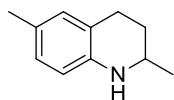
2,6-Dimethyl-1,2,3,4-tetrahydroquinoline, 3l:[13] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 6.78-6.76 (m, 2H), 6.40 (d, J = 8.3 Hz, 1H), 3.52 (bs, 1H), 3.39-3.31 (m, 1H), 2.85-2.76 (m, 1H), 2.71-2.65 (m, 1H), 2.20 (s, 3H), 1.94-1.87 (m, 1H), 1.62-1.52 (m, 1H), 1.19 (d, J = 6.2 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 142.4, 129.8, 127.2, 126.3, 121.2, 114.3, 47.3, 30.4, 26.6, 22.6, 20.4. HRMS for C$_{11}$H$_{16}$N [M+H]$^+$: m/z calc., 162.1277; found, 162.1279.
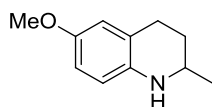
6-Methoxy-2-methyl-1,2,3,4-tetrahydroquinoline, 3m:[13] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 6.60-6.57 (m, 2H), 6.44 (d, J = 8.4 Hz, 1H), 3.72 (s, 3H), 3.47 (bs, 1H), 3.36-3.29 (m, 1H), 2.88-2.80 (m, 1H), 2.73-2.67 (m, 1H), 1.94-1.88 (m, 1H), 1.62-1.52 (m, 1H), 1.19 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 151.9, 138.9, 122.5, 115.3, 114.7, 112.9, 55.8, 47.5, 30.3, 26.9, 22.6. HRMS for C$_{11}$H$_{16}$NO [M+H]$^+$: m/z calc., 178.1226; found, 178.1229.
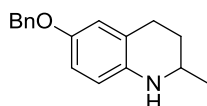
6-(Benzyloxy)-2-methyl-1,2,3,4-tetrahydroquinoline, 3n: ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.42-7.27 (m, 5H), 6.65-6.63 (m, 2H), 6.43-6.41 (m, 1H), 4.95 (s, 2H), 3.47 (bs, 1H), 3.35-3.28 (m, 1H), 2.86-2.78 (m, 1H), 2.71-2.65 (m, 1H), 1.92-1.86 (m, 1H), 1.61-1.51 (m, 1H), 1.18 (d, J = 6.2 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 151.1, 139.2, 137.8, 128.5, 127.7, 127.5, 122.5, 116.0, 115.2, 114.0, 70.9, 47.5, 30.3, 26.9, 22.6. HRMS for C$_{17}$H$_{20}$NO [M+H]$^+$: m/z calc., 254.1545; found, 254.1541.
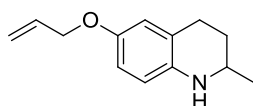
6-(Allyloxy)-2-methyl-1,2,3,4-tetrahydroquinoline, 3o: ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 6.62-6.59 (m, 2H), 6.43 (d, J = 8.1 Hz, 1H), 6.09-5.99 (m, 1H), 5.38 (dd, J = 17.3, 1.6 Hz, 1H), 5.24 (dd, J = 10.5, 1.4 Hz, 1H), 4.44 (dt, J = 5.3, 1.4 Hz, 2H), 3.44 (bs, 1H), 3.37-3.29 (m, 1H), 2.87-2.79 (m, 1H), 2.72-2.66 (m, 1H), 1.94-

1.88 (m, 1H), 1.62-1.52 (m, 1H), 1.19 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 150.8, 139.1, 134.0, 122.5, 117.2, 115.9, 115.2, 113.9, 69.7, 47.5, 30.3, 26.9, 22.6. HRMS for C$_{13}$H$_{18}$NO [M+H]$^+$: m/z calc., 204.1383; found, 204.1391.
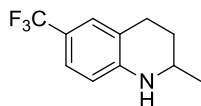
2-Methyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline, 3p:[25] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.18-7.17 (m, 2H), 6.44 (d, J = 8.9 Hz, 1H), 4.03 (bs, 1H), 3.49-3.41 (m, 1H), 2.86-2.71 (m, 2H), 1.98-1.92 (m, 1H), 1.61-1.52 (m, 1H), 1.23 (d, J = 6.3 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -60.8. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 147.3, 126.3 (q, J = 3.7 Hz), 125.0 (q, J = 270.3 Hz), 124.0 (q, J = 3.8 Hz), 120.3, 118.1 (q, J = 32.3 Hz), 112.9, 47.1, 29.4, 26.4, 22.4. HRMS for C$_{11}$H$_{13}$F$_3$N [M+H]$^+$: m/z calc., 216.0995; found, 216.1000.
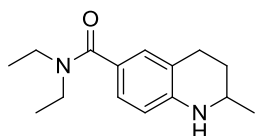
N,N-Diethyl-2-methyl-1,2,3,4-tetrahydroquinoline-6-carboxamide, 3r: ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.05 (s, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.41 (d, J = 8.2 Hz, 1H), 3.97 (bs, 1H), 3.45-3.40 (m, 5H), 2.86-2.69 (m, 2H), 1.97-1.91 (m, 1H), 1.62-1.53 (m, 1H), 1.22 (d, J = 6.3 Hz, 3H), 1.17 (d, J = 7.0 Hz, 6H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 172.0, 145.7, 128.4, 125.6, 125.3, 120.5, 112.9, 47.2, 29.8, 26.4, 22.5, 13.6 (br), one carbon signal is not observed. HRMS for C$_{15}$H$_{23}$N$_2$O [M+H]$^+$: m/z calc., 247.1805; found, 247.1812.
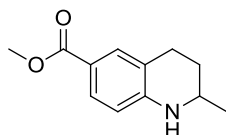
Methyl 2-methyl-1,2,3,4-tetrahydroquinoline-6-carboxylate, 3s: ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.66-7.64 (m, 2H), 6.40 (d, J = 8.9 Hz, 1H), 4.26 (bs, 1H), 3.83 (s, 3H), 3.52-3.44 (m, 1H), 2.86-2.74 (m, 2H), 1.99-1.93 (m, 1H), 1.62-1.52 (m, 1H), 1.24 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 167.5, 148.6, 131.1, 129.1, 119.8, 117.7, 112.6, 51.5, 47.2, 29.4, 26.3, 22.4. HRMS for C$_{12}$H$_{16}$NO$_2$ [M+H]$^+$: m/z calc., 206.1176; found, 206.1182.
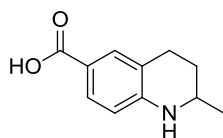
2-Methyl-1,2,3,4-tetrahydroquinoline-6-carboxylic acid, 3t: ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.72-7.69 (m, 2H), 6.40 (d, J = 9.0 Hz, 1H), 3.54-3.46 (m, 1H), 2.86-2.75 (m, 2H), 2.00-1.93 (m, 1H), 1.62-1.52 (m, 1H), 1.24 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 172.1, 149.4, 131.8, 129.9, 119.7, 116.5, 112.5, 47.2, 29.4, 26.3, 22.4. HRMS for C$_{11}$H$_{14}$NO$_2$ [M+H]$^+$: m/z calc., 192.1019; found, 192.1024.
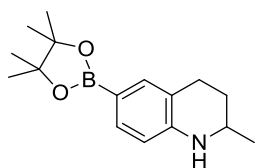
2-Methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydroquinoline, 3u: ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.43-7.41 (m, 2H), 6.43 (d, J = 7.7 Hz, 1H), 3.92 (bs, 1H), 3.47-3.39 (m, 1H), 2.85-2.70 (m, 2H), 1.95-1.89 (m, 1H), 1.61-1.51 (m, 1H), 1.31 (s, 12H), 1.20 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 147.5, 136.1, 133.8, 119.9, 113.0, 83.1, 47.1, 29.9, 26.3, 24.8, 22.6, one carbon signal is not observed. HRMS for C$_{16}$H$_{24}$BNO$_2$ [M]$^+$: m/z calc., 273.2009; found, 273.2005.
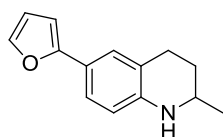
6-(Furan-2-yl)-2-methyl-1,2,3,4-tetrahydroquinoline, 3v: ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.37-7.36 (m, 1H), 7.29-7.27 (m, 2H), 6.48 (d, J = 8.9 Hz, 1H), 6.41-6.38 (m, 2H), 3.90 (bs, 1H), 3.47-3.39 (m, 1H), 2.90-2.73 (m, 2H), 1.98-1.92 (m, 1H), 1.65-1.55 (m, 1H), 1.23 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 155.0, 144.2, 140.6, 125.0, 122.9, 121.1, 120.4, 114.0, 111.4, 101.8, 47.3, 30.0, 26.6, 22.5. HRMS for C$_{14}$H$_{16}$NO [M+H]$^+$: m/z calc., 214.1226; found, 214.1230.
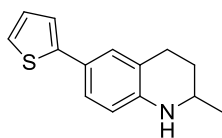
2-Methyl-6-(thiophen-2-yl)-1,2,3,4-tetrahydroquinoline, 3w: ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.24-7.21 (m, 2H), 7.13-7.10 (m, 2H), 7.01-6.99 (m, 1H), 6.45 (d, J = 8.9 Hz, 1H), 3.80 (bs, 1H), 3.46-3.38 (m, 1H), 2.89-2.72 (m, 2H), 1.97-1.91 (m, 1H), 1.64-1.54 (m, 1H), 1.21 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 145.6, 144.4, 127.8, 127.1, 124.8, 123.5, 122.6, 121.2, 120.7, 114.1, 47.3, 30.0, 26.6, 22.6. HRMS for C$_{14}$H$_{16}$NS [M+H]$^+$: m/z calc., 230.0998; found, 230.1005.
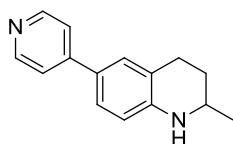
2-Methyl-6-(pyridin-4-yl)-1,2,3,4-tetrahydroquinoline, 3x: ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.53 (d, J = 6.0 Hz, 2H), 7.42 (d, J = 6.2 Hz, 2H), 7.33-7.27 (m, 2H), 6.53 (d, J = 8.8 Hz, 1H), 3.99 (bs, 1H), 3.48-3.46 (m, 1H), 2.88-2.84 (m, 1H), 2.83-2.84 (m, 1H), 1.97-1.93 (m, 1 H), 1.63-1.60 (m, 1H), 1.24 (d, J = 6.4 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 150.0, 148.4, 145.9, 127.8, 125.8, 125.4, 121.2, 120.3, 114.1, 47.2, 29.8, 26.6, 22.5. HRMS for C$_{15}$H$_{17}$N$_2$ [M+H]$^+$: m/z calc., 225.1392; found, 225.1397.
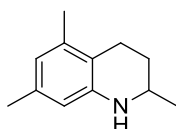
2,5,7-Trimethyl-1,2,3,4-tetrahydroquinoline, 3y: ^{1}H NMR (CDCl$_3$, 250 MHz, 298 K) δ (ppm): 6.35 (s, 1H), 6.20 (s, 1H), 3.61 (bs, 1H), 3.38-3.25 (m, 1H), 2.72-2.49 (m, 2H), 2.18 (s, 3H), 2.13 (s, 3H), 2.05-1.92 (m, 1H), 1.65-1.49 (m, 1H), 1.19 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 63 MHz, 298 K) δ (ppm): 144.8, 136.9, 135.8, 120.0, 116.9, 112.7, 46.7, 30.6, 23.6, 22.5, 21.0, 19.3.
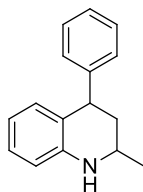
2-Methyl-4-phenyl-1,2,3,4-tetrahydroquinoline, 3z:[26] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.33-7.30 (m, 2H), 7.25-7.20 (m, 3H), 6.98-6.95 (m, 1H), 6.59-6.57 (m, 1H), 6.53-6.49 (m, 2H), 4.14 (dd, J = 12.5, 5.5 Hz, 1H), 3.84 (bs, 1H), 3.64-3.56 (m, 1H), 2.13 (ddd, J = 12.9, 5.5, 2.3 Hz, 1H), 1.88-1.79 (m, 1H), 1.23 (d, J = 6.2 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 145.9, 145.2, 129.7, 128.7, 128.5, 127.1, 126.4, 124.9, 117.4, 114.1, 47.7, 44.6, 41.2, 22.6. HRMS for C$_{16}$H$_{18}$N [M+H]$^+$: m/z calc., 224.1434; found, 224.1443.

3.4.7 Data of 1,2,3,4-tetrahydroisoquinolines (5a-5f) and piperidines (7a-7j)
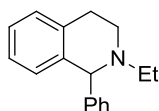
2-Ethyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline, 5a:[27] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.31-7.22 (m, 5H), 7.12-7.06 (m, 2H), 6.99-6.96 (m, 1H), 6.68 (d, J = 7.8 Hz, 1H), 4.58 (s, 1H), 3.21-3.16 (m, 1H), 3.14-3.08 (m, 1H), 2.88-2.82 (m, 1H), 2.66-2.57 (m, 2H), 2.40-2.31 (m, 1H), 1.04 (t, J = 7.1 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 144.3, 138.7, 134.8, 129.7, 128.9, 128.4, 128.2, 127.1, 125.8, 125.6, 68.0, 48.2, 46.7, 29.1, 11.5. HRMS for C$_{17}$H$_{20}$N [M+H]$^+$: m/z calc., 238.1596; found, 238.1599.
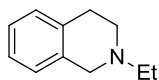
2-Ethyl-1,2,3,4-tetrahydroisoquinoline, 5b:[28] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.14-6.99 (m, 4H), 3.62 (s, 2H), 2.92 (t, J = 5.9 Hz, 2H), 2.73 (t, J = 5.9 Hz, 2H), 2.58 (q, J = 7.1 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 134.8, 134.3, 128.6, 126.6, 126.1, 125.6, 55.8, 52.2, 50.6, 29.1, 12.4.
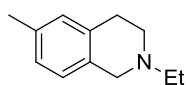
2-Ethyl-6-methyl-1,2,3,4-tetrahydroisoquinoline, 5e: ^{1}H NMR (CDCl$_3$, 250 MHz, 298 K) δ (ppm): 6.91 (bs, 3H), 3.52 (s, 2H), 2.87 (t, J = 5.9 Hz, 2H), 2.71 (t, J = 5.9

Hz, 2H), 2.56 (q, J = 7.2 Hz, 2H), 2.28 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 135.5, 134.1, 131.8, 129.1, 126.5, 126.4, 55.6, 52.2, 50.8, 29.1, 21.0, 12.4. HRMS for C$_{12}$H$_{18}$N [M+H]$^+$: m/z calc., 176.1439; found, 176.1442.
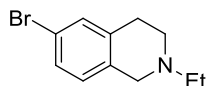
6-Bromo-2-ethyl-1,2,3,4-tetrahydroisoquinoline, 5f: ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.38 (t, J = 4.6 Hz, 1H), 6.99 (d, J = 4.9 Hz, 2H), 3.61 (s, 2H), 2.87 (t, J = 6.0 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 2.58 (q, J = 7.2 Hz, 2H), 1.19 (t, J = 7.1 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 137.4, 134.2, 130.1, 126.9, 125.8, 125.2, 55.9, 51.9, 50.7, 30.3, 12.4.
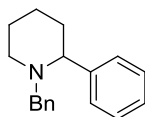
1-Benzyl-2-phenylpiperidine, 7a:[14] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.47-7.20 (m, 10H), 3.78 (d, J = 13.5 Hz, 1H), 3.12 (d, J = 9.4 Hz, 1H), 3.00-2.81 (m, 2H), 2.03-1.87 (m, 1H), 1.78 (d, J = 12.5 Hz, 2H), 1.71-1.52 (m, 3H), 1.37 (td, J = 8.4, 3.8 Hz, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 128.8, 128.5, 128.0, 127.5, 126.9, 126.6, 69.2, 59.7, 53.3, 36.9, 25.9, 25.2. (2 C signals not observed due to low intensity). HRMS for C$_{18}$H$_{22}$N [M+H]$^+$: m/z calc., 252.1752; found, 252.1753.
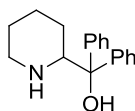
Diphenyl(piperidin-2-yl)methanol, 7b:[29] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.36-7.32 (m, 11 H), 4.87 (bs, 1H), 2.58 (t, J = 7.3 Hz, 2H), 2.44 (q, J = 6.6 Hz, 1H), 2.30 (t, J = 7.3 Hz, 2H), 1.45 (quin, J = 7.5 Hz, 2H), 1.32-1.25 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 141.6, 128.5, 128.2, 128.1, 85.6, 52.6, 47.1, 38.1, 25.6, 22.2.
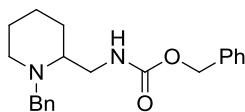
Benzyl ((1-benzylpiperidin-2-yl)methyl)carbamate, 7c:[14] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.33-7.15 (m, 10H), 5.33 (bs, 1H), 5.09 (s, 2H), 3.98 (d, J = 13.5 Hz, 1H), 3.54-3.42 (m, 1H), 3.37-3.26 (m, 1 H), 3.20 (d, J = 13.5 Hz, 1H), 2.88-2.73 (m, 1H),

2.47-2.31 (m, 1H), 2.12-1.94 (m, 1H), 1.77-1.59 (m, 2H), 1.56-1.45 (m, 2H), 1.45-1.22 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 161.1, 156.8, 139.0, 136.8, 128.8, 128.5, 128.3, 127.8, 126.9, 66.6, 59.3, 57.7, 51.8, 42.7, 28.8, 24.8, 23.7. HRMS for C$_{21}$H$_{27}$N$_2$O$_2$ [M+H]$^+$: m/z calc., 339.2073; found, 339.2066.
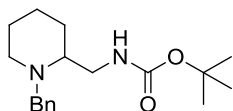
Tert-butyl ((1-benzylpiperidin-2-yl)methyl)carbamate, 7d:[14] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.33-7.24 (m, 5H), 5.05 (bs, 1H), 4.00 (d, J = 13.5 Hz, 1H), 3.44-3.41 (m, 1H), 3.28-3.20 (m, 2H), 2.83-2.80 (m, 1H), 2.41-2.40 (m, 1H), 2.06-2.01 (m, 1H), 1.72-1.63 (m, 2H), 1.54-1.26 (m, 13H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 156.4, 139.1, 128.9, 128.3, 126.9, 79.0, 59.5, 57.6, 51.8, 42.2, 28.9, 28.5, 24.7, 23.7. HRMS for C$_{18}$H$_{29}$N$_2$O$_2$ [M+H]$^+$: m/z calc., 305.2229; found, 305.2231.
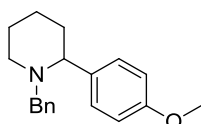
1-Benzyl-2-(4-methoxyphenyl)piperidine, 7e: ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.43-7.33 (m, J = 8.2 Hz, 2H), 7.32-7.13 (m, 5H), 6.92-6.79 (m, J = 8.4 Hz, 2H), 3.85-3.66 (m, 4H), 3.05 (dd, J = 2.4, 11.0 Hz, 1H), 2.95 (d, J = 11.5 Hz, 1H), 2.78 (d, J = 13.7 Hz, 1H), 1.97-1.86 (m, 1H), 1.81-1.71 (m, 2H), 1.66-1.52 (m, 3H), 1.42-1.28 (m, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 158.5, 139.9, 137.8, 128.7, 128.4, 128.0, 126.5, 113.9, 68.5, 59.7, 55.3, 53.5, 37.1, 26.1, 25.3.
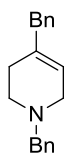
1,4-Dibenzyl-1,2,3,6-tetrahydropyridine, 7h:[14] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.35-7.15 (m, 10 H), 5.39-5.34 (m, 1H), 3.57 (s, 2H), 3.28 (s, 2H), 3.00-2.98 (m, 2H), 2.53 (t, J = 5.8 Hz, 2H), 2.08-2.02 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 139.5, 135.9, 129.3, 129.1, 128.7, 128.3, 128.2, 127.1, 126.0, 124.2, 62.7, 52.8, 49.8, 43.5, 30.9. HRMS for C$_{19}$H$_{22}$N [M+H]$^+$: m/z calc., 264.1747; found, 264.1753.
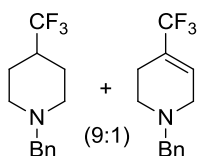
Isolated as 9:1 mixture; ***1-Benzyl-4-(trifluoromethyl)piperidine, 7i***: ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.33-7.23 (m, 5H), 3.50 (s, 2H), 2.97-2.94 (m, 2H), 2.02-1.90 (m, 3H), 1.82-1.79 (m, 2H), 1.68-1.58 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 138.2, 129.0, 128.3, 127.8 (q, J = 278.0 Hz), 127.1, 63.1, 52.4, 40.4 (q, J = 27.2 Hz), 24.7 (q, J = 2.6 Hz). HRMS for C$_{13}$H$_{17}$F$_3$N [M+H]$^+$: m/z calc., 244.1313; found, 244.1311. ***1-Benzyl-4-(trifluoromethyl)-1,2,3,6-tetrahydropyridine, 7i-1***:[14] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.33-7.23 (m, 5H), 6.27-6.23 (m, 1H), 3.61 (s, 2H), 3.09-3.06 (m, 2H), 2.62 (t, J = 5.7 Hz, 2H), 2.30-2.27 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 137.8, 128.6 (q, J = 44.3 Hz), 128.4, 128.3, 127.3, 127.2 (q, J = 28.1 Hz), 123.5 (q, J = 272.0 Hz), 62.3, 51.5, 48.5, 23.2. HRMS for C$_{13}$H$_{15}$F$_3$N [M+H]$^+$: m/z calc., 242.1157; found, 242.1154.
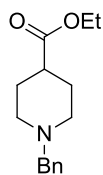
Ethyl 1-benzylpiperidine-4-carboxylate, 7j:[30] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.32-7.22 (m, 5H), 4.12 (q, J = 7.1 Hz, 2H), 3.49 (s, 2H), 2.89-2.81 (m, 2H), 2.33-2.21 (m, 1H), 2.07-1.97 (m, 2H), 1.90-1.72 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 175.2, 138.4, 129.0, 128.2, 126.9, 63.2, 60.2, 52.9, 41.2, 28.3, 14.2. HRMS for C$_{15}$H$_{22}$NO$_2$ [M+H]$^+$: m/z calc., 248.1651; found, 248.1647.

3.4.8 Data of indolines and other saturated *N*-heterocycles
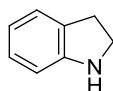
Indoline, 9a:[22] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.11 (d, J = 7.2 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.70 (t, J = 7.4 Hz, 1H), 6.64 (d, J = 7.7 Hz, 1H), 3.73 (bs, 1H), 3.54 (t, J = 8.4 Hz, 2H), 3.02 (t, J = 8.4 Hz, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 151.6, 129.3, 127.2, 124.6, 118.7, 109.4, 47.3, 29.9. HRMS for C$_8$H$_{10}$N [M+H]$^+$: m/z calc., 120.0813; found, 120.0817.
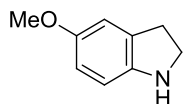
5-Methoxyindoline, 9b:[22] ^{1}H NMR (CDCl₃, 400 MHz, 298 K) δ (ppm): 6.75 (s, 1H), 6.59 (d, J = 1.4 Hz, 2H), 3.74 (s, 3H), 3.53 (t, J = 8.3 Hz, 2H), 3.35 (bs, 1H), 3.01 (t, J = 8.3 Hz, 2H). ^{13}C NMR (CDCl₃, 100 MHz, 298 K) δ (ppm): 153.6, 145.3, 131.2, 112.2, 111.6, 110.1, 56.0, 47.8, 30.5. HRMS for $C_9H_{12}NO$ [M+H]⁺: m/z calc., 150.0919; found, 150.0926.
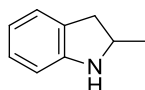
2-Methylindoline, 9d:[22] ^{1}H NMR (CDCl₃, 400 MHz, 298 K) δ (ppm): 7.07 (d, J = 7.3 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.68 (t, J = 7.4 Hz, 1H), 6.59 (d, J = 7.7 Hz, 1H), 4.02-3.94 (m, 1H), 3.67 (bs, 1H), 3.13 (dd, J = 15.4, 8.5 Hz, 1H), 2.63 (dd, J = 15.4, 7.8 Hz, 1H), 1.28 (d, J = 6.2 Hz, 3H). ^{13}C NMR (CDCl₃, 100 MHz, 298 K) δ (ppm): 151.0, 128.9, 127.2, 124.7, 118.5, 109.2, 55.2, 37.8, 22.3. HRMS for $C_9H_{12}N$ [M+H]⁺: m/z calc., 134.0970; found, 134.0972.
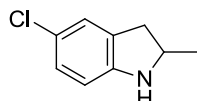
5-Chloro-2-methylindoline, 9e:[31] ^{1}H NMR (CDCl₃, 400 MHz, 298 K) δ (ppm): 7.01 (s, 1H), 6.95 (dd, J = 8.2, 2.0 Hz, 1H), 6.49 (d, J = 8.2 Hz, 1H), 4.04-3.96 (m, 1H), 3.69 (bs, 1H), 3.12 (dd, J = 15.6, 8.6 Hz, 1H), 2.61 (dd, J = 15.7, 7.7 Hz, 1H), 1.27 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl₃, 100 MHz, 298 K) δ (ppm): 149.5, 130.8, 127.0, 124.9, 123.0, 109.8, 55.6, 37.6, 22.2. HRMS for $C_9H_{11}ClN$ [M+H]⁺: m/z calc., 168.0580; found, 168.0581.
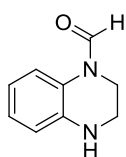
3,4-Dihydroquinoxaline-1(2H)-carbaldehyde, 11a: ^{1}H NMR (CDCl₃, 400 MHz, 298 K) δ (ppm): 8.73 (s, 1H), 7.06 (dd, J = 8.0, 1.2 Hz, 1H), 7.00 (td, J = 7.7, 1.4 Hz, 1H), 6.74-6.67 (m, 1H), 6.64 (dd, J = 8.0, 1.4 Hz, 1H), 4.05 (bs, 1H), 3.92-3.86 (m, 2H), 3.41 (t, J = 4.8 Hz, 2H). ^{13}C NMR (CDCl₃, 100 MHz, 298 K) δ (ppm): 160.1, 136.5, 125.9, 123.7, 117.9, 117.7, 115.1, 41.2, 37.3.
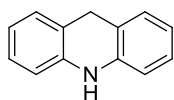
9,10-Dihydroacridine, 11b:[13] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.15-6.99 (m, 4H), 6.85 (td, J = 7.4, 1.0 Hz, 2H), 6.66 (d, J = 7.8 Hz, 2H), 5.94 (bs, 1H), 4.05 (s, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 140.1, 128.6, 127.0, 120.7, 120.1, 113.4, 31.4.
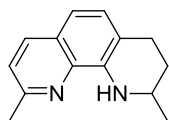
2,9-Dimethyl-1,2,3,4-tetrahydro-1,10-phenanthroline, 11c:[32] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.88 (d, J = 8.3 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 5.84 (bs, 1H), 3.60-3.55 (m, 1H), 3.03-2.95 (m, 1H), 2.89-2.82 (m, 1H), 2.68 (s, 3H), 2.06-2.02 (m, 1H), 1.77-1.67 (m, 1H), 1.37 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 155.8, 140.1, 136.8, 136.0, 127.8, 125.3, 121.3, 116.6, 113.3, 46.6, 30.0, 26.7, 25.2, 22.5. HRMS for C$_{14}$H$_{17}$N$_2$ [M+H]$^+$: m/z calc., 213.1386; found, 213.1393.
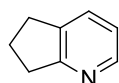
6,7-Dihydro-5H-cyclopenta[b]pyridine, 11d:[33] ^{1}H NMR (CDCl$_3$, 250 MHz, 298 K) δ (ppm): 8.32 (d, J = 4.8 Hz, 1H), 7.48 (dd, J = 7.5, 0.9 Hz, 1H), 7.01 (dd, J = 7.5, 5.0 Hz, 1H), 3.04-2.90 (m, 4H), 2.12 (pen, J = 7.5 Hz, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 165.6, 147.4, 136.8, 132.0, 120.9, 34.2, 30.7, 23.0. HRMS for C$_8$H$_{10}$N [M+H]$^+$: m/z calc., 120.0813; found, 120.0811.
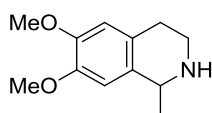
6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, 11f:[34] ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 6.63 (s, 1H), 6.57 (s, 1H), 4.05 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.28-3.23 (m, 1H), 3.03-2.97 (m, 1H), 2.83-2.73 (m, 1H), 2.68-2.62 (m, 1H), 1.84 (bs, 1H), 1.44 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 147.3, 147.2, 132.4, 126.8, 111.7, 109.0, 56.0, 55.9, 51.2, 41.8, 29.6, 22.9. HRMS for C$_{12}$H$_{18}$NO$_2$ [M+H]$^+$: m/z calc., 208.1332; found, 208.1336.

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Chapter 4

Primary Amines by Transfer Hydrogenative Reductive Amination of Ketones

4.1 Introduction

Primary amines are important motifs in organic compounds because of the presence of this functional group in numerous bioactive molecules and their widespread pharmaceutical applications (Scheme 4.1).[1] Hence, the efficient and economical production of primary amines is of high priority.[2]
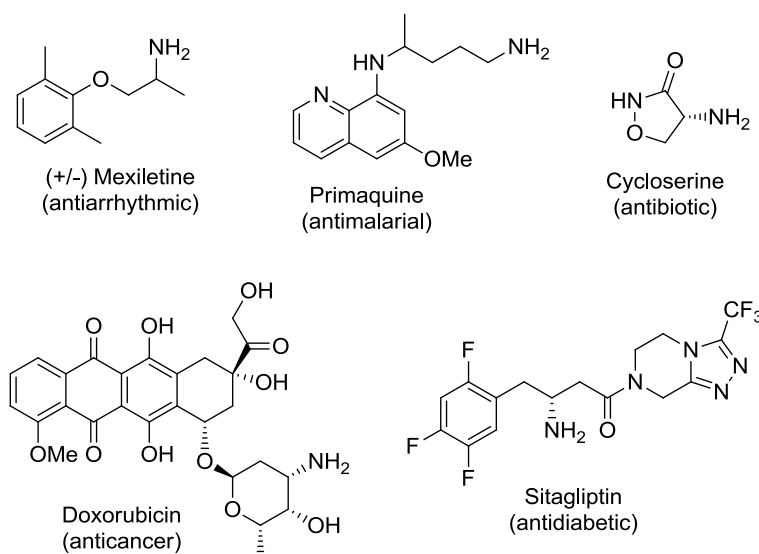
Scheme 4.1: Examples of drugs containing primary amines.

There are several methods with which these amines can be synthesised. Typical examples include the reduction of nitriles, amides and nitro compounds,[3] alkylation of ammonia with organic halides,[4] and hydroamination of alkenes.[5] However, one of the most desired and convenient ways of synthesising primary amines is by direct reductive amination (DRA),[6-8] in which a carbonyl group is condensed with an ammonia source and subsequently reduced in situ without the need of isolating the often unstable imine intermediate (Scheme 4.2). A well-known example is the classic Leuckart-Wallach reaction.[9]
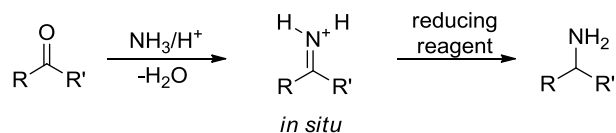
Scheme 4.2: General scheme of direct reductive amination (DRA).

Reducing agents such as pyridine borane, $NaBH_3CN$ and $NaBH(OAc)_3$ are commonly employed in the DRA process.[10] However, for successful, complete DRA, excess amount of these boron reducing agents is often required. $NaBH_3CN$ is highly toxic and the final product is usually contaminated with cyanide. $NaBH(OAc)_3$ is poorly soluble in most commonly used organic solvents and pyridine borane, on the other hand, can be unsafe to use on industrial scales due to its propensity to violently decompose.[11] Heterogeneous catalysts have also been widely used in DRA;[12] however poor chemoselectivity limits their performance. In this context, a homogeneously catalysed DRA would be of great interest. Indeed, a lot of efforts have been made in developing homogeneous organocatalytic,[13] hydrogenative[14] and transfer hydrogenative[8,15] catalytic systems for DRA in the past few years. However, they are mainly directed to the production of secondary and tertiary amines. In terms of primary amines, DRA reactions have been much less explored.[16-18]

The first successful hydrogenative homogeneous metal catalysed DRA with ammonia was reported by Beller and co-workers.[16] Although high selectivity was achieved towards primary amines formation, high temperatures and pressures were required (135 °C, 65 bar H_2). Most of the reported reactions were conducted with aromatic aldehydes and poor yields were obtained when aliphatic amines were used. Kadyrov and co-workers also described the use of hydrogenative DRA with ammonia. However, the selectivity towards primary amine formation (versus

alcohol) and the yields obtained were relatively poor.[17] Subsequently, enantioselective DRA of β-keto amides and β-keto esters were also reported, albeit requiring high pressures of H_2.[18]

One way of overcoming these problems would be the transfer-hydrogenative DRA, by using a hydrogen source other than hydrogen gas. This is an operationally simple and versatile method for reduction, avoiding the need for high-pressure reactors that are typically required for hydrogenation.[11,19] The Leuckart-Wallach reaction uses formic acid as the reductant and no catalyst. However, it requires high temperatures and is poorly chemoselective.[9] Despite the huge potential of catalytic DRA, only a few examples have been reported for the synthesis of primary amines by homogeneous metal-catalysed transfer hydrogenative DRA.[20-23]

The first successful example of such a DRA with HCO_2NH_4 was reported by Kitamura and co-workers (Scheme 4.3).[20] The reaction conditions were milder (low temperature) than those used in the hydrogenative DRA and the catalyst was also effective in the DRA of α-keto acids. The substrate scope was, however, not satisfactory, and the selectivity towards primary amines (versus ketone reduction and *N*-alkylation) was still an issue. Subsequently, Kadyrov and co-workers reported the enantioselective DRA with HCO_2NH_4 (Scheme 4.4).[21] The use of additional NH_3 was found to be crucial to enhance the enantioselectivity. High yields and enantioselectivities were only achieved in the case of aromatic ketones and inferior results were obtained when examples of aliphatic ketones were attempted. In addition, the selectivity towards primary amines was low, as *N*-formyl derivatives were obtained as the major products, which subsequently had to be hydrolysed. Ogo and co-workers reported a water-soluble catalyst that enabled DRA of α-keto acids

under aqueous conditions (Scheme 4.5).[23] Optimal pH of 5 was critical for the selective synthesis of α-amino acids.
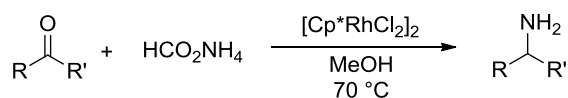
Scheme 4.3: Rhodium catalysed transfer hydrogenative DRA.
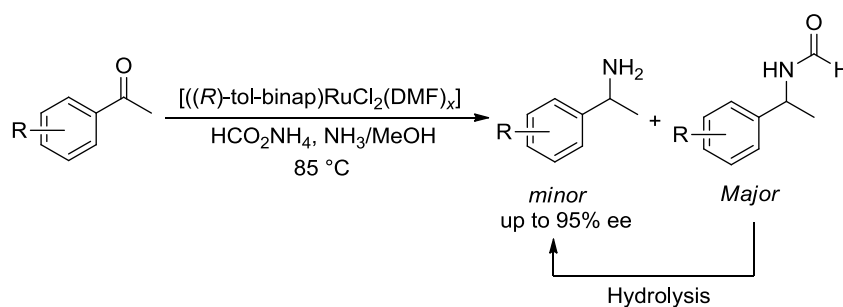
Scheme 4.4: Ruthenium catalysed transfer hydrogenative DRA.
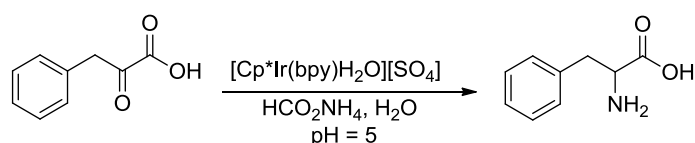
Scheme 4.5: Iridium catalysed transfer hydrogenative DRA under aqueous condition.

Although the few reports above have described the synthesis of primary amines by DRA, the results are still far from satisfactory. From the literature, we can highlight some major issues for both hydrogenative and transfer-hydrogenative DRA:

1) Substrate scope is limited, especially for ketones with additional functional groups.

2) Selectivity towards primary amine is still a major challenge.

3) Catalysts capable of the DRA of aliphatic ketones are highly desirable.

4) In terms of economy, a robust, versatile catalyst for the synthesis of primary amines by DRA is of high priority.

Thus, developing a catalyst that overcomes these issues would be of great interest. Following the successful exploration of cyclometalated Ir(III) complexes in the

transfer hydrogenation of α-substituted ketones and *N*-Heterocycles in water, we report in this chapter that such complexes are also highly versatile and chemoselective for the synthesis of primary amines by direct reductive amination.[24]

4.2 Results and discussion

4.2.1 Optimisation of reaction conditions

Aiming to find a robust catalyst for the DRA concerned, a range of complexes **C1-C12** (Scheme 4.6) were firstly prepared. These complexes are diverse in both the conjugation and electronic property of the aromatic rings coordinated to the iridium metal.
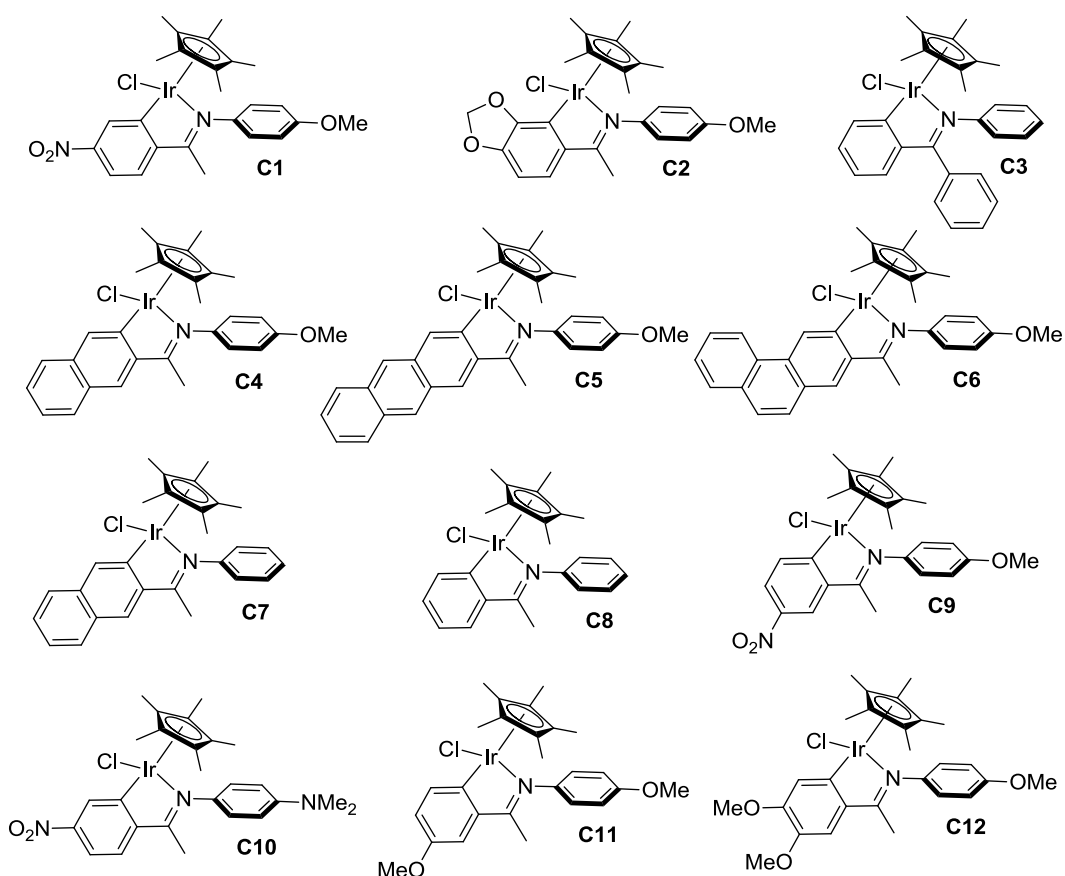
Scheme 4.6: Cyclometalated iridium complexes examined in this chapter.

In this study, 2-acetonaphthone was chosen as a model substrate for the optimisation of reaction conditions. Initial reduction experiments were carried out at an S/C ratio

of 1000:1, by using 10 equivalents of HCO_2NH_4 and temperature of 80 °C. The results are summarised in Table 4.1. Only 6% conversion was obtained when the reductive amination was carried out in the presence of the iridium dimer $[Cp^*IrCl_2]_2$. Catalyst **C8**, bearing no substituents on the phenyl rings afforded 36% conversion with a high selectivity towards the primary amine **2a** (28% relative to the starting **1a**); however, the byproducts alcohol (**3a**), secondary amine (**4a**) and *N*-formyl (**5a**) were also observed in 5, 1 and 2% yields, respectively. These byproducts are common in metal-catalysed DRA reactions, although the later *N*-formyl derivative could be converted into the desired primary amine by one additional step of hydrolysis. Catalysts or reaction conditions disfavouring the production of these byproducts, especially alcohol and secondary amine, would be highly beneficial. Catalyst **C9** and **C1**, with a *meta*-NO_2 and *para*-NO_2 group (with respect to imine) on the ligand did not improve the activity (Table 4.1, entries 3 and 4). When the OMe group was replaced with a more electron-donating –NMe_2 group, the activity decreased (**C10**; Table 4.1, entry 5). Since the amino group might get protonated, the electron donating ability of the NMe_2 probably decreases. Interestingly, catalyst **C11**, with an electron-rich OMe group at the *meta*-position significantly improved the catalytic activity, giving a 70% conversion (64% primary amine) in 4 h (Table 4.1, entry 6). The result was slightly improved by introducing another methoxy group at the *para*-position also (**C12**; Table 4.1, entry 7). Gratifyingly, 98% conversion (90% primary amine) was achieved when catalyst **C2**, which contained a 1,3-dioxol group on the phenyl ring was used (Table 4.1, entry 8). Other aromatic rings, such as naphthyl, phenanthrenyl and anthracenyl were also targeted. To our delight, catalyst **C4** which contains a naphthyl ring gave excellent results, with 99% conversion and a very high selectivity towards primary amines (Table 4.1, entry 10).

Table 4.1: Optimising reaction conditions of DRA
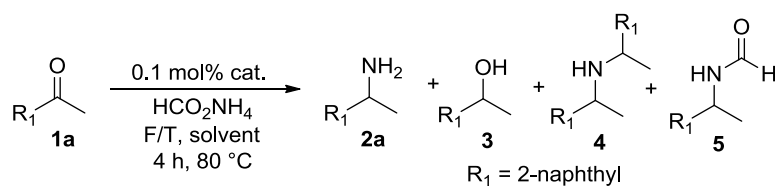
Entry[a]	Catalyst	Solvent	Conv. (%)[b]	2a[b]	3[b]	4[b]	5[b]
1	[Cp*IrCl$_2$]$_2$	MeOH	6	-	1	-	5
2	**C8**	MeOH	36	28	5	1	2
3	**C9**	MeOH	9	5	1	1	2
4	**C1**	MeOH	38	35	-	1	2
5	**C10**	MeOH	12	7	3	1	1
6	**C11**	MeOH	70	64	2	2	2
7	**C12**	MeOH	86	79	2	2	3
8	**C2**	MeOH	98	90	3	2	3
9	**C7**	MeOH	42	34	4	1	3
10	**C4**	MeOH	99	94	1	2	2
11[c]	**C4**	MeOH	54	53	-	-	1
12[d]	**C4**	MeOH	82	65	9	3	5
13	**C5**	MeOH	93	84	1	2	6
14	**C6**	MeOH	65	53	4	3	5
15	**C3**	MeOH	62	47	5	4	6
16	**C4**	H$_2$O	99	1	98	-	-
17	**C4**	toluene	15	4	3	1	7
18	**C4**	DMF	18	3	-	2	13
19	**C4**	EtOAc	35	1	13	2	19
20	**C4**	TFE	96	81	4	3	8

[a] Reaction conditions: 2-acetonaphthone (0.5 mmol), HCO$_2$NH$_4$ (5 mmol), catalyst (5x10^{-4} mmol), HCO$_2$H/Et$_3$N (5:2) azeotrope (0.5 mL) and solvent (3 mL), stirred at 80 °C in a carousel tube for 4 h. [b] Determined by ^{1}H NMR spectroscopy (%). [c] In the absence of F/T azeoptrope. [d] Five equivalents of ammonium formate used.

Addition of the formic acid-triethyl amine (F/T) azeotrope was found to promote the

reaction. In its absence, the **C4**-catalysed reaction proceeded in only 54% conversion

in 4 h (Table 4.1, entry 11). The F/T azeotrope increases the acidity of the reaction medium, and indeed it is known that the imine formation and its subsequent reduction benefits from the acidic conditions.[25] When the reaction was conducted with five equivalents of ammonium formate, the conversion decreased and formation of more byproducts was observed (Table 4.1, entry 12). In contrast, the catalysts **C5** and **C6**, bearing an anthracene and phenanthrene ring, respectively, gave lower conversions (Table 4.1, entries 13 and 14). This is at least partly due to their low solubility in the reaction medium. It was confirmed that the reaction did not proceed in the absence of a catalyst.

The reaction in various solvents was investigated next. MeOH was found to be the best medium, giving high selectivity towards the primary amine relative to other solvents (Table 4.1, entries 17-20). Interestingly, when the reaction was conducted in water, the reduction of ketone dominated, with the alcohol product observed in 98% ratio (Table 4.1, entry 16). Our group have recently shown that aqueous media of lower pH favour the ketone reduction over the imine formation.[26]

4.2.2 DRA of aromatic ketones with HCO_2NH_4

The substrate scope was examined with catalyst **C4** under the optimised conditions (0.1 mol% **C4**, 80 °C in MeOH). The results of DRA of aromatic ketones are summarised in Table 4.2. All the phenyl derivatives, regardless of the nature of the substituents and their positions, gave excellent yields (Table 4.2, entries 3-16). The naphthyl derivatives also reacted well giving high yields (Table 4.2, entries 1 and 2). Disubstituted aromatic ketones and those with increasing chain length at the α-position did not affect the yields of the product (Table 4.2, entries 17-19). When an α,β-unsaturated ketone was subjected to the DRA under the present conditions,
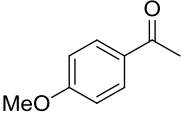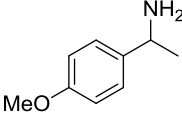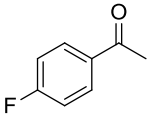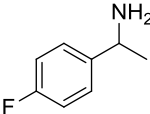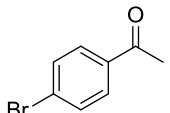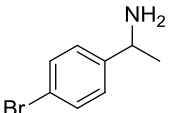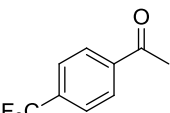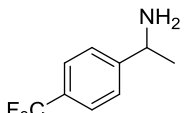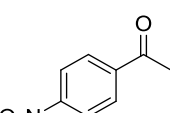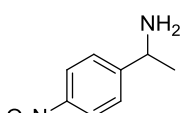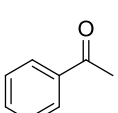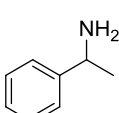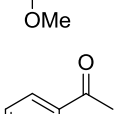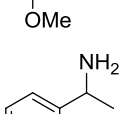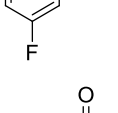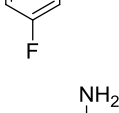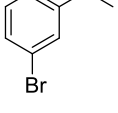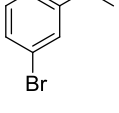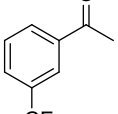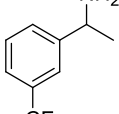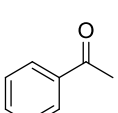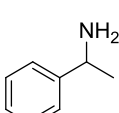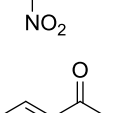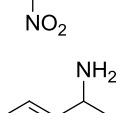
reduction of the carbon double bond was observed as well (Table 4.2, entry 20). This suggests that when a double bond is present next to a carbonyl, 1,4-reduction pathway is favoured over 1,2-reduction, and it is not surprising, as 1,4-reduction is frequently observed in transfer hydrogenation.[27]   The cyclic substrates, 1-indanone and 1-tetralone, both gave their corresponding amines in excellent yields (Table 4.2, entries 21 and 22). In contrast to the α,β-unsaturated ketone, when 2-acetylbenzofuran was used, the double bond was retained, with 1-(benzofuran-2-yl)ethanamine obtained in 91% yield (Table 4.2, entry 23), a result that reflects the aromaticity of the substrate. A thiophene ring was also tolerated well, affording 1-(2,5-dimethylthiophen-3-yl)ethanamine in an excellent yield (Table 4.2, entry 24). It was found that a prolonged reaction time increases the concentration of *N*-formyl derivatives in these reactions. In fact, reaction times of 4-12 h were sufficient for the completion of the DRA.

Table 4.2: DRA of aromatic ketones with HCO_2NH_4

Entry[a]	Ketones	Amines		Yields (%)[b]
1			**2a**	93
2			**2b**	94
3			**2c**	84
4			**2d**	91

5			**2e**	88
6			**2f**	89
7			**2g**	91
8			**2h**	85
9			**2i**	90
10			**2j**	89
11			**2k**	90
12			**2l**	87
13			**2m**	82
14			**2n**	88
15			**2o**	84
16			**2p**	86

17			**2q**	90
18			**2r**	92
19			**2s**	88
20			**2t**	82
21			**2u**	90
22			**2v**	87
23			**2w**	91
24			**2x**	92
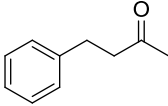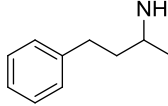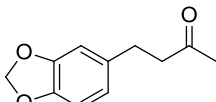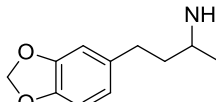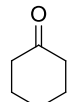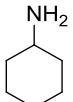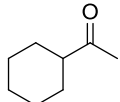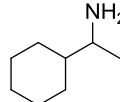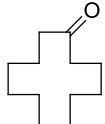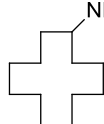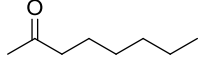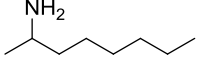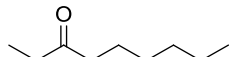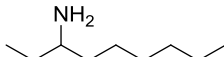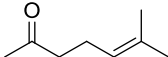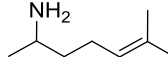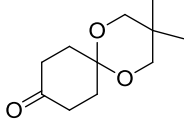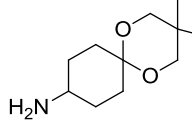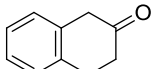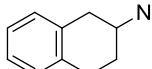
[a] Reaction conditions: ketone (0.5 mmol), HCO_2NH_4 (5 mmol), catalyst (5×10^{-4} mmol), HCO_2H/Et_3N (5:2) azeotrope (0.5 mL) and MeOH (3 mL), stirred at 80 °C in a carousel tube for 12 h.

[b] Yield of isolated product.

4.2.3 DRA of aliphatic ketones with HCO$_2$NH$_4$

Reactions of aliphatic ketones with HCO$_2$NH$_4$ are summarised in Table 4.3. As can be seen, 4-phenylbutan-2-one and its variant 4-(3,4-methylenedioxy)phenyl-2-butanone both were converted to their corresponding amines in excellent yields (Table 4.3, entries 1 and 2). Cyclohexanamine and 1-cyclohexylethanamine were also obtained in good yields (Table 4.3, entries 3 and 4). Interestingly, a bulkier substrate, cyclododecanone, was also aminated in a high yield without any predicament (Table 4.3, entry 5). Long-chain aliphatic substrates worked well, furnishing good yields regardless of the position of the carbonyl unit (Table 4.3, entries 6 and 7). Still interestingly, 6-methylhept-5-en-2-one gave its corresponding amine in a very good yield, leaving its C=C double bond intact. This shows the selectivity of the catalyst towards C=N bond reduction over a C=C bond. Indeed, the reduction of C=C double bond is only observed when it is present at a position α to the C=O group. 3,3-Dimethyl-1,5-dioxaspiro[5.5]undecan-9-one, a useful monoprotected form of the dione, was selectively aminated in excellent yield without the hydrolysis of its 1,3-dioxane being observed (Table 4.3, entry 9). Thus, the catalytic system offers a simple and efficient way of obtaining aminocyclohexanones, which are useful intermediates, especially for the synthesis of Pramipexole, a dopamine agonist of the non-ergoline class used for the treatment of signs and symptoms of idiopathic Parkinson's disease.[28] 2-Aminotetralin, another key precursor, was also obtained in a very good yield from its corresponding β-tetralone (Table 4.3, entry 10). 2-Aminotetralins are used in the synthesis of many therapeutic agents and have also been known to possess other pharmacological activities, including dopamine receptor activity.[29]
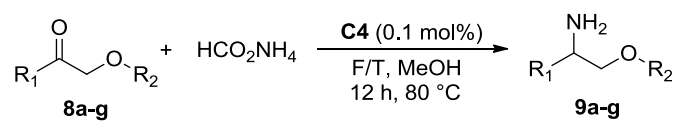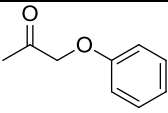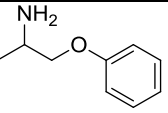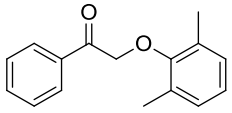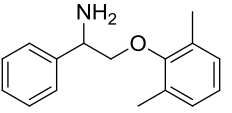
Table 4.3: DRA of aliphatic ketones with HCO_2NH_4
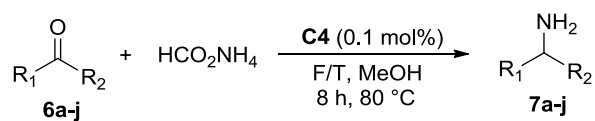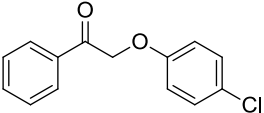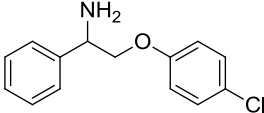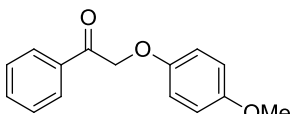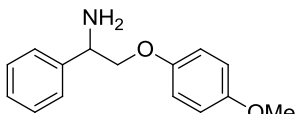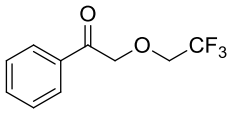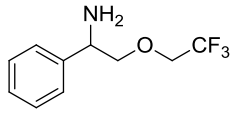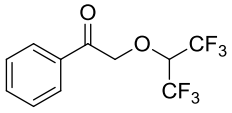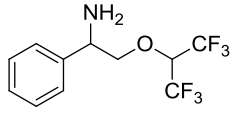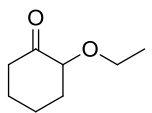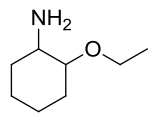
Entry[a]	Ketones	Amines		Yield (%)[b]
1			**7a**	91
2			**7b**	93
3			**7c**	80
4			**7d**	83
5			**7e**	90
6			**7f**	80
7			**7g**	81
8			**7h**	83
9			**7i**	90
10			**7j**	87

[a] Reaction conditions: ketone (0.5 mmol), HCO_2NH_4 (5 mmol), catalyst (5×10^{-4} mmol), HCO_2H/Et_3N (5:2) azeotrope (0.5 mL) and MeOH (3 mL), stirred at 80 °C for 8 h. [b] Yield of isolated product.

4.2.4 DRA of β-keto ethers with HCO₂NH₄

Next, the substrate scope was expanded to β-keto ethers. The product β-amino ethers, generated from the DRA, are of biological interest as the analogues are effective sodium channel blockers.[30] To the best of our knowledge, the homogeneous metal-catalysed transfer-hydrogenative DRA of β-keto ethers has previously never been reported. Our protocol is mild and efficient, allowing direct access to β-amino ethers in a one-pot fashion. The results are presented in Table 4.4. As can be seen, 1-phenoxypropan-2-one, containing an aliphatic ketone and a phenoxy group, was aminated to give **9a** in a high yield (Table 4.4, entry 1). The amino ether product offers a valuable building block for the synthesis of various antiepileptic agents.[31] Aromatic β-keto ethers, regardless of the substituent nature, all reacted well under the present conditions (Table 4.4, entries 2-4). Interestingly, unusual β-keto ethers bearing an aromatic ketone and fluoro-alkoxy group were also tolerated, leading to their corresponding amines in a good yield (Table 4.4, entries 5-6). 2-Ethoxycyclohexanamine was also obtained in a good yield, showing again the excellent activity of **C4** towards the DRA of β-keto ethers (Table 4.4, entry 7).

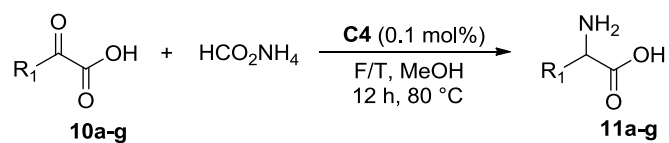**Table 4.4**: DRA of β-keto ethers with HCO$_2$NH$_4$

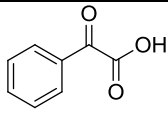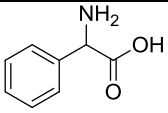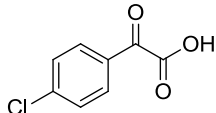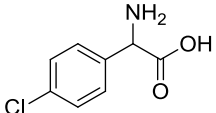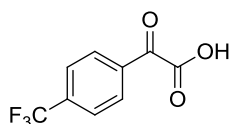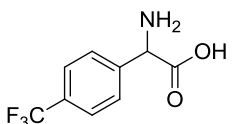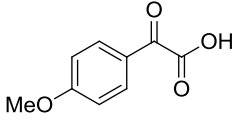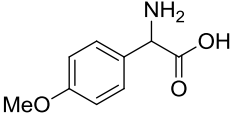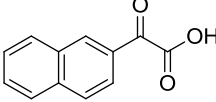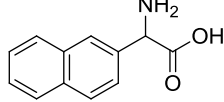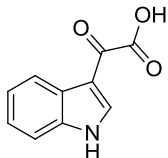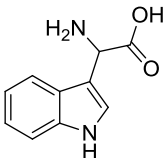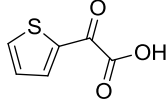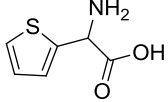| Entry[a]	Ketones	Amines		Yield (%)[b]
1			**9a**	87
2			**9b**	93
3			**9c**	90
4			**9d**	91
5			**9e**	74
6			**9f**	77
7[c]			**9g**	81

[a] Reaction conditions: ketone (0.5 mmol), HCO$_2$NH$_4$ (5 mmol), catalyst (5x10^{-4} mmol), HCO$_2$H/Et$_3$N (5:2) azeotrope (0.5 mL) and MeOH (3 mL), stirred at 80 °C for 12 h. [b] Yield of isolated product. [c] *Syn/anti* ratio = 6:1.

4.2.5 DRA of α-keto acids with HCO$_2$NH$_4$

To further demonstrate the versatility of **C4**, the DRA of α-keto acids was targeted next and the results are summarised in Table 4.5. Non-natural α-amino acids are in the focus of interest, as they are widely used as building blocks in drug synthesis, especially in the synthesis of semi-synthetic broad-spectrum antibiotics like Ampicillin and Amoxicillin.[32] Transfer hydrogenative DRA of α-keto acids offers an easy way of generating these non-natural α-amino acids, in particular, as they are generally difficult to be synthesised through enzymatic methods.[20,33] Electron neutral substrates, 2-oxo-2-phenylacetic acid and 2-(naphthalen-2-yl)-2-oxoacetic acid, were successfully aminated to their corresponding amines in near quantitative yields (Table 4.5, entries 1 and 5). Both electron-poor and -rich substrates gave excellent yields of their amines (Table 4.5, entries 2-4). Interestingly, α-keto acids containing a heteroatom posed no poisoning effect on the catalyst, giving excellent yields (Table 4.5, entries 6-7). The protocol is attractive not only because high yields are obtained, but also because the α-amino acid products precipitate from the reaction mixture and can be obtained by a simple filtration.

Table 4.5: DRA of α-keto acids with HCO$_2$NH$_4$

Entry[a]	Ketones	Amines		Yield (%)[b]
1			**11a**	95
2			**11b**	91
3			**11c**	90
4			**11d**	88
5			**11e**	96
6			**11f**	94
7			**11g**	92

[a] Reaction conditions: ketone (0.5 mmol), HCO$_2$NH$_4$ (5 mmol), catalyst (5x10^{-4} mmol), HCO$_2$H/Et$_3$N (5:2) azeotrope (0.5 mL) and MeOH (3 mL), stirred at 80 °C for 12 h. [b] Yield of isolated product.

4.2.6 Synthesis of Mexiletine

To showcase the synthetic utility of the DRA, the protocol was applied to a synthesis of Mexiletine, a class Ib antiarrhythmic agent that interferes with the sodium channel (Scheme 4.7).[34] 1-(2,6-Dimethylphenoxy)propan-2-one was synthesised by reacting 2,6-dimethylphenol with chloroacetone.[35] Transfer-hydrogenative DRA of the resulting β-keto ether by **C4** afforded the target Mexiletine with an overall yield of 77% (Scheme 4.7). This two-step synthesis is economical and high-yielding under mild reaction conditions. A conventional three-step method, by using Raney nickel under hydrogenative conditions,[36,37] is shown in Scheme 4.8.
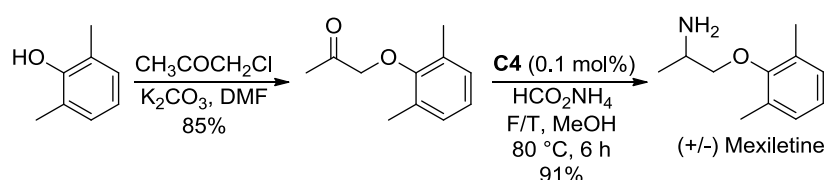
Scheme 4.7: Synthesis of Mexiletine by transfer hydrogenative DRA.
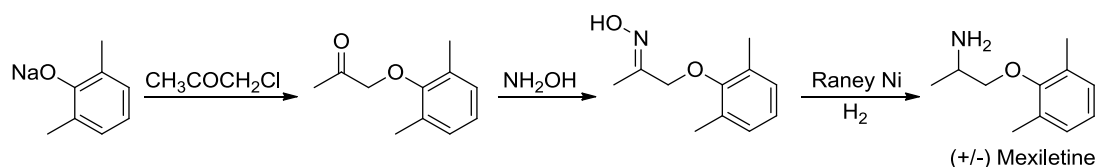
Scheme 4.8: A conventional three-step synthesis of Mexiletine.

4.2.7 Mechanistic considerations

A reaction mechanism for the DRA is proposed in Scheme 4.9. Reduction by the catalyst **C4** most likely proceeds by the ionic mechanism,[38] as the catalyst does not offer metal-ligand bifunctionality.[39] Complex **C4** is first converted into **I** in the presence of formic acid. The decarboxylation of formate by iridium leads to the iridium hydride species **II**.[40,41] Simultaneously, an imine is generated through the condensation of a ketone with ammonia. This imine is protonated under the acidic conditions and enters the catalytic cycle as the iminium ion, where it is reduced to the product by direct hydride transfer to the protonated C=N bond.[38, 42]
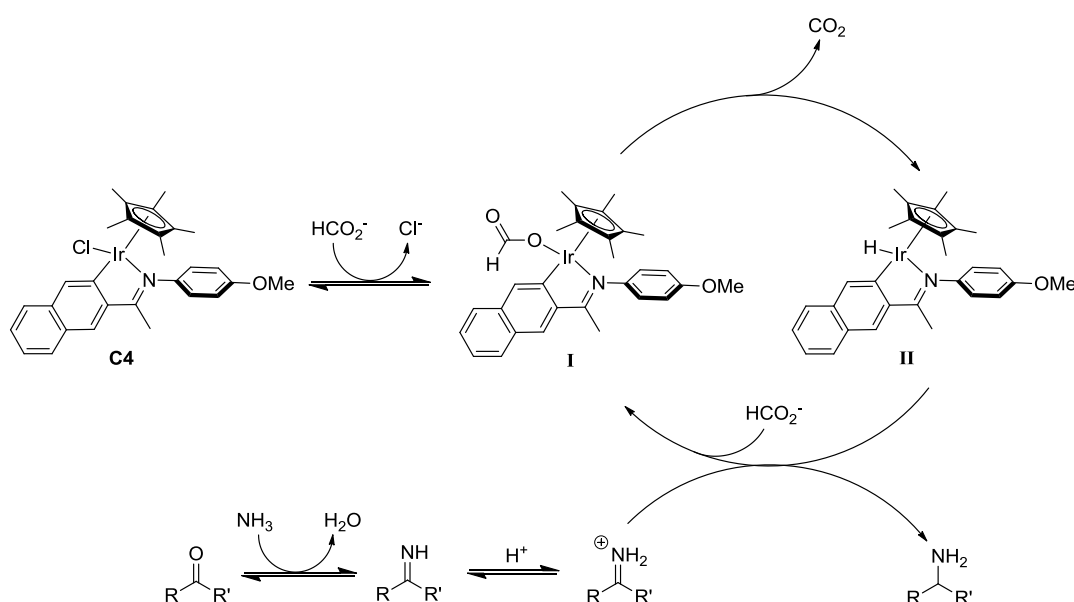
Scheme 4.9: Proposed DRA mechanism under the present conditions.

In the preliminary studies, the DRA reaction of acetonaphthone **1a** was monitored in situ by ^{1}H-NMR spectroscopy under the normal catalytic conditions but at room temperature. Formation of hydride **II** was confirmed and shown to be instantaneous. However, no other new species were observed at this temperature, which indicated that hydride transfer or imine generation may be more difficult than the hydride formation in the overall DRA. Condensation of **1a** with ammonia was not observed

even after heating the sample at 50 $^{\circ}$C for 10 min. Complex **II** was isolated and characterised by X-ray diffraction (Figure 4.1). Our previous study suggests that the imine is reduced by the cyclometalated iridium hydride at room temperature only when it is present in its protonated but not neutral form.[40] These results are in agreement with the proposed ionic mechanism.
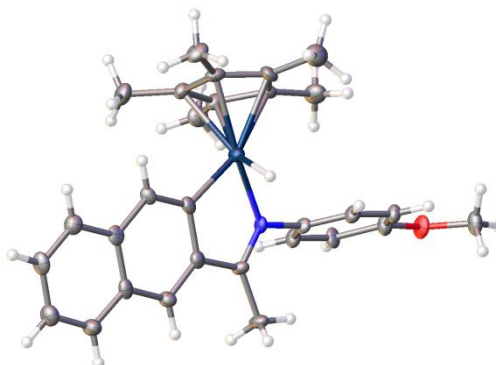
Figure 4.1: Molecular structure of the hydride **II** determined by X-ray diffraction. Thermal ellipsoids are displayed at 50% probability

4.3 Conclusion

This chapter demonstrates that primary amines can be readily accessed by the DRA of various ketones by using economic, safe and easy-to-handle ammonium formate. Cyclometalated iridium complexes hold the key, allowing the DRA to proceed with high productivity and excellent chemoselectivity toward primary amines under mild transfer-hydrogenative conditions. Aromatic ketones, aliphatic ones, α-keto acids and β-keto ethers are all viable substrates under the current conditions, showing the versatility of the iridicycle catalyst identified.

4.4 Experimental

4.4.1 General information

Unless otherwise specified, all reagents were commercially purchased and used without further purification. Dichloromethane (DCM) was dried over CaH_2 and distilled prior to use. MeOH was dried over magnesium and distilled prior to use. NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer unless otherwise specified. HRMS analyses were carried out by the EPSRC National Mass Spectrometry Service Centre at Swansea University. Cyclometalated iridium hydride was in situ formed and was also prepared according to the literature procedure.[40] β-Keto ethers (**8a-g**) were prepared according to the literature.[35] **8e**, **8f** and **9f** are unknown compounds. ^{1}H-NMR, ^{13}C-NMR and HRMS were collected for all the products. ^{1}H-NMR and ^{13}C-NMR are consistent with the reported literature (see below).

4.4.2 Typical procedure for the DRA of ketones

Ketone (0.5 mmol), **C4** (0.32 mg, 5×10^{-4} mmol) and ammonium formate (315 mg, 5 mmol) were placed in a carousel reaction tube. MeOH (3 mL) was introduced with a syringe and the resulting mixture was bubbled with nitrogen for 2 min. The F/T azeotrope (0.5 mL) was then added and the mixture was stirred at 80 °C for 8-12 h. The reaction mixture was cooled to room temperature and the solvent evaporated under vacuum. 1M HCl solution was added to the resulting residue and the mixture was washed with diethyl ether (2 x 15 mL) to remove neutral compounds. The aqueous layer was basified with dilute KOH solution and was bought to a pH of 10-12. It was than extracted with DCM (3 x 30 mL) and the combined organic layers

were dried over anhydrous sodium sulphate. Filtration, followed by evaporation of solvent under reduced pressure gave the desired product.

4.4.3 Representative procedure for the DRA of α-keto acids

2-Oxo-2-phenylacetic acid (75.1 mg, 0.50 mmol), **C4** (0.32 mg, 5×10^{-4} mmol) and ammonium formate (315 mg, 5.00 mmol) were placed in a carousel reaction tube. MeOH (3 mL) was introduced with a syringe and the resulting mixture was bubbled with nitrogen for 2 min. The F/T azeotrope (0.5 mL) was then added and the mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature and the resultant precipitate filtered off and washed with MeOH to give 2-amino-2-phenylacetic acid as a white solid (71.8 mg, 95% yield).

4.4.4 Data of the cyclometalated iridium complexes
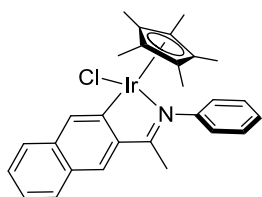
Complex C7: Yellow solid: ^{1}H NMR (CDCl$_3$, 400 MHz, 253 K) δ (ppm): 8.17 (s, 1H), 8.08 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.81 (dd, J = 8.2, 2.8 Hz, 2H), 7.57-7.41 (m, 3H), 7.35-7.29 (m, 2H), 6.93 (d, J = 7.6 Hz, 1H), 2.58 (s, 3H), 1.45 (s, 15H). ^{13}C NMR (CDCl$_3$, 100 M Hz, 253 K) δ (ppm): 181.2, 159.6, 150.7, 148.0, 137.0, 132.3, 130.2, 129.6, 129.3, 129.2, 127.7, 127.5, 126.6, 126.5, 123.8, 123.6, 122.3, 89.0, 17.4, 8.7. HRMS for C$_{28}$H$_{29}$ClIrN [M]$^+$: m/z calc., 607.1605; found, 607.1603.
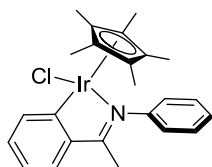
Complex C8: Orange solid; ^{1}H NMR (CDCl$_3$, 400 MHz, 253 K) δ (ppm): 7.85 (d, J = 7.3 Hz, 2H), 7.56 (d, J = 7.6 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.42 (t, J = 7.4 Hz, 1H), 7.32-7.21 (m, 2H), 7.06 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 7.5 Hz, 1H), 2.47 (s,

3H), 1.41 (s, 15H). ^{13}C NMR (CDCl$_3$, 100 MHz, 253 K) δ (ppm): 181.5, 168.2, 150.7, 147.7, 135.1, 132.3, 130.1, 128.7, 127.7, 126.4, 123.6, 122.5, 121.6, 89.2, 17.2, 8.7. Anal. calc. for C$_{24}$H$_{27}$ClIrN (%): C, 51.74; H, 4.88; N, 2.51. Found: C, 51.31; H, 4.79; N, 2.35. HRMS (FAB) for C$_{24}$H$_{27}$ClIrN [M]$^+$: m/z calc., 557.1448; found, 557.1442.
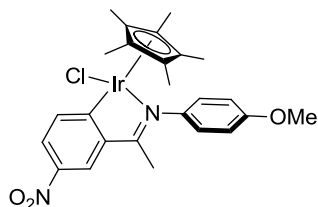
Complex C9: Red solid: ^{1}H NMR (CDCl$_3$, 400 MHz, 253 K) δ (ppm): 8.36 (d, J = 2.3 Hz, 1H), 8.07 (dd, J = 8.4, 2.3 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.76 (dd, J = 8.8, 2.0 Hz, 1H), 7.02 (dd, J = 8.9, 2.4 Hz, 1H), 6.95 (dd, J = 8.4, 2.4 Hz, 1H), 6.85 (dd, J = 8.4, 2.1 Hz, 1H), 3.89 (s, 3H), 2.56 (s, 3H), 1.45 (s, 15H). ^{13}C NMR (CDCl$_3$, 100 MHz, 253 K) δ (ppm): 181.9, 180.8, 157.9, 148.6, 143.3, 142.7, 135.7, 126.0, 124.5, 123.3, 123.2, 115.2, 112.5, 90.6, 55.7, 17.4, 8.8. Anal. calc. for C$_{25}$H$_{28}$ClIrN$_2$O$_3$ (%): C, 47.50; H, 4.46; N, 4.43. Found: C, 47.70; H, 4.26; N, 4.20. HRMS (FAB) for C$_{25}$H$_{28}$Cl^{191}IrN$_2$O$_3$ [M]$^+$: m/z calc., 630.1389; found, 630.1390.

Complex C10: Black solid: ^{1}H NMR (CDCl$_3$, 400 MHz, 253 K) δ (ppm): 8.62 (d, J = 2.2 Hz, 1H), 7.88 (dd, J = 8.6, 2.2 Hz, 1H), 7.78-7.65 (m, 1H), 7.60 (d, J = 8.6 Hz, 1H), 6.89-6.61 (m, 3H), 3.03 (s, 6H), 2.51 (s, 3H), 1.47 (s, 15H). ^{13}C NMR (CDCl$_3$, 100 MHz, 253 K) δ (ppm): 179.6, 168.1, 154.0, 149.0, 148.7, 140.1, 129.2, 128.4, 124.1, 123.0, 117.0, 113.3, 110.3, 90.0, 40.9, 17.8, 8.8. HRMS (FAB) for C$_{26}$H$_{31}$Cl^{191}IrN$_3$O$_2$ [M]$^+$: m/z calc., 643.1705; found, 643.1698.

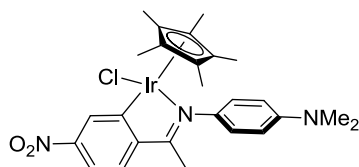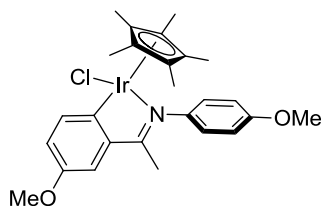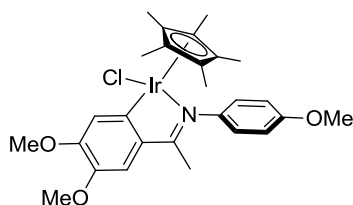***Complex C11:*** Red solid: ^1H NMR (CDCl$_3$, 400 MHz, 253 K) δ (ppm): 7.79 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.07 (d, J = 2.5 Hz, 1H), 7.02-6.95 (m, 2H), 6.91 (d, J = 8.1 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 2.44 (s, 3H), 1.44 (s, 15H). ^{13}C NMR (CDCl$_3$, 100 MHz, 253 K) δ (ppm): 181.4, 157.8, 157.5, 154.9, 148.0, 144.2, 135.3, 124.9, 123.4, 119.5, 114.9, 113.0, 112.3, 88.9, 55.6, 55.4, 17.3, 8.8. Anal. calc. for C$_{26}$H$_{31}$ClIrNO$_2$ (%): C, 50.60; H, 5.06; N, 2.27. Found: C, 50.53; H, 5.08; N, 2.16. HRMS (FAB) for C$_{26}$H$_{31}$IrNO$_2$ [M-Cl]$^+$: m/z calc., 582.1984; found, 582.1980.

Complex C12: Red solid: ^1H NMR (CDCl$_3$, 400 MHz, 253 K) δ (ppm): 7.80 (d, J = 8.1 Hz, 1H), 7.31 (s, 1H), 7.03 (s, 1H), 6.98 (d, J = 8.3 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 4.06 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 2.44 (s, 3H), 1.44 (s, 15H). ^{13}C NMR (CDCl$_3$, 100 MHz, 253 K) δ (ppm): 180.3, 161.7, 157.3, 151.8, 144.3, 144.1, 139.3, 125.1, 123.8, 115.9, 114.9, 112.2, 110.8, 88.9, 55.9, 55.7, 55.6, 17.4, 8.9. Anal. calc. for C$_{27}$H$_{33}$ClIrNO$_3$ (%):C, 50.10; H, 5.14; N, 2.16. Found: C, 50.07; H, 5.10; N, 2.10. HRMS (FAB) for C$_{27}$H$_{33}$Cl^{191}IrNO$_3$ [M]$^+$: m/z calc., 645.1749; found, 645.1758.
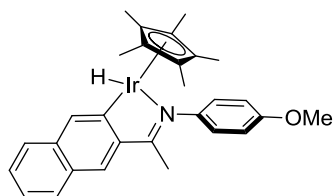
***Complex I1:*** Purple solid: ^1H NMR (Benzene-d_6, 400 MHz, 300 K) δ (ppm): 8.59 (s, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.88 (s, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 6.93-6.55 (m, 2H), 3.35 (s, 3H), 2.00 (s, 3H), 1.72 (s, 15H), -15.23 (s, 1H). Anal. calc. for C$_{29}$H$_{32}$IrNO (%):C, 57.78; H, 5.35; N, 2.32.

Found: C, 57.48; H, 5.68; N, 2.34. HRMS (APCI) for $C_{29}H_{31}NO^{191}Ir$ [M-H]$^+$: m/z calc., 600.2006; found, 600.2002.

4.4.5 Data of the β-keto ethers
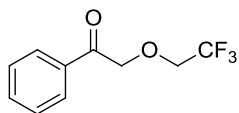
***1-Phenyl-2-(2,2,2-trifluoroethoxy)ethanone, 8f:*** ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.92 (d, J = 7.7 Hz, 2H), 7.64 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 4.99 (s, 2H), 4.08 (q, J = 8.7 Hz, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 195.3, 134.6, 134.4, 129.3, 128.2, 124.2 (q, J = 278.9, CF$_3$), 74.6, 68.9 (q, J = 34.4 Hz, CH$_2$CF$_3$). ^{19}F NMR (CDCl$_3$, 376 MHz, 300 K) δ (ppm): -74.6. HRMS for $C_{10}H_{10}O_2F_3$ [M+H]$^+$: m/z calc., 219.0627; found, 219.0626.
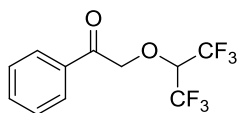
2-(1,1,1,3,3,3-Hexafluoropropan-2-yloxy)-1-phenylethanone, 8g: ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.92 (d, J = 7.8 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 5.14 (s, 2H), 4.55 (sep, J = 5.8 Hz, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 193.7, 134.7, 134.4, 129.4, 128.3, 123.2 (q, J = 283.4, 2CF$_3$), 75.8 (sep, J = 32.7 Hz, OCH(CF$_3$)$_2$), 74.3. ^{19}F NMR (CDCl$_3$, 376 MHz, 300 K) δ (ppm): -73.5. HRMS for $C_{11}H_8O_2F_6Na$ [M+Na]$^+$: m/z calc., 309.0326; found, 309.0318.

4.4.6 Data of the aromatic primary amines
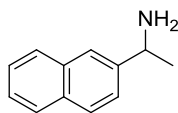
1-(Naphthalen-2-yl)ethanamine, 2a:[8] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.88-7.77 (m, 4H), 7.55-7.43 (m, 3H), 4.30 (q, J = 6.5 Hz, 1H), 2.56 (bs, 2H), 1.51 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 144.7, 133.9, 133.1, 128.7, 128.3, 128.0, 126.5, 126.0, 124.9, 124.4, 51.8, 25.6. HRMS for $C_{12}H_{14}N$ [M+H]$^+$: m/z calc., 172.1121; found, 172.1119.
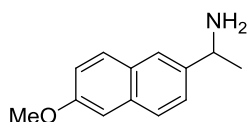
1-(6-Methoxynaphthalen-2-yl)ethanamine, 2b:[43] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.73-7.67 (m, 3H), 7.44 (dd, J = 8.4, 1.8 Hz, 1H), 7.16-7.09 (m, 2H), 4.24 (q, J = 6.6 Hz, 1H), 3.90 (s, 3H), 1.55 (bs, 2H), 1.45 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 157.9, 143.4, 134.1, 129.6, 129.3, 127.4, 125.4, 124.1, 119.2, 106.1, 55.7, 51.7, 26.1. HRMS for C$_{13}$H$_{15}$NO [M]$^+$: m/z calc., 201.1148; found, 201.1146.
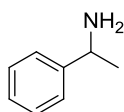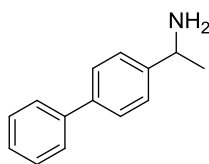

1-Phenylethanamine, 2c:[8] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.36-7.29 (m, 4H), 7.26-7.19 (m, 1H), 4.11 (q, J = 6.6 Hz, 1H), 1.53 (bs, 2H), 1.38 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 148.2, 128.9, 127.2, 126.1, 51.7, 26.1. HRMS for C$_8$H$_{12}$N [M+H]$^+$: m/z calc., 122.0964; found, 122.0964.

1-(Biphenyl-4-yl)ethanamine, 2d:[44] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.68-7.60 (m, 4H), 7.52-7.44 (m, 4H), 7.42-7.36 (m, 1H), 4.21 (q, J = 6.6 Hz, 1H), 1.70 (bs, 2H), 1.49 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 147.3, 141.4, 140.2, 129.2, 127.7, 127.6, 127.5, 126.6, 51.5, 26.1. HRMS for C$_{14}$H$_{16}$N [M+H]$^+$: m/z calc., 198.1277; found, 198.1277.
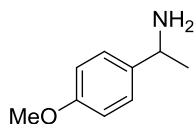
1-(4-Methoxyphenyl)ethanamine, 2e:[8] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.26 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.07 (q, J = 6.6 Hz, 1H), 3.78 (s, 3H), 1.51 (bs, 2H), 1.36 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 158.9, 140.4, 127.1, 114.2, 55.7, 51.1, 26.2. HRMS for C$_9$H$_{14}$NO [M+H]$^+$: m/z calc., 152.1070; found, 152.1069.
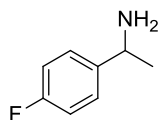
1-(4-Fluorophenyl)ethanamine, 2f: ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.27-7.21 (m, 2H), 6.97-6.90 (m, 2H), 4.05 (q, J = 6.6 Hz, 1H), 1.59 (bs, 2H), 1.29 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 162.1 (d, J = 244.3 Hz), 143.7 (d, J = 3.1 Hz), 127.6 (d, J = 7.9 Hz), 115.6 (d, J = 21.1 Hz), 51.1, 26.2. HRMS for C$_8$H$_{11}$NF [M+H]$^+$: m/z calc., 140.0870; found, 140.0867.
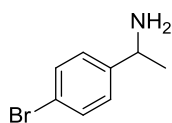
1-(4-Bromophenyl)ethanamine, 2g:[45] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.37 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 4.02 (q, J = 6.6 Hz, 1H), 1.60 (bs, 2H), 1.29 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 147.0, 131.9, 128.0, 120.8, 51.2, 26.1. HRMS for C$_8$H$_{11}$NBr [M+H]$^+$: m/z calc., 200.0069; found, 200.0068.
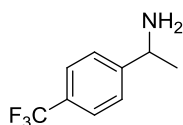
1-(4-(Trifluoromethyl)phenyl)ethanamine, 2h:[46] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.61 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 4.22 (q, J = 6.6 Hz, 1H), 1.70 (bs, 2H), 1.42 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 152.0, 129.5 (d, J = 32.4 Hz), 127.5, 126.5 (2C), 125.8 (q, J = 3.7 Hz), 123.3 (d, J = 272.1 Hz, CF$_3$), 51.4, 26.1. HRMS for C$_9$H$_{11}$NF$_3$ [M+H]$^+$: m/z calc., 190.0838; found, 190.0834.
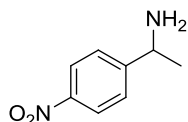
1-(4-Nitrophenyl)ethanamine, 2i:[11] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.09 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 4.18 (q, J = 6.6 Hz, 1H), 1.60 (bs, 2H), 1.33 (d, J = 6.7 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 155.6, 147.2, 127.1, 124.2, 51.3, 26.2. HRMS for C$_8$H$_{11}$N$_2$O$_2$ [M+H]$^+$: m/z calc., 167.0815; found, 167.0815.
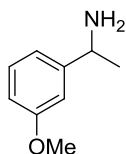
1-(3-Methoxyphenyl)ethanamine, 2j:[47] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.25 (d, J = 7.5 Hz, 1H), 6.95-6.89 (m, 2H), 6.80-6.75 (m, 1H), 4.09 (q, J = 6.6 Hz, 1H), 3.81 (s, 3H), 1.62 (bs, 2H), 1.38 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 160.2, 150.0, 129.9, 118.5, 112.5, 111.8, 55.6, 51.7, 26.0. HRMS for C$_9$H$_{14}$NO [M+H]$^+$: m/z calc., 152.1070; found, 152.1071.
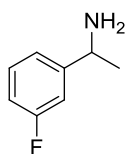
1-(3-Fluorophenyl)ethanamine, 2k:[47] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.34-7.28 (m, 1H), 7.16-7.05 (m, 2H), 6.94 (td, J = 8.5, 2.6 Hz, 1H), 4.14 (q, J = 6.6 Hz, 1H), 1.61 (bs, 2H), 1.39 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 163.4 (d, J = 245.6 Hz), 150.9 (d, J = 6.5 Hz), 130.3 (d, J = 8.2 Hz), 121.8 (d, J = 2.7 Hz), 114.0 (d, J = 21.2 Hz), 113.0 (d, J = 21.4 Hz), 51.4 (d, J = 1.7 Hz), 26.1. HRMS for C$_8$H$_{11}$FN [M+H]$^+$: m/z calc., 140.0870; found, 140.0867.
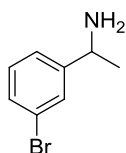
1-(3-Bromophenyl)ethanamine, 2l:[48] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.43 (t, J = 1.7 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.19 (d, J = 6.8 Hz, 1H), 7.11 (t, J = 7.7 Hz, 1H), 4.01 (q, J = 6.6 Hz, 1H), 2.02 (bs, 2H), 1.29 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 150.1, 130.5, 130.4, 129.4, 124.9, 123.0, 51.3, 25.8. HRMS for C$_8$H$_{11}$BrN [M+H]$^+$: m/z calc., 200.0069; found, 200.0069.
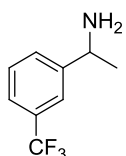
1-(3-(Trifluoromethyl)phenyl)ethanamine, 2m:[47] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.63 (s, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.50 (d, J = 7.3 Hz, 1H), 7.44 (dd,

J = 7.5, 7.3 Hz, 1H), 4.20 (q, J = 6.6 Hz, 1H), 1.94 (bs, 2H), 1.41 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 148.7, 131.2 (q, J = 32.2 Hz), 129.7, 129.3, 124.7 (q, J = 272.4 Hz, CF$_3$), 124.1 (q, J = 3.9 Hz), 123.0 (q, J = 3.6 Hz), 51.4, 26.0. HRMS for C$_9$H$_{11}$F$_3$N [M+H]$^+$: m/z calc., 190.0838; found, 190.0837.
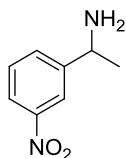
1-(3-Nitrophenyl)ethanamine, 2n:[49] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.25 (s, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.49 (dd, J = 8.2, 7.7 Hz, 1H), 4.27 (q, J = 6.6 Hz, 1H), 1.58 (bs, 2H), 1.42 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 150.2, 148.8, 132.6, 129.7, 122.3, 121.3, 51.2, 26.2. HRMS for C$_8$H$_{11}$O$_2$N$_2$ [M+H]$^+$: m/z calc., 167.0815; found, 167.0812.
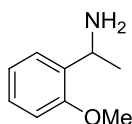
1-(2-Methoxyphenyl)ethanamine, 2o:[50] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.33 (dd, J = 7.5, 1.6 Hz, 1H), 7.20 (ddd, J = 8.3, 7.3, 1.7 Hz, 1H), 6.94 (td, J = 7.4, 1.1 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 4.35 (q, J = 6.7 Hz, 1H), 3.84 (s, 3H), 1.65 (bs, 2H), 1.39 (d, J = 6.7 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 157.2, 136.2, 128.0, 126.1, 121.0, 110.9, 55.6, 46.4, 23.7. HRMS for C$_9$H$_{14}$ON [M+H]$^+$: m/z calc., 152.1070; found, 152.1068.
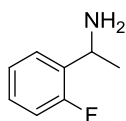
1-(2-Fluorophenyl)ethanamine, 2p:[51] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.43 (td, J = 7.6, 1.7 Hz, 1H), 7.26-7.19 (m, 1H), 7.14 (td, J = 7.5, 1.1 Hz, 1H), 7.06-7.00 (m, 1H), 4.40 (q, J = 6.7 Hz, 1H), 1.75 (bs, 2H), 1.44 (d, J = 6.7 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 160.8 (d, J = 244.6 Hz), 134.8 (d, J = 13.6 Hz), 128.5 (d, J = 8.4 Hz), 127.1 (d, J = 5.0 Hz), 124.6 (d, J = 3.5 Hz), 115.8 (d, J = 22.2 Hz), 45.8 (d, J = 2.8 Hz), 24.4. HRMS for C$_8$H$_{11}$FN [M+H]$^+$: m/z calc., 140.0870; found, 140.0867.
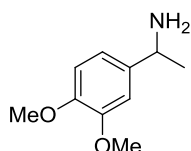
1-(3,4-Dimethoxyphenyl)ethanamine, 2q:[47] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 6.83 (s, 1H), 6.81-6.71 (m, 2H), 4.00 (q, J = 6.6 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 1.41 (bs, 2H), 1.28 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 149.4, 148.2, 140.9, 118.0, 111.5, 109.5, 56.3, 56.2, 51.4, 26.2. HRMS for C$_{10}$H$_{15}$NO$_2$Na [M+Na]$^+$: m/z calc., 204.0995; found, 204.0994.
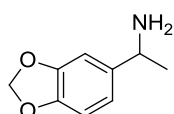
1-(Benzo[d][1,3]dioxol-5-yl)ethanamine, 2r:[52] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 6.87 (d, J = 1.6 Hz, 1H), 6.81-6.73 (m, 2H), 5.93 (s, 2H), 4.05 (q, J = 6.5 Hz, 1H), 1.56 (bs, 2H), 1.35 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 148.1, 146.7, 142.4, 119.1, 108.5, 106.7, 101.3, 51.5, 26.2. HRMS for C$_9$H$_{12}$NO$_2$ [M+H]$^+$: m/z calc., 166.0863; found, 166.0860.
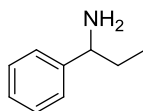
1-Phenylpropan-1-amine, 2s:[47] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.38-7.31 (m, 4H), 7.28-7.23 (m, 1H), 3.82 (t, J = 6.8 Hz, 1H), 1.77-1.67 (m, 4H, including NH$_2$), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 146.8, 128.8, 127.3, 126.8, 58.2, 32.8, 11.4. HRMS for C$_9$H$_{14}$N [M+H]$^+$: m/z calc., 136.1121; found, 136.1118.
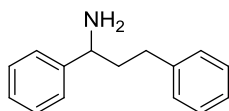
1,3-Diphenylpropan-1-amine, 2t:[53] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.27-7.22 (m, 4H), 7.21-7.15 (m, 3H), 7.12-7.04 (m, 3H), 3.84 (t, J = 7.0 Hz, 1H), 3.01 (bs, 2H), 2.58-2.41 (m, 2H), 2.06-1.90 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 145.0, 142.0, 129.1, 128.8 (2C), 127.8, 127.0, 126.3, 56.2, 40.6, 33.0. HRMS for C$_{15}$H$_{18}$N [M+H]$^+$: m/z calc., 212.1434; found, 212.1432.
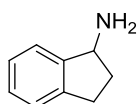
2,3-Dihydro-1H-inden-1-amine, 2u:[54] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.38-7.33 (m, 1H), 7.28-7.21 (m, 3H), 4.39 (t, J = 7.5 Hz, 1H), 3.04-2.94 (m, 1H), 2.89-2.78 (m, 1H), 2.58-2.48 (m, 1H), 1.75-1.68 (m, 3H, including NH$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 147.8, 143.5, 127.6, 126.9, 125.1, 123.7, 57.7, 37.8, 30.5. HRMS for C$_9$H$_{12}$N [M+H]$^+$: m/z calc., 134.0964; found, 134.0962.
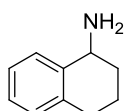
1,2,3,4-Tetrahydronaphthalen-1-amine, 2v:[8] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.42 (d, J = 7.2 Hz, 1H), 7.24-7.14 (m, 2H), 7.10 (d, J = 7.2 Hz, 1H), 4.00 (t, J = 5.7 Hz, 1H), 2.90-2.71 (m, 2H), 2.11-1.91 (m, 2H), 1.85-1.68 (m, 2H), 1.62 (bs, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 141.5, 137.1, 129.4, 128.4, 127.0, 126.4, 49.8, 33.9, 30.0, 20.0. HRMS for C$_{10}$H$_{14}$N [M+H]$^+$: m/z calc., 148.1121; found, 148.1118.
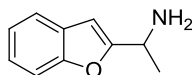
1-(Benzofuran-2-yl)ethanamine, 2w:[55] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.43 (ddd, J = 7.5, 1.6, 0.9 Hz, 1H), 7.37-7.33 (m, 1H), 7.18-7.08 (m, 2H), 6.41 (t, J = 0.9 Hz, 1H), 4.13 (q, J = 6.7 Hz, 1H), 2.04 (bs, 2H), 1.44 (d, J = 6.7 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 163.2, 155.1, 128.9, 124.1, 123.0, 121.2, 111.4, 100.8, 45.9, 22.3. HRMS for C$_{10}$H$_{12}$NO [M+H]$^+$: m/z calc., 162.0913; found, 162.0912.
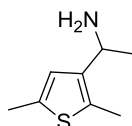
1-(2,5-Dimethylthiophen-3-yl)ethanamine, 2x:[56] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 6.69 (s, 1H), 4.14 (q, J = 6.6 Hz, 1H), 2.41 (s, 3H), 2.35 (s, 3H), 1.75 (bs, 2H), 1.34 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 143.4, 136.3, 130.3, 123.7, 45.3, 24.9, 15.6, 13.0. HRMS for C$_8$H$_{13}$NSNa [M+Na]$^+$: m/z calc., 178.0661; found, 178.0657.

4.4.7 Data of the aliphatic primary amines
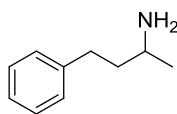
4-Phenylbutan-2-amine, 7a: ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.33-7.27 (m, 2H), 7.24-7.19 (m, 3H), 2.95 (sex, J = 6.4 Hz, 1H), 2.75-2.63 (m, 2H), 1.73-1.62 (m, 2H), 1.27 (bs, 2H), 1.13 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 142.7, 128.8, 128.7, 126.1, 47.0, 42.3, 33.3, 24.5. HRMS for C$_{10}$H$_{16}$N [M+H]$^+$: m/z calc., 150.1277; found, 150.1275.
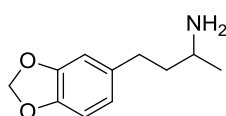
4-(Benzo[d][1,3]dioxol-5-yl)butan-2-amine, 7b:[8] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 6.65 (d, J = 7.8 Hz, 1H), 6.62 (d, J = 1.2 Hz, 1H), 6.57 (dd, J = 7.8, 1.2 Hz, 1H), 5.84 (s, 2H), 2.86 (sex, J = 6.4 Hz, 1H), 2.59-2.44 (m, 2H), 1.75 (bs, 2H), 1.60-1.51 (m, 2H), 1.05 (d, J = 6.4 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 147.9, 145.9, 136.5, 121.4, 109.2, 108.5, 101.1, 46.8, 42.3, 32.9, 24.3. HRMS for C$_{11}$H$_{16}$NO$_2$ [M+H]$^+$: m/z calc., 194.1176; found, 194.1175.
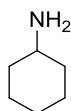
Cyclohexanamine, 7c:[57] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 2.69-2.51 (m, 1H), 1.87-1.52 (m, 5H), 1.32-0.95 (m, 7H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 50.9, 37.3, 26.1, 25.5. HRMS for C$_6$H$_{14}$N [M+H]$^+$: m/z calc., 100.1121; found, 100.23.
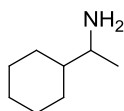
1-Cyclohexylethanamine, 7d:[20] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 2.67 (quin, J = 6.4 Hz, 1H), 1.82-1.63 (m, 5H), 1.46 (bs, 2H), 1.30-1.10 (m, 4H), 1.04 (d, J = 6.5 Hz, 3H), 1.02-0.91 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 52.0, 45.8, 29.5, 29.3, 27.0, 26.8, 26.7, 21.2. HRMS for C$_8$H$_{18}$N [M+H]$^+$: m/z calc., 128.1434; found, 128.1432.
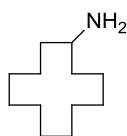
Cyclododecanamine, 7e:[58] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 2.97-2.88 (m, 1H), 1.82 (bs, 2H), 1.63-1.52 (m, 2H), 1.45-1.25 (m, 20H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 48.1, 33.4, 24.6, 24.2, 23.8, 23.7, 21.7. HRMS for C$_{12}$H$_{26}$N [M+H]$^+$: m/z calc., 184.2060; found, 184.2060.
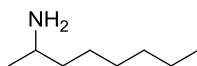
Octan-2-amine, 7f:[20] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 2.90-2.77 (m, 1H), 1.93 (bs, 2H), 1.34-1.13 (m, 10H), 1.00 (d, J = 6.3 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 47.3, 40.5, 32.2, 29.8, 26.8, 24.2, 23.0, 14.4. HRMS for C$_8$H$_{20}$N [M+H]$^+$: m/z calc., 130.1590; found, 130.1589.
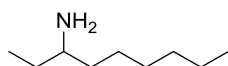
Nonan-3-amine, 7g: ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 2.63-2.51 (m, 1H), 2.07 (bs, 2H), 1.37-1.14 (m, 12H), 0.88-0.79 (m, 6H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 53.1, 37.6, 32.3, 30.7, 29.9, 26.5, 23.0, 14.5, 10.7. HRMS for C$_9$H$_{22}$N [M+H]$^+$: m/z calc., 144.1747; found, 144.1746.
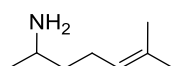
6-Methylhept-5-en-2-amine, 7h:[59] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 5.04 (td, J = 7.1, 1.1 Hz, 1H), 2.90-2.76 (m, 1H), 2.04-1.86 (m, 2H), 1.62 (s, 3H), 1.54 (s, 3H), 1.48 (bs, 2H), 1.35-1.24 (m, 2H), 1.00 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 132.0, 124.6, 47.1, 40.5, 26.1, 25.4, 24.2, 18.1. HRMS for C$_8$H$_{18}$N [M+H]$^+$: m/z calc., 128.1434; found, 128.1432.
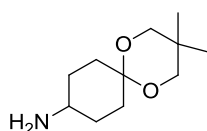
3,3-Dimethyl-1,5-dioxaspiro[5.5]undecan-9-amine, 7i: ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 3.48 (s, 2H), 3.45 (s, 2H), 2.79-2.65 (m, 1H), 2.23-2.11 (m, 2H), 1.76-1.64 (m, 2H), 1.55-1.25 (m, 6H, including NH$_2$), 0.93 (s, 6H). ^{13}C NMR

(CDCl$_3$, 100 MHz, 300 K) δ (ppm): 98.9, 72.0, 71.6, 51.5, 34.0, 32.3, 31.9, 24.5. HRMS for C$_{11}$H$_{22}$NO$_2$ [M+H]$^+$: m/z calc., 200.1645; found, 200.1648.
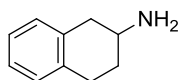
1,2,3,4-Tetrahydronaphthalen-2-amine, 7j:[60] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.06-6.96 (m, 4H), 3.18-3.04 (m, 1H), 2.97-2.88 (m, 1H), 2.85-2.74 (m, 2H), 2.55-2.44 (m, 1H), 1.99-1.88 (m, 1H), 1.78 (bs, 2H), 1.59-1.46 (m, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 135.5, 134.9, 129.0, 128.4, 125.5, 125.4, 47.1, 39.0, 32.5, 27.8. HRMS for C$_{10}$H$_{14}$N [M+H]$^+$: m/z calc., 148.1121; found, 148.1120.

4.4.8 Data of the β-amino ethers
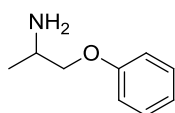
1-Phenoxypropan-2-amine, 9a:[61] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.34-7.27 (m, 2H), 7.00-6.91 (m, 3H), 3.89 (dd, J = 8.9, 1.1 Hz, 1H), 3.70 (dd, J = 8.9, 1.1 Hz, 1H), 3.41-3.32 (m, 1H), 1.69 (bs, 2H), 1.19 (d, J = 6.5 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 159.3, 129.9, 121.2, 114.9, 74.8, 46.7, 20.2. HRMS for C$_9$H$_{14}$NO [M+H]$^+$: m/z calc., 152.1070; found, 152.1069.
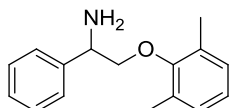
2-(2,6-Dimethylphenoxy)-1-phenylethanamine, 9b:[62] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.47 (d, J = 7.2 Hz, 2H), 7.38 (dt, J = 7.4, 1.7 Hz, 2H), 7.31 (dt, J = 7.2, 1.9 Hz, 1H), 7.01 (d, J = 7.4 Hz, 2H), 6.95 (dd, J = 8.2, 6.6 Hz, 1H), 4.48 (dd, J = 8.0, 4.3 Hz, 1H), 3.87 (m, 2H), 2.34 (bs, 2H), 2.28 (s, 6H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 155.8, 142.2, 131.2, 129.3, 128.9, 128.0, 127.3, 124.3, 77.6, 56.7, 16.7. HRMS for C$_{16}$H$_{20}$NO [M+H]$^+$: m/z calc., 242.1539; found, 242.1542.
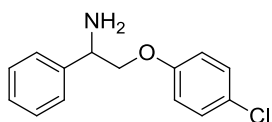
2-(4-Chlorophenoxy)-1-phenylethanamine, 9c:[62] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.47 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.35 (dt, J = 7.2, 2.5 Hz, 1H), 7.24 (dt, J = 9.0, 2.8 Hz, 2H), 6.85 (dt, J = 9.0, 2.8 Hz, 2H), 4.44 (dd, J = 8.8, 3.6 Hz, 1H), 4.07 (dd, J = 9.0, 3.7 Hz, 1H), 3.92 (t, J = 9.1 Hz, 1H), 2.13 (bs, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 157.7, 141.8, 129.8, 129.1, 128.3, 127.3, 126.2, 116.3, 74.5, 55.6. HRMS for C$_{14}$H$_{15}$NOCl [M+H]$^+$: m/z calc., 248.0837; found, 248.0840.
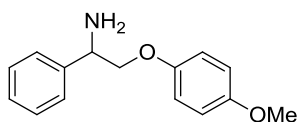
2-(4-Methoxyphenoxy)-1-phenylethanamine, 9d: ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.48 (d, J = 7.2 Hz, 2H), 7.42-7.37 (m, 2H), 7.33 (dt, J = 7.2, 1.8 Hz, 1H), 6.89-6.82 (m, 4H), 4.43 (dd, J = 9.0, 3.6 Hz, 1H), 4.06 (dd, J = 9.0, 3.6 Hz, 1H), 3.90 (t, J = 9.1 Hz, 1H), 3.79 (s, 3H), 2.20 (bs, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 154.4, 153.2, 142.1, 129.0, 128.1, 127.4, 116.0, 115.0, 75.0, 56.1, 55.7. HRMS for C$_{15}$H$_{18}$NO$_2$ [M+H]$^+$: m/z calc., 244.1332; found, 244.1335.
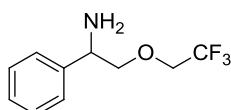
1-Phenyl-2-(2,2,2-trifluoroethoxy)ethanamine, 9e:[63] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.41-7.27 (m, 5H), 4.24 (dd, J = 9.0, 3.6 Hz, 1H), 3.91-3.80 (m, 2H), 3.75 (dd, J = 9.0, 3.6 Hz, 1H), 3.57 (t, J = 9.0 Hz, 1H), 2.25 (bs, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 141.7, 129.0, 128.2, 127.3, 125.7 (q, J = 279.6, CF$_3$), 79.0, 69.2 (q, J = 34.2 Hz, OCH$_2$CF$_3$), 55.8. ^{19}F NMR (CDCl$_3$, 376 MHz, 300 K) δ (ppm): -74.5. HRMS for C$_{10}$H$_{13}$NOF$_3$ [M+H]$^+$: m/z calc., 220.0944; found, 220.0946.
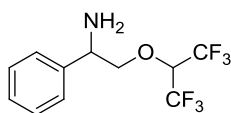
2-(1,1,1,3,3,3-Hexafluoropropan-2-yloxy)-1-phenylethanamine, 9f: ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.33-7.23 (m, 5H), 4.23 (dd, J = 9.1, 3.4 Hz, 1H), 4.05 (sep, J = 5.9 Hz, 1H), 3.90 (dd, J = 9.1, 3.4 Hz, 1H), 3.70 (t, J = 9.1 Hz, 1H), 1.99 (bs, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 140.9, 129.1, 128.4, 127.3, 123.3 (q, J = 283.7, 2CF$_3$), 81.6, 76.8 (sep, J = 32.1 Hz, OCH(CF$_3$)$_2$), 55.8. ^{19}F NMR (CDCl$_3$, 376 MHz, 300 K) δ (ppm): -74.3. HRMS for C$_{11}$H$_{12}$NOF$_6$ [M+H]$^+$: m/z calc., 288.0823; found, 288.0812.
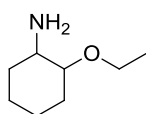
2-Ethoxycyclohexanamine, 9g:[64] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): *syn:anti* = 6:1; for *Syn* isomer: 3.58 (dq, J = 9.3, 7.0 Hz, 1H), 3.44 (dq, J = 9.3, 7.0 Hz, 1H), 3.37 (dddd, J = 3.6, 3.4, 3.4, 3.0 Hz, 1H), 2.88 (ddd, J = 7.7, 4.2, 3.6 Hz, 1H), 1.86-1.77 (m, 1H), 1.77-1.65 (bs, 2H), 1.63-1.51 (m, 4H), 1.44-1.35 (m, 1H), 1.34-1.24 (m, 2H), 1.21 (t, J = 7.0 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 79.0, 64.0, 51.3, 31.7, 27.7, 23.1, 21.8, 16.1. HRMS for C$_8$H$_{18}$NO [M+H]$^+$: m/z calc., 144.1383; found, 144.1382.

4.4.9 Data of the α-amino acids
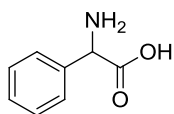
2-Amino-2-phenylacetic acid, 11a:[65] ^{1}H NMR (DMSO-*d$_6$* + HCl, 400 MHz, 300 K) δ (ppm): 8.96 (bs, 3H), 7.53-7.47 (m, 2H), 7.47-7.40 (m, 3H), 5.05 (s, 1H). ^{13}C NMR (DMSO-*d$_6$* + HCl, 100 MHz, 300 K) δ (ppm): 169.9, 133.5, 129.6, 129.2, 128.5, 55.9. HRMS for C$_8$H$_{10}$NO$_2$ [M+H]$^+$: m/z calc., 152.0706; found, 152.0706.
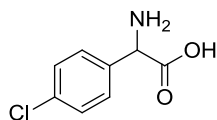
2-Amino-2-(4-chlorophenyl)acetic acid, 11b:[66] ^{1}H NMR (DMSO-d_6 + HCl, 400 MHz, 300 K) δ (ppm): 9.04 (bs, 3H), 7.57-7.48 (m, 4H), 5.11 (s, 1H). ^{13}C NMR (DMSO-d_6 + HCl, 100 MHz, 300 K) δ (ppm): 169.6, 134.4, 132.5, 130.5, 129.2, 55.1. HRMS for $C_8H_9NO_2Cl$ [M+H]$^+$: m/z calc., 186.0316; found, 186.0316.
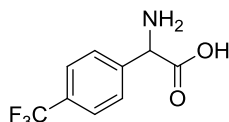
2-Amino-2-(4-(trifluoromethyl)phenyl)acetic acid, 11c:[67] ^{1}H NMR (DMSO-d_6 + HCl, 400 MHz, 300 K) δ (ppm): 9.14 (bs, 3H), 7.82 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H), 5.24 (s, 1H). ^{13}C NMR (DMSO-d_6 + HCl, 100 MHz, 300 K) δ (ppm): 169.3, 137.9, 130.0 (q, J = 31.9), 129.5, 126.1 (q, J = 3.5 Hz), 124.3 (q, J = 272.9 Hz), 55.4. ^{19}F NMR (CDCl$_3$, 376 MHz, 300 K) δ (ppm): -61.7. HRMS for $C_9H_9NO_2F_3$ [M+H]$^+$: m/z calc., 220.0580; found, 220.0581.
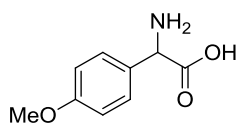
2-Amino-2-(4-methoxyphenyl)acetic acid, 11d:[68] ^{1}H NMR (DMSO-d_6 + HCl, 400 MHz, 300 K) δ (ppm): 8.88 (bs, 3H), 7.43 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 4.99 (s, 1H), 3.76 (s, 3H). ^{13}C NMR (DMSO-d_6 + HCl, 100 MHz, 300 K) δ (ppm): 170.2, 160.2, 129.9, 125.4, 114.6, 55.7, 55.3. HRMS for $C_9H_{11}NO_3Na$ [M+Na]$^+$: m/z calc., 204.0631; found, 204.0633.
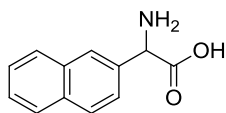
2-Amino-2-(naphthalen-2-yl)acetic acid, 11e:[69] ^{1}H NMR (DMSO-d_6 + HCl, 400 MHz, 300 K) δ (ppm): 9.10 (bs, 3H), 8.08 (s, 1H), 8.03-7.89 (m, 3H), 7.66-7.52 (m, 3H). ^{13}C NMR (DMSO-d_6 + HCl, 100 MHz, 300 K) δ (ppm): 169.9, 133.2, 132.8, 131.0, 129.0, 128.3, 128.2, 128.1, 127.4, 127.3, 125.5, 56.0. HRMS for $C_{12}H_{11}NO_2Na$ [M+Na]$^+$: m/z calc., 224.0682; found, 224.0683.
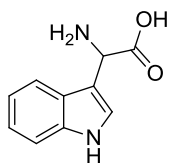
2-Amino-2-(1H-indol-3-yl)acetic acid, 11f:[70] ^{1}H NMR (DMSO-d_6 + HCl, 400 MHz, 300 K) δ (ppm): 11.6 (bs, 1H), 8.77 (bs, 3H), 7.67 (d, J = 7.9 Hz, 1H), 7.56 (d, J = 1.9 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H) 7.15 (t, J = 7.4 Hz, 1H), 7.07 (t, J = 7.3 Hz, 1H), 5.29 (s, 1H). ^{13}C NMR (DMSO-d_6 + HCl, 100 MHz, 300 K) δ (ppm): 170.6, 136.4, 126.3, 125.5, 122.2, 119.7, 119.2, 112.3, 106.8, 49.2.
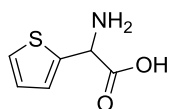
2-Amino-2-(thiophen-2-yl)acetic acid, 11g:[71] ^{1}H NMR (DMSO-d_6 + HCl, 400 MHz, 300 K) δ (ppm): 9.03 (bs, 3H), 7.64 (d, J = 5.1 Hz, 1H), 7.32 (d, J = 3.2 Hz, 1H), 7.10 (dd, J = 5.1, 3.6 Hz, 1H) 5.40 (s, 1H). ^{13}C NMR (DMSO-d_6 + HCl, 100 MHz, 300 K) δ (ppm): 169.2, 134.4, 129.2, 128.4, 127.6, 51.3. HRMS for $C_6H_7NO_2SNa$ [M+Na]$^+$: m/z calc., 180.0090; found, 180.0089.

4.4.10 Data of the Mexiletine
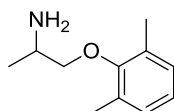
1-(2,6-Dimethylphenoxy)propan-2-amine:[72] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.03 (d, J = 7.3 Hz, 2H), 6.94 (dd, J = 8.2, 6.8 Hz, 1H), 3.68 (dd, J = 9.0, 4.2 Hz, 1H), 3.57 (dd, J = 9.0, 7.6 Hz, 1H), 3.45-3.36 (m, 1H), 2.31 (s, 6H), 1.92 (bs, 2H), 1.20 (d, J = 6.5 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 155.9, 131.2, 129.3, 124.2, 78.6, 47.7, 20.1, 16.7. HRMS for $C_{11}H_{18}NO$ [M+H]$^+$: m/z calc., 180.1383; found, 180.1383.

4.4.11 Crystallographic data of complex II
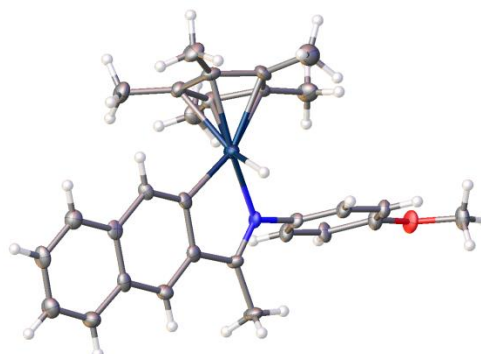
CCDC 942737

Table 1 Crystal data and structure refinement for complex II

Identification code	942737
Empirical formula	$C_{29}H_{32}IrNO$
Formula weight	602.76
Temperature/K	100.15
Crystal system	monoclinic
Space group	I2/a
a/Å	17.6600(18)
b/Å	8.7325(9)
c/Å	30.881(4)
α/°	90.00
β/°	92.0600(10)
γ/°	90.00
Volume/Å^3	4759.3(9)
Z	8
ρ_{calc}mg/mm^3	1.682
m/mm^{-1}	5.632
F(000)	2384.0
Crystal size/mm^3	$0.25 \times 0.25 \times 0.1$
2Θ range for data collection	2.64 to 52.76°
Index ranges	$-22 \leq h \leq 22$, $-10 \leq k \leq 10$, $-38 \leq l \leq 38$
Reflections collected	23179

Independent reflections	4860[R(int) = 0.0456]
Data/restraints/parameters	4860/48/300
Goodness-of-fit on F^2	1.113
Final R indexes [I>=2σ (I)]	$R_1 = 0.0545$, $wR_2 = 0.1189$
Final R indexes [all data]	$R_1 = 0.0626$, $wR_2 = 0.1248$
Largest diff. peak/hole / e Å^{-3}	8.45/-3.51
μ(MoKα)	5.632 mm^{-1}

4.5 References

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Chapter 5

Acceptorless Dehydrogenation of *N*-Heterocycles

5.1 Introduction

Catalytic dehydrogenation (CDH) is one of the most important reactions in the manufacturing of commodity chemicals.[1] For instance, annually approximately 17 million tons of styrene are produced by CDH of ethyl benzene over oxide catalysts. However, CDH has been much less used in the synthesis of fine chemicals, pharmaceuticals and agrochemicals, although it offers considerable benefits with respect to atom economy and environmental impact due to the avoidance of using stoichiometric oxidants. In recent years, CDH of alkanes, alcohols and amines has been realized with transition-metal complexes, although sacrificial hydrogen acceptors and additives are frequently used.[2,3] However, homogeneous catalysts capable of dehydrogenating heterocycles are very rare, and those catalysts that are active are mostly heterogeneous ones, which usually show poor functionality tolerance and require harsh reaction conditions.[4,5]

Fujita and Yamaguchi reported the first example of homogeneous dehydrogenation of tetrahydroquinolines using a Cp*Ir(2-hydroxypyridine) catalyst.[6] A limitation is that only a few examples of 1,2,3,4-tetrahydroquinolines were demonstrated and the reaction conditions were relatively forcing [2 mol% catalyst for 20 h in refluxing *p*-xylene (bp 138 °C) or 5 h in mesitylene (bp 165 °C)]. A significant advantage is that the same catalyst is capable of the reverse reaction, i.e. hydrogenation of quinolines to tetrahydroquinolines under H_2 (1 atm) in quantitative yield (Scheme 5.1). Recently, the same group demonstrated the first homogeneous perdehydrogenation of fused bicyclic *N*-heterocycles using a Cp*Ir catalyst bearing a 1,10-phenanthroline-2,9-dione ligand (Scheme 5.2).[7] The reverse, perhydrogenation was also viable, albeit with high pressures of H_2 (70 atm).
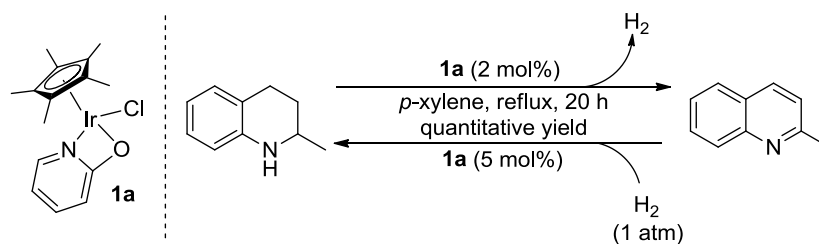
Scheme 5.1: Dehydrogenation and hydrogenation of 2-methyl tetrahydroquinoline.
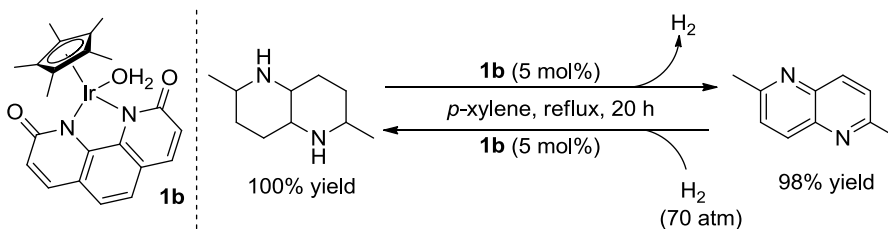
Scheme 5.2: Perdehydrogenation and perhydrogenation of 2,6-dimethyldecahydro-1,5-naphthyridine.

Ru hydride complexes (**1c**-**1e**) are also efficient for acceptorless dehydrogenation of *N*-heterocycles.[8] Among them, Shvo's complex shows the best activity with almost quantitative yield of the desired products. Relatively high temperature and catalyst loadings are required for the reaction to proceed and again, only a few examples of *N*-heterocycles were demonstrated which are shown in Scheme 5.3.

	Substrate	Product	Time (h)	Conv. with catalyst		
				1c [a]	**1d** [a]	**1e** [b]
			48	45	32	98
RuH$_2$(CO)(PPh$_3$)$_3$ **1c**			24	73	78	99
RuH$_2$(PPh$_3$)$_4$ **1d**			24	87	74	100
Shvo's catalyst **1e**			24	95	89	98
			24	97	73	100

[a] 5 mol% catalyst, mesitylene, 165 °C; [b] 2.5 mol% catalyst loading

Scheme 5.3: Representative examples of dehydrogenation with Ru-H complexes.

More recently, Jones reported a well defined Fe complex **1f**, bearing a bis(phosphino)amine pincer ligand that promoted the acceptorless dehydrogenation of a range of *N*-heterocycles (Scheme 5.4).[9] Remarkably, a challenging piperidine substrate was also fully dehydrogenated to its corresponding pyridine. In addition, catalyst **1f** is also active in the hydrogenation of unsaturated *N*-heterocycles.
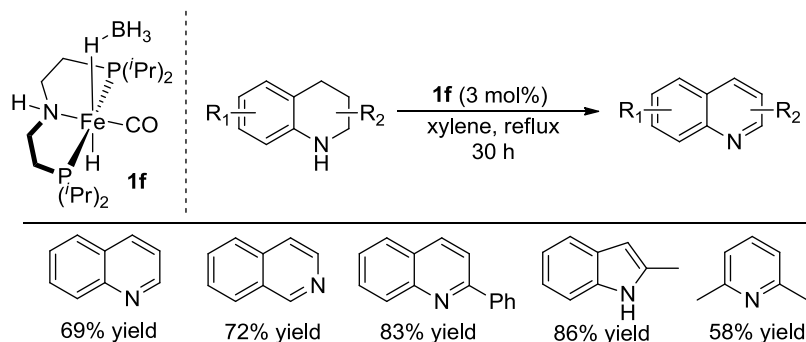
Scheme 5.4: Representative examples of dehydrogenation with a Fe complex.

Given the importance of nitrogen-containing aromatics in numerous naturally occurring alkaloids and synthetic pharmaceuticals, and as potential hydrogen storage materials,[10] developing a single catalytic system with higher CDH activity and wider scope would be of significant interest.

As shown in earlier chapters, the cyclometalated Cp*Ir(III) imino complexes are excellent catalysts for reductive amination and for ketones and *N*-heterocycles reduction.[11] They readily form hydrides under H_2 pressure or when treated with formate, and can release H_2 with the aid of an acid. Inspired by the work of Fujita and Yamaguchi, we envisioned that when reacted with an amine, complex **C** could undergo β-hydrogen elimination, thus generating an imino bond and H_2 upon protonation (Scheme 5.5). However, **C** differs from Fujita-Yamaguchi catalyst (**1a**) not only structurally but also probably mechanistically if it catalyses the dehydrogenation. Containing no bifunctional ligand, the hydride generated from **C**

can only be protonated intermolecularly. In contrast, **1a** operates by ligand-promoted

dehydrogenation.[12,13]
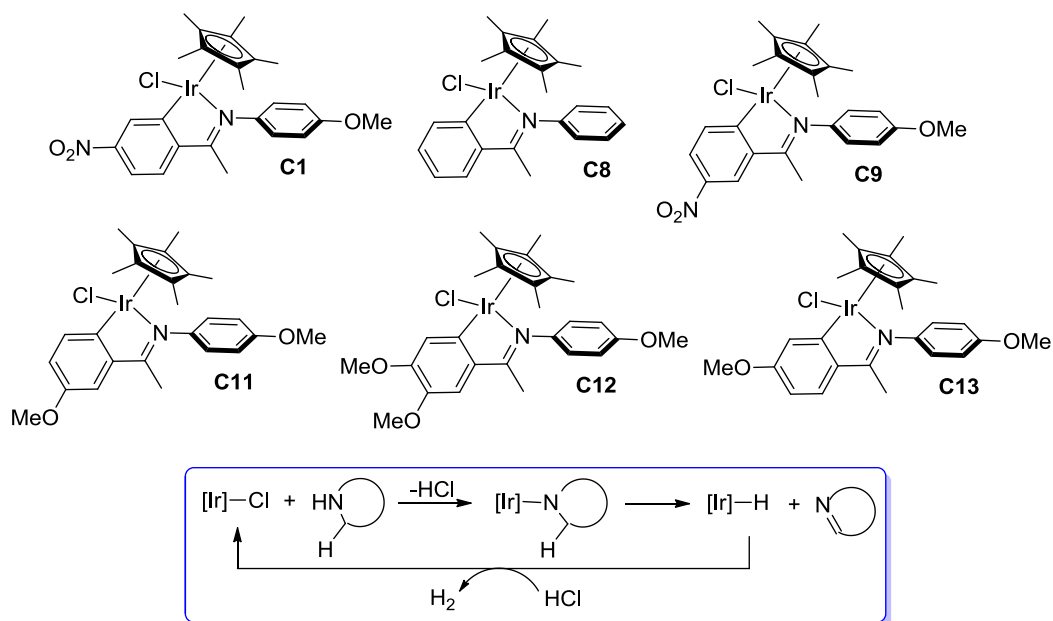
Scheme 5.5: Cyclometalated Cp*Ir(III) imino complexes and hypothesised dehydrogenation of *N*-

-heterocycles.

Following the success of Cp*Ir(III) imino complexes in hydrogenation reactions as

demonstrated in earlier chapters, it would be interesting to test if the same complexes

could be exploited for the CDH (Scheme 5.5). This chapter reports that such

complexes are indeed capable of dehydrogenating not only tetrahydroquinolines but

other *N*-heterocycles as well.[14] These results further demonstrate the versatility of

Cp*Ir(III) imino complexes in both hydrogenation and dehydrogenation reactions.

5.2 Results and discussion

5.2.1 Optimisation of reaction conditions

2-Methyl-1,2,3,4-tetrahydroquinoline (**2a**) was chosen as a model substrate for the optimisation. As expected, in the absence of a catalyst, formation of 2-methyl-quinoline (**3a**) was not detected in 2,2,2-trifluoro-ethanol (TFE; bp 78 °C) after 2 h at reflux (Table 5.1, entry 1). After screening a variety of precatalysts and solvents (Table 5.1, entries 2-19), we were pleased to observe that complex **C11**, which bears electron-donating OMe groups efficiently catalysed the CDH of **2a** in TFE furnishing 88% conversion in 2 h. Full conversion, along with release of H_2, was reached with 0.1 mol% catalyst overnight (Table 5.1, entry 7). Formation of H_2 was confirmed by GC analysis and quantified with the water displacement method (*vide infra*). Other complexes and solvents were less effective.

TFE appears to play multiple roles in the CDH. It may promote the dissociation of chlorine from the catalyst and hence the coordination of **2a** to **C11** before CDH takes place (Scheme 5.6). In support of this view, addition of a chloride salt inhibits the CDH (Table 5.1, entry 20). However, adding a silver or sodium salt did not improve the reactivity of **C11** when the reaction was carried out in toluene (Table 5.1, entries 21-22). It was noted that strong reflux is necessary for higher conversions, and remarkably, when nitrogen was bubbled through the solution, the CDH occurred even at room temperature, thus affording 52% conversion overnight. These observations indicate that the CDH is rate-limited by the step of dihydrogen formation,[12] which is probably facilitated by TFE through protonation of the intermediate hydride (Scheme 5.7).[15]

$$[Ir]-Cl \ + \ CF_3CH_2OH \ \rightleftharpoons \ [Ir]^+ \ + \ Cl^---HOCH_2CF_3$$
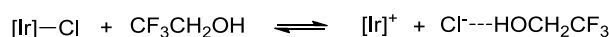
Scheme 5.6: TFE promoted dissociation of chlorine from the catalyst.

$$[Ir]-H \ + \ CF_3CH_2OH \ \rightleftharpoons \ [Ir]-H---HOCH_2CF_3$$

$$[Ir]^+ CF_3CH_2O^- \ + \ H_2 \ \rightleftharpoons \ [Ir]^+-\overset{H}{\underset{H}{|}} \ + \ CF_3CH_2O^-$$
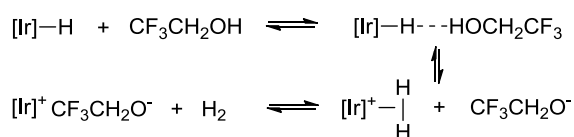
Scheme 5.7: TFE facilitated dihydrogen formation.

Consistent with this, the CDH became progressively slower when alcohols of lower acidity were used, for example, TFE (pK$_a$ 12.5) versus 2,2-difluoro-ethanol (DFE; pK$_a$ 13.1), and ethanol (pK$_a$ 15.8; Table 5.1, entries 7, 10 and 11). Thus, CDH by **C11** appears mechanistically distinct from that by the Fujita-Yamaguchi catalyst (**1a**). To further demonstrate that the high activity of this CDH results from the combination of **C11** and TFE, that is, a solvent-assisted CDH, **C11** was compared with **1a**. Under the conditions of Table 5.1, the later afforded less than 2% conversion (Table 5.1, entry 23). In contrast, the conversion was less than 1% with the former but 77% with the latter under Fujita's conditions (2 mol%, *p*-xylene, reflux, 20 h).

Table 5.1: Optimising reaction conditions for the CDH
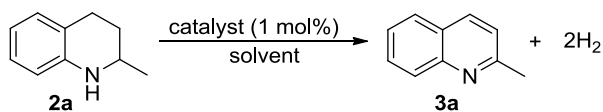
Entry[a]	Catalyst	Additive	Solvent	Conv. (%)[b]
1[c]	none	-	TFE	n.r.
2	[Cp*IrCl$_2$]$_2$	-	TFE	3
3	IrCl$_3$.3H$_2$O	-	TFE	<1
4	**C8**	-	TFE	42
5	**C13**	-	TFE	74
6	**C1**	-	TFE	25
7[d]	**C11**	-	TFE	88
8	**C9**	-	TFE	29
9	**C12**	-	TFE	72
10	**C11**	-	DFE	23
11	**C11**	-	EtOH	4
12	**C11**	-	^{i}PrOH	<1
13	**C11**	-	MeOH	14
14	**C11**	-	H$_2$O	3
15[c]	**C11**	-	THF	n.r.
16[c]	**C11**	-	DMF	n.r.
17	**C11**	-	MeCN	<1
18[c]	**C11**	-	toluene	n.r.
19[e]	**C11**	-	*p*-xylene	<1
20[f]	**C11**	TBAC	TFE	56
21	**C11**	AgBF$_4$	toluene	6
22[c]	**C11**	NaBF$_4$	toluene	n.r.
23	**1a**	-	TFE	2
24 [g]	**1a**	-	*p*-xylene	77

[a] Reaction conditions: **2a** (0.5 mmol) and catalyst (1 mol%) in solvent (3 mL) stirred at reflux under nitrogen for 2 h; 1 mol% additive when used. [b] Determined by ^{1}H-NMR spectroscopy. [c] No reaction observed. [d] Full conversion with 0.1 mol% **C11** overnight. [e] **2a** (1.0 mmol) and catalyst (2 mol%), reflux, 20h. [f] 20 mol% TBAC used. [g] 2 mol% **1a** used. Cp* = C$_5$Me$_5$, DFE = difluoroethanol, n.r. = no reaction, TBAC = tetrabutylammonium chloride.

5.2.2 CDH of tetrahydroquinolines

With the **C11**/TFE catalytic system in hand, a variety of tetrahydroquinolines (**2**) were subjected to the CDH (Table 5.2). These were dehydrogenated to give quinolines in good to excellent yields with 0.1 mol% of **C11**. Slightly lower yields were obtained with the nonsubstituted 1,2,3,4-tetrahydroquinoline (**2b**) and 3-methyl-1,2,3,4-tetrahydroquinoline (**2c**), even at a higher catalyst loading of 1 mol% (Table 5.2, entries 2 and 3).[16] All the 6-substituted substrates afforded the corresponding products in high yields (Table 5.2, entries 5-8), regardless of the nature of the substituent. The less basic **2j** was also dehydrogenated in excellent yield (Table 5.2, entry 10). The acridine **3k** and the 1,2,3,4-tetrahydro variant **3l**, used as antitumor drugs and an analogue of acetylcholinesterase inhibitor,[17] were obtained from **2k** and **2l**, respectively, in excellent yields (Table 5.2, entries 11 and 12). Notably, the 2,2'-biquinoline **3m**, a well-known diamine ligand, was generated along with liberation of 4 equivalents of H_2 from the octahydro form **2m** (Table 5.2, entry 13). The catalyst is chemoselective, as seen in the CDH of **2i** bearing a primary alcohol group, affording **3i** with exclusive dehydrogenation selectivity towards the *N*-heterocyclic ring (Table 5.2, entry 9).

Table 5.2: CDH of tetrahydroquinolines

Entry[a]	Substrate		Product		yield (%)[b]
1		**2a**		**3a**	95
2[c]		**2b**		**3b**	87
3[c]		**2c**		**3c**	72
4		**2d**		**3d**	87
5		**2e**		**3e**	94
6		**2f**		**3f**	97
7		**2g**		**3g**	93
8		**2h**		**3h**	94
9		**2i**		**3i**	81
10		**2j**		**3j**	92
11		**2k**		**3k**	92
12		**2l**		**3l**	88
13[c]		**2m**		**3m**	81

[a] Reaction conditions: **2** (0.5 mmol) and **C11** (0.1 mol%) in TFE (3 mL) stirred at reflux under nitrogen for 20 h. [b] Yield of isolated product. [c] Used 1 mol% **C11**.

5.2.3 CDH of tetrahydroisoquinolines and tetrahydro-β-carbolines

Isoquinolines and β-carbolines have broad pharmaceutical applications.[18] They can be obtained by traditional oxidation of the easily accessible tetrahydro or 3,4-dihydro analogs.[19] Following the CDH of **2**, tetrahydroisoquinolines and tetrahydro-β-carbolines (**4**) were examined. These substrates are challenging to fully dehydrogenate, because of their tendency to form stable imine intermediates.[20] Table 5.3 shows that **4** can be dehydrogenated to isoquinolines (**5**) in good to excellent yields in general at a 0.1 mol% catalyst loading (entries 1-8). Among the substrates examined, only the nonsubstituted **4a** and sterically demanding **4e** necessitated a higher catalyst loading of 1 mol%. In the case of the former, **5a** was obtained in only 30% yield. Worth noting is that the tetrahydroharman **4i** was fully dehydrogenated to give the aribine **5i**, an important β-carboline alkaloid (Table 5.3, entry 9), and **4j** was converted into **5j** in high yield (Table 5.3, entry 10).

Table 5.3: CDH of tetrahydroisoquinolines and tetrahydro-β-carbolines

Entry[a]	Substrate		Product		yield (%)[b]
1[c,d]		**4a**		**5a**	30
2		**4b**		**5b**	90
3		**4c**		**5c**	92
4		**4d**		**5d**	93
5[c]		**4e**		**5e**	82
6		**4f**		**5f**	95
7		**4g**		**5g**	93
8		**4h**		**5h**	96
9[c]		**4i**		**5i**	93
10		**4j**		**5j**	95

[a] Reaction conditions: **4** (0.5 mmol) and **C11** (0.1 mol%) in TFE (3 mL) stirred at reflux under nitrogen for 20 h. [b] Yield of isolated product. [c] Used 1 mol% **C11**. [d] Yield as determined by ^{1}H-NMR spectroscopy.

5.2.4 CDH of 3,4-dihydroisoquinolines

The CDH of 3,4-dihydroisoquinolines (**6**), which can be produced by the classical Bischler-Napieralski reaction, were targeted next (Table 5.4).[21] Although high yields were achieved, surprisingly a high catalyst loading (1 mol%) was required (Table 5.4, entries 1-6). Under the reaction conditions used for 1,2,3,4-tetrahydroisoquinolines **4** (Table 5.3), CDH of **6** was hardly detectable, thus suggesting that the CDH of **4** does not proceed via the intermediacy of **6**.

Table 5.4: CDH of 3,4-dihydroisoquinolines

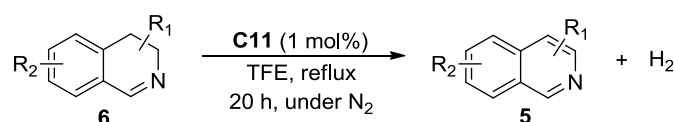| Entry[a]	Substrate		Product		yield (%)[b]
1		**6a**		**5b**	89
2		**6b**		**5c**	92
3		**6c**		**5f**	93
4		**6d**		**5g**	94
5		**6e**		**5h**	95
6		**6f**		**5i**	81

[a] Reaction conditions: **6** (0.5 mmol) and **C11** (1 mol%) in TFE (3 mL) stirred at reflux under nitrogen for 20 h. [b] Yield of isolated product.

Apart from CDH, **C11** also catalyses the hydrogenation of **6a** into **4b** with excellent conversion at 20 °C and 1 atm H$_2$ pressure (Scheme 5.8). The highly stable **5b** was hydrogenated as well, although more forcing reaction conditions were needed. Together with the results in Tables 5.3 and 5.4, these results weave a unique network which links the three forms of isoquinoline by hydrogenation and dehydrogenation using a single catalyst (**C11**; Scheme 5.8).
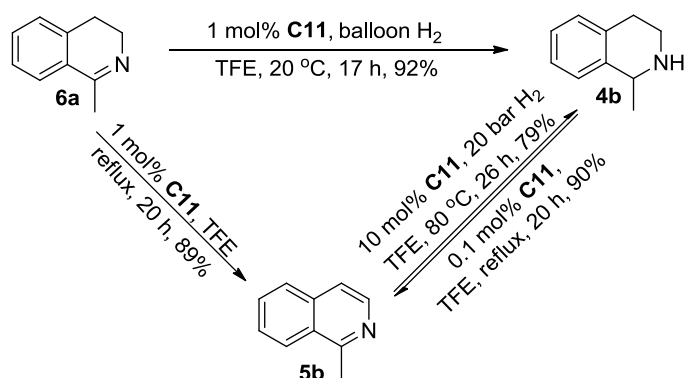
Scheme 5.8: Hydrogenation/dehydrogenation-linked interchangeable transformations between isoquinoline and derivatives.

5.2.5 CDH of indoline derivatives and tetrahydroquinoxalines

Bearing in mind that there are diverse ways for the preparation of indolines,[22] direct CDH adds a valuable alternative to the strategies of indole synthesis. Using **C11**, various indoline derivatives were dehydrogenated, affording indoles in excellent yields (Table 5.5). In particular, sterically demanding 2,3-dimethyl and 2-phenylindolines were dehydrogenated to indoles in 96% yield (Table 5.5, entries 5 and 7). However, as with **4a**, the nonsubstituted **7a** was more difficult to dehydrogenate (Table 5.5, entry 1).

Table 5.5: CDH of indoline derivatives
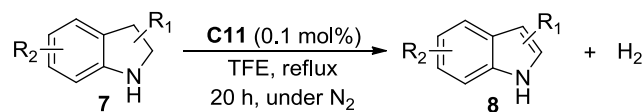
Entry[a]	Substrate		Product		yield (%)[b]
1[c]		**7a**		**8a**	91
2		**7b**		**8b**	95
3[d]		**7c**		**8c**	93
4		**7d**		**8d**	90
5		**7e**		**8e**	96
6		**7f**		**8f**	98
7		**7g**		**8g**	96

[a] Reaction conditions: **7** (0.5 mmol) and **C11** (0.1 mol%) in TFE (3 mL) stirred at reflux under nitrogen for 20 h. [b] Yield of isolated product. [c] Used 1 mol% **C11**. [d] Used 0.5 mol% **C11**.

Traditional synthesis of quinoxalines makes use of reactions such as condensation and oxidative cyclisation.[23] To the best of our knowledge CDH has not been employed for the synthesis of quinoxalines. We therefore investigated the dehydrogenation of tetrahydroquinoxalines (**9**; Table 5.6). The CDH worked, giving rise to good to excellent yields of the quinoxalines **10** with 0.1 mol% of **C11**. However, a higher catalyst loading was necessary for the sterically bulky **9d** and **9e** (Table 5.6, entries 4 and 5).

Table 5.6: CDH of tetrahydroquinoxalines
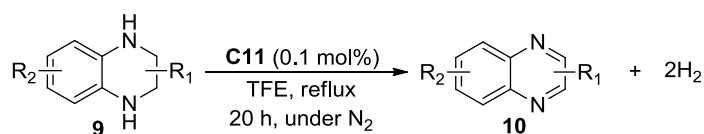
Entry[a]	Substrate		Product		yield (%)[b]
1		**9a**		**10a**	92
2		**9b**		**10b**	79
3		**9c**		**10c**	93
4[c]		**9d**		**10d**	85
5[c]		**9e**		**10e**	82
6		**9f**		**10f**	62
7		**9g**		**10g**	64

[a] Reaction conditions: **9** (0.5 mmol) and **C11** (0.1 mol%) in TFE (3 mL) stirred at reflux under nitrogen for 20 h. [b] Yield of isolated product. [c] Used 1 mol% **C11**.

### 5.2.6 CDH in total synthesis of alkaloids

To showcase the synthetic utility of the CDH, the protocol was applied to a rapid total synthesis of two well-known, naturally occurring alkaloids, papaverine and harmine. Papaverine is an opium alkaloid antispasmodic drug, clinically used for the treatment of vasospasm and occasionally for erectile dysfunction.[24] Harmine is a

major β-carboline alkaloid found in *pegunam harmala* extract. It is an inhibitor of monoamine reuptake system and has also shown cytotoxic activities against a series of tumor cell lines.[25] Our synthesis of papaverine started with the condensation of commercially available homoveratric acid and homoveratrylamine under microwave-assisted, neat conditions, thus generating the corresponding amide in almost quantitative yield (Scheme 5.9). The amide was then treated with POCl$_3$ to furnish a cyclic imine by the Bischler-Napieralski reaction.[21] The last step of the synthesis was accomplished by **C11** catalysed CDH of the 3,4-dihydroisoquinoline. The three-step synthesis, employing commercially available materials with an overall yield of 78%, appears to offer a most efficient and economically sound method for this significant alkaloid.[26]
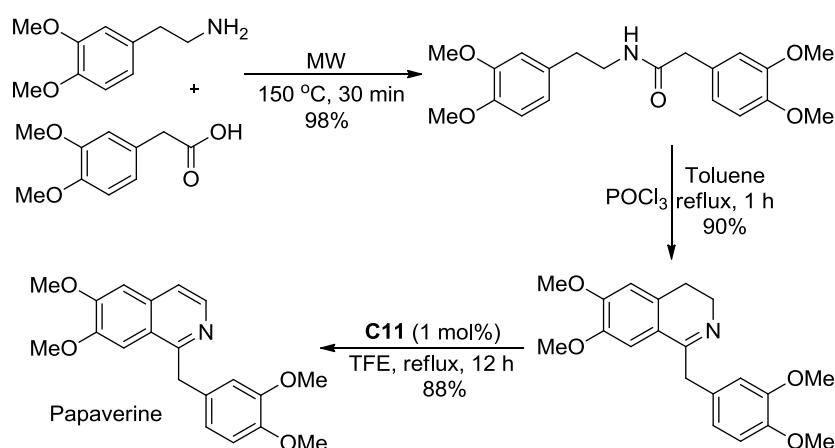

Scheme 5.9: Synthesis of papaverine.

Scheme 5.10 shows the synthesis of harmine starting with a Pictet-Spengler reaction[21] of acetaldehyde with 6-methoxytryptamine. CDH of the resulting tetrahydroharmine by **C11** afforded the target alkaloid, with an overall yield of 57%. In comparison with other known methods,[27] this concise synthesis of harmine using commercially available materials is high-yielding and less wasteful under mild reaction conditions.

Scheme 5.10: Synthesis of harmine.
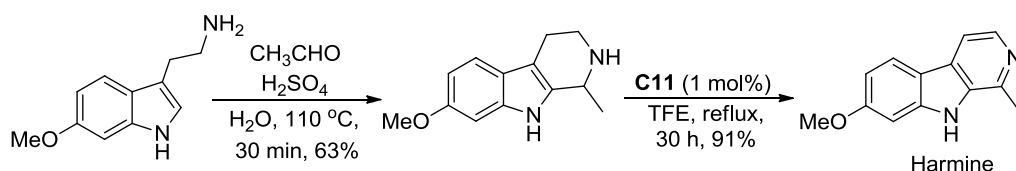
5.2.7 Mechanistic considerations

Preliminary mechanistic studies of CDH of 2-methyl-1,2,3,4-tetrahydroquinoline (**2a**) and 1-methyl-1,2,3,4-tetrahydroisoquinoline (**4b**) shed light on how these CDH reactions may take place. In the presence of **C11** in TFE-d_3, **2a** undergoes rapid H-D exchange at the C2-position at room temperature. However, no other species were observed apart from **2a** and trace amounts of **3a** in the ^{1}H NMR spectrum (Figure 5.1). This suggests again that dehydrogenation, without releasing H$_2$, is a fast process.
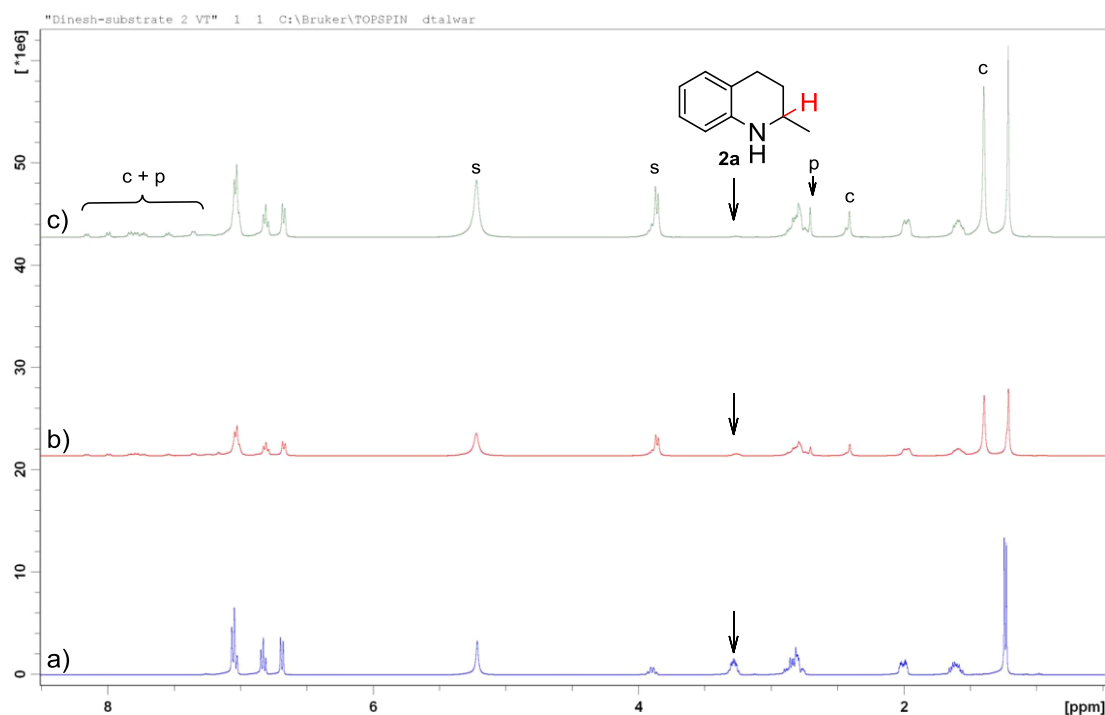

Figure 5.1: ^{1}H NMR spectra recorded at 298 K: a) **2a** (0.25 mmol, 37 mg) in TFE-d$_3$ (0.8 mL); b) a) + **C11** (0.05 mmol), 3.5 min after addition; c) 20 min after addition of **C11**. c = catalyst, s = solvent, p = product.

Under the normal reflux conditions (Table 5.2), **3a** was obtained with deuterium incorporation at the C3 and methyl position. To further confirm the deuteration, the dehydrogenation of **2f** was carried out using TFE-d_3 under reflux conditions for 20 h (whereby the Me of OMe at C6 could be used as an internal standard). **2f** was converted to **3fd** with partial deuteration (60%) at C3 and multiple deuterations (61% in total) at the R group (Scheme 5.11).
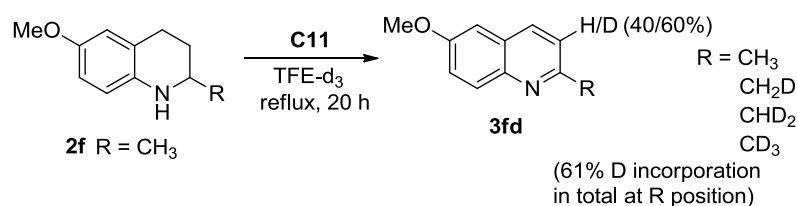

Scheme 5.11: Dehydrogenation of **2f** in TFE-d_3.

On this basis, CDH of **2a** is suggested to proceed by the pathway shown in Scheme 5.12. At low temperature, **2a** is in equilibrium with **2a$_1$**, which is probably protonated by or hydrogen-bonded with the medium, and **2a$_2$**, with the equilibrium strongly favouring **2a**. At high temperature **2a$_1$** isomerises to **2a$_4$** by acid catalysis, which hydrogenates **2a$_3$**, thus resulting in the formation of **3a** and **2a**.
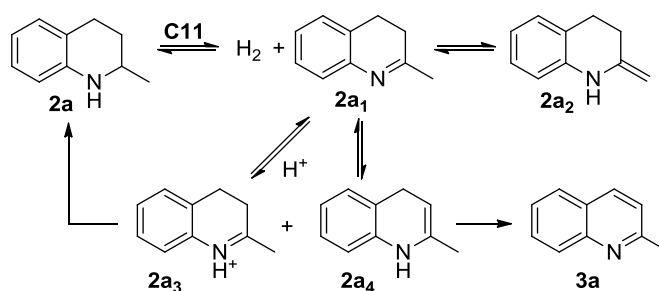
Scheme 5.12: Proposed pathway for the CDH of tetrahydroquinolines.

When **4b** was subjected to CDH with 0.1 mol% of **C11** in refluxing TFE for a short time, both **6a** and **5b** were observed (Scheme 5.13, Eq. 1). However, **6a** showed no observable CDH under these conditions (Eq. 2), although it gave **4b** and **5b** at 1

mol% of **C11** (Eq. 3). In contrast, using of 0.1 mol% of **C11** but in the presence of

4c, **6a** was converted into **4b** and **5b** (Eq. 4), thus showing that **6a** can readily

undergo CDH, probably by **4b**, if a hydride donor such as **4c**, is present.
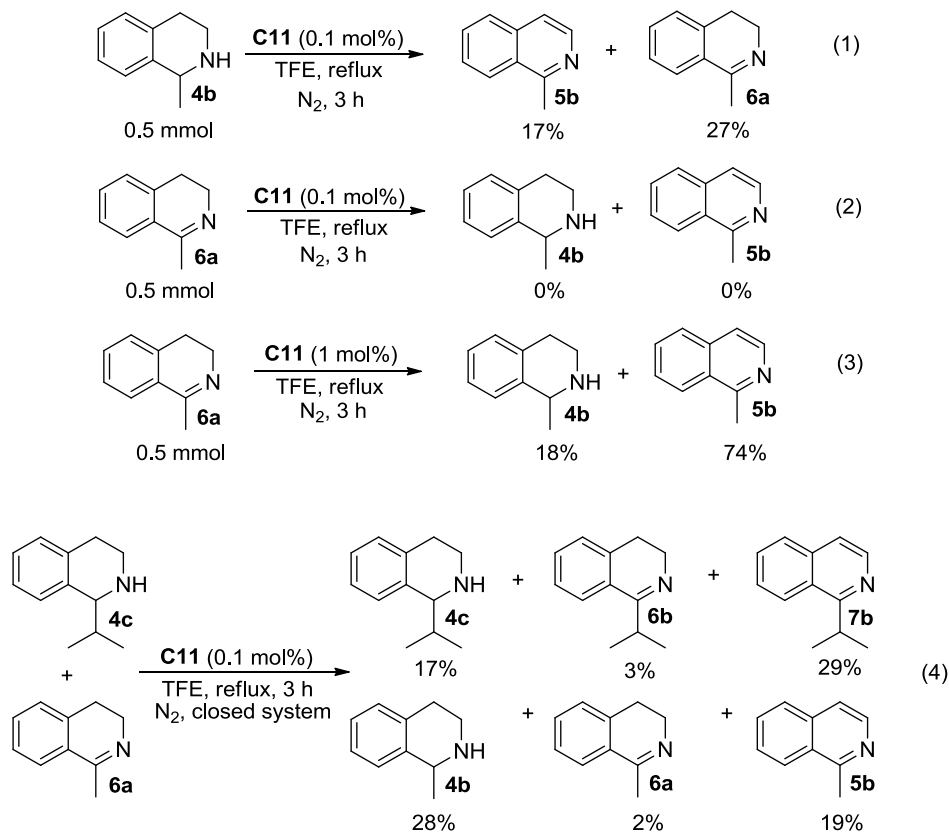

Scheme 5.13: Control experiments.

These observations suggest that the CDH of **4b** involves a pathway as shown in

Scheme 5.14, where **4b** can be dehydrogenated into either **6a** or **4b$_1$**. But it is **4b$_1$**

that gives rise to the product **5b**. The formation of **5b** from **6a** proceeds by its first

reduction to **4b**. When **6a** alone is dehydrogenated, it is likely to be reduced to **4b** in

the first place by TFE, a solvent of well-known to resistance to oxidation. This

explains why **6** is more difficult to dehydrogenate than **4**.
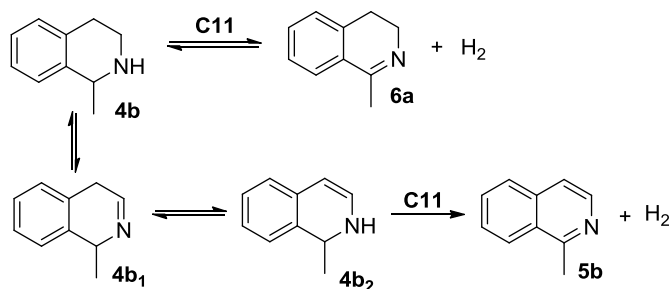
Scheme 5.14: Proposed pathway for the CDH of tetrahydro- and dihydroisoquinolines.

The hypothesis on TFE acting as a hydride donor finds support in the observation of Ir-H hydride resonance at δ -10.10 ppm in the ^{1}H NMR spectrum when **C11** was dissolved in TFE and heated to 60 °C for 1 h in a high pressure sapphire NMR tube. The formation of 2,2,2-trifluoroacetaldehyde was also observable at δ 9.66 ppm as a quartet (Figure 5.2).
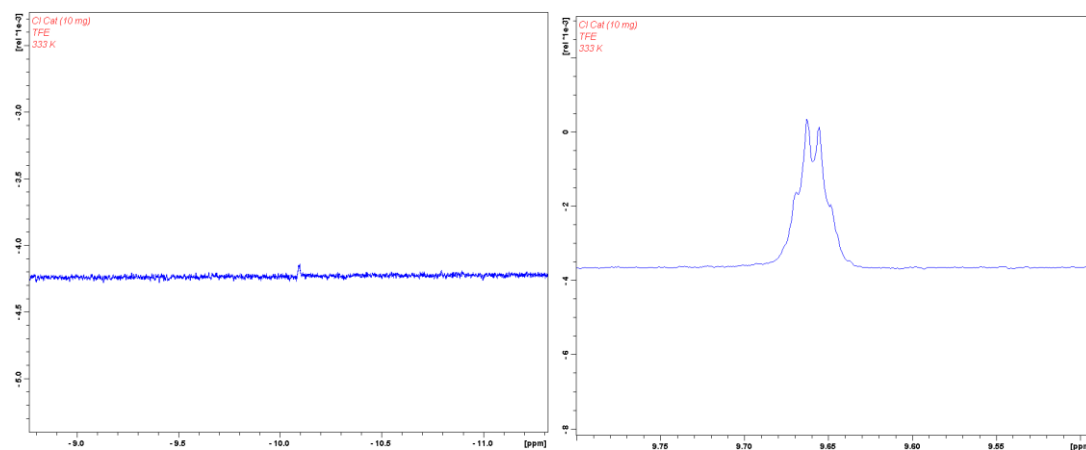
Figure 5.2: ^{1}H NMR spectrum of TFE + **C11** recorded at 60 °C after 1 h, showing the hydride and aldehydes region. Conditions: TFE (1 mL) + **C11** (10 mg, 0.017 mmol).

5.3 Conclusion

In summary, this chapter demonstrates the development of a versatile catalytic system for the oxidant-free, acceptorless CDH of various benzo-fused *N*-heterocycles.[14] The high activity and broad substrate scope of the catalytic system make the protocol a promising alternative for laboratory as well as industrial

applications, and this is reinforced by the ease of operation, atom economy and environmental benefits offered by CDH.

5.4 Experimental

5.4.1 General information

Unless otherwise specified, reagents and solvents were purchased commercially and used as received. Substrates **2a**, **2c**, **2e**, **2f**, **2g**, **2h**, **2i**, **2j**, and **2l** were prepared by the reduction of corresponding quinolines, and **9a**, **9b**, **9c**, **9f**, and **9g** by reduction of the corresponding quinoxalines.[28] Substrate **2m** was prepared by the hydrogenation of 2,2'-biquinoline according to the literature method using Adam's catalyst.[29] Substrates **7b** and **7e** were prepared by the hydrogenation of the corresponding indoles according to the literature method.[30] **7f** was obtained from reduction by using sodium borocyanohydride,[31] while **7g** was synthesised through tin-mediated reduction of the corresponding indoles.[32] **9d** and **9e** were prepared by the reduction with sodium borohydride of the corresponding quinoxalines, which were prepared by the condensation of diamines with diketones or dialdehydes according to the literature methods.[33,34] Dihydroisoquinolines were prepared by the Bischler-Napieralski synthesis and were subsequently reduced to give their tetrahydro variants.[28,34] NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer unless otherwise specified. Elemental analysis and mass spectrometry analysis were carried out at the Microanalysis Centre of University of Liverpool and the EPSRC National Mass Spectrometry Service Centre at Swansea University.

5.4.2 General procedure for the dehydrogenation of *N*-heterocyclic amines

N-Heterocyclic amine (0.50 mmol) and **C11** (0.31 mg, 5×10^{-4} mmol, measured using a stock TFE solution) were dissolved in TFE (3 mL) in a carousel reaction tube. The tube was then degassed and the reaction mixture was refluxed under N_2 for 20 h. It was then cooled to room temperature and the solvent was evaporated under vacuum. The resulting crude solid was purified using flash chromatography to give the corresponding product. All the dehydrogenation products are known, except **5g**, and their NMR spectra were consistent with the literature.

5.4.3 Typical procedure for the hydrogen evolution experiment

A solution of 2-methyl-1,2,3,4-tetrahydroquinoline (0.5 mmol) in TFE (2 mL) was added to a thick walled glass vessel fitted with a side arm and a rubber septum which had been preheated to the appropriate temperature by means of an oil bath. The vessel was previously degassed three times and placed under an N_2 atmosphere. The vessel was connected to the gas collection apparatus (standard water displacement apparatus, using a graduated cylinder to determine volume) and the entire system was flushed with N_2 for 5 minutes and allowed to equilibrate for 5 minutes. A solution of the catalyst **C11** (18.6 mg, 6 mol%) in TFE (1 mL) was added *via* syringe through the septum. Any small volume of gas collected resulting from addition of the catalyst solution was noted and subtracted from the values for gas collected. The reaction was stirred vigorously at a constant temperature until gas evolution ceased (2.5 h). The volume of collected gas was noted, supposing that all the gas consisted of hydrogen. The presence of hydrogen in the collected gas was confirmed by GC. After the reaction was complete, the solution was evaporated to give a crude product

which was analysed by ^{1}H NMR, which confirmed full conversion of the 2-methylquinoline product.

The calculation of the volume of 1 mole of H_2 at 25 °C was carried out using Van der Waals equation, as shown below:

$$\left(p + \frac{n^2 a}{V^2}\right)(V - nb) = nRT$$

Where;

**R**: 8.3145 m³ Pa mol^{-1} K^{-1} **T**: 298.15 K   **p**: 101,325 Pa (1 atm)

a: 0.002476 m^6·Pa·mol^{-2} **b**: 0.02661x10^{-3} m^3·mol^{-1}

Thus, *V (H$_2$, 25 °C, 1 atm)* = 24.49 L·mol^{-1}

The collected volume of gas in the experiment above was 24.2 mL, which corresponds to 0.98 mmol of H_2. Since the dehydrogenation is 0.5 mmol in scale, this is consistent with the release of 2 equivalents of H_2 per mole of 2-methyl-1,2,3,4-tetrahydroquinoline.

5.4.4 Data for the quinolines
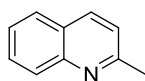
2-Methylquinoline (3a):[35] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.02 (d, J = 8.4 Hz, 2H), 7.75 (dd, J = 8.2, 1.0 Hz, 1H), 7.67 (ddd, J = 8.6, 6.8, 1.6 Hz, 1H), 7.46 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 2.74 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 159.4, 148.3, 136.6, 129.8, 129.0, 127.9, 126.9, 126.1, 122.4, 25.8. MS (CI) for C$_{10}$H$_{10}$N [M+H]$^+$: m/z 144.2.
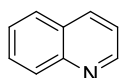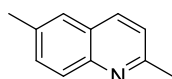
Quinoline (3b):[36] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.92 (dd, J = 4.2, 1.7 Hz, 1H), 8.13 (t, J = 9.3 Hz, 2H), 7.81 (d, J = 8.1 Hz, 1H), 7.71 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.38 (dd, J = 8.1, 4.2 Hz, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 150.8, 148.7, 136.4, 129.9, 129.8, 128.7, 128.2, 126.9, 121.5. Anal. calc. for C$_9$H$_7$N (%): C, 83.69; H, 5.46; N, 10.84. Found: C, 83.60; H, 5.42; N, 10.77. MS (CI) for C$_9$H$_8$N [M+H]$^+$: m/z 130.2.
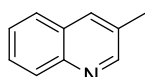
3-Methylquinoline (3c):[36] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.78 (d, J = 2.1 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.93 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.65 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.54-7.50 (m, 1H), 2.53 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 152.3, 146.9, 135.1, 130.9, 129.5, 128.9, 128.5, 127.5, 127.0, 19.2. Anal. calc. for C$_{10}$H$_9$N (%): C, 83.88; H, 6.34; N, 9.78. Found: C, 83.74; H, 6.58; N, 9.91. MS (CI) for C$_{10}$H$_{10}$N [M+H]$^+$: m/z 144.0.
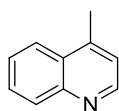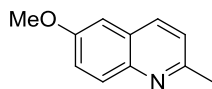

4-Methylquinoline (3d):[37] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.76 (d, J = 4.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.96 (dd, J = 8.4, 1.6 Hz, 1H), 7.69 (ddd, J = 8.4, 6.8, 1.6 Hz, 1H), 7.54 (ddd, J = 8.4, 6.8, 1.3 Hz, 1H), 7.19 (dd, J = 4.4, 0.8 Hz, 1H), 2.67 (J = 0.8 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 150.6, 148.4, 144.6, 130.4, 129.5, 128.7, 126.7, 124.2, 122.2, 19.0. Anal. calc. for C$_{10}$H$_9$N (%): C, 83.88; H, 6.34; N, 9.78. Found: C, 84.28; H, 6.57; N, 9.89. MS (CI) for C$_{10}$H$_{10}$N [M+H]$^+$: m/z 144.2.
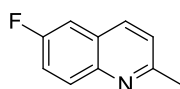

2,6-Dimethylquinoline (3e):[38] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.94 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.55-7.47 (m, 2H), 7.24 (d, J = 8.3 Hz, 1H), 2.72 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 158.4, 146.9, 135.9, 135.8, 132.0, 128.7, 126.9, 126.8, 122.3, 25.7, 21.9. Anal. calc. for

C$_{11}$H$_{11}$N (%): C, 84.04; H, 7.05; N, 8.91. Found: C, 83.81; H, 7.08; N, 8.87. MS (CI) for C$_{11}$H$_{12}$N [M+H]$^+$: m/z 158.1.


6-Methoxy-2-methylquinoline (3f):[36] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.92 (t, J = 8.2 Hz, 2H), 7.33 (dd, J = 9.2, 2.8 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H), 7.04 (d, J = 2.8 Hz, 1H), 3.91 (s, 3H), 2.70 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 157.6, 156.7, 144.3, 135.4, 130.4, 127.7, 122.6, 122.2, 105.6, 55.9, 25.4. Anal. calc. for C$_{11}$H$_{11}$NO (%): C, 76.28; H, 6.40; N, 8.09. Found: C, 76.23; H, 6.46; N, 8.12. MS (CI) for C$_{11}$H$_{12}$NO [M+H]$^+$: m/z 174.2.

6-Fluoro-2-methylquinoline (3g):[39] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.02-7.98 (m, 2H), 7.45 (td, J = 8.8, 2.8 Hz, 1H), 7.38 (dd, J = 8.9, 2.8 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 2.73 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 160.1 (d, J$_{CF}$ = 246.7), 158.7 (d, J$_{CF}$ = 2.7 Hz), 145.3, 135.9 (d, J$_{CF}$ = 5.2 Hz), 131.4 (d, J$_{CF}$ = 9.5 Hz), 127.4 (d, J$_{CF}$ = 9.8 Hz), 123.1, 119.9 (d, J$_{CF}$ = 26.1 Hz) 110.9 (d, J$_{CF}$ = 22.1 Hz), 25.6. MS (CI) for C$_{10}$H$_8$FN [M+H]$^+$: m/z 162.1. HRMS for C$_{10}$H$_9$FN [M+H]$^+$: m/z calc., 162.0714; found, 162.0713.
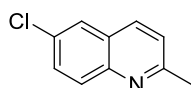

6-Chloro-2-methylquinoline (3h):[40] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.96 (dd, J = 8.6, 4.0 Hz, 2H), 7.75 (d, J = 2.3 Hz, 1H), 7.61 (dd, J = 9.0, 2.3 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 2.74 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 159.8, 146.7, 135.6, 131.7, 130.7, 130.6, 127.5, 126.6, 123.3, 25.7. Anal. calc. for C$_{10}$H$_8$ClN (%): C, 67.62; H, 4.54; N, 7.89. Found: C, 67.40; H, 4.25; N, 7.91. MS (CI) for C$_{10}$H$_9$ClN [M+H]$^+$: m/z 178.2.
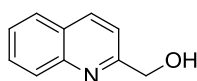

Quinolin-2-ylmethanol (3i):[41] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.15 (d, J = 8.8 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.74 (ddd, J =

8.0, 6.8, 1.2 Hz, 1H), 7.55 (t, J = 7.4 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 4.93 (s, 2H), 4.57 (br, 1H),. ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 159.3, 147.1, 137.3, 130.2, 129.0, 128.1, 128.0, 126.8, 118.7, 64.5. Anal. calc. for C$_{10}$H$_9$NO (%): C, 75.45; H, 5.70; N, 8.80. Found: C, 74.99; H, 5.71; N, 8.60. MS (CI) for C$_{10}$H$_{10}$NO [M+H]$^+$: m/z 160.2.
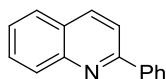
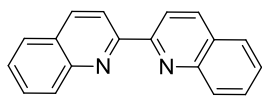***2-Phenylquinoline (3j)***:[42] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.29-8.12 (m, 4H), 7.88 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H) 7.78-7.69 (m, 1H), 7.58-7.44 (m, 4H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 157.8, 148.7, 140.1, 137.2, 130.2, 130.1, 129.7, 129.3, 128.0, 127.9, 127.6, 126.7, 119.4. Anal. calc. for C$_{15}$H$_{11}$N (%): C, 87.77; H, 5.40; N, 6.82. Found: C, 87.56; H, 5.26; N, 6.62. MS (CI) for C$_{15}$H$_{12}$N [M+H]$^+$: m/z 206.1.
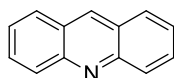
Acridine (3k):[43] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.79 (s, 1H), 8.25 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 7.80 (ddd, J = 8.4, 6.8, 1.6 Hz, 2H), 7.55 (t, J = 7.2 Hz, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 149.5, 136.3, 130.8, 129.8, 128.6, 127.0, 126.1. Anal. calc. for C$_{13}$H$_9$N (%): C, 87.12; H, 5.06; N, 7.82. Found: C, 86.24; H, 4.97; N, 7.72. MS (CI) for C$_{13}$H$_{10}$N [M+H]$^+$: m/z 180.2.
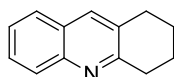
***1,2,3,4-Tetrahydroacridine (3l)***:[44] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.98 (d, J = 8.4 Hz, 1H), 7.81 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.61 (ddd, J = 8.4, 7.0, 1.2 Hz, 1H), 7.44 (t, J = 7.2 Hz, 1H), 3.14 (t, J = 6.4 Hz, 2H), 2.98 (t, J = 6.4 Hz, 2H), 2.03-1.96 (m, 2H), 1.95-1.87 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 159.7, 147.0, 135.4, 131.4, 128.9, 128.7, 127.6, 127.3, 126.0, 34.0, 29.7, 23.7, 23.3. Anal. calc. for C$_{13}$H$_{13}$N (%): C, 85.21; H, 7.15; N, 7.64. Found: C, 84.84; H, 7.18; N, 7.51. MS (CI) for C$_{13}$H$_{14}$N [M+H]$^+$: m/z 184.2.

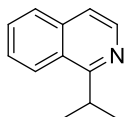***2,2'-Biquinoline (3m)***:[45] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.85 (d, J = 8.6 Hz, 2H), 8.32 (d, J = 8.6 Hz, 2H), 8.23 (d, J = 8.5 Hz, 2H), 7.88 (dd, J = 8.1, 1.2 Hz, 2H), 7.75 (ddd, J = 8.5, 6.9, 1.5 Hz, 2H), 7.57 (ddd, J = 8.1, 6.9, 1.2 Hz, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 156.7, 148.4, 137.1, 130.4, 129.9, 128.9, 128.1, 127.4, 119.9. Anal. calc. for C$_{18}$H$_{12}$N$_2$ (%): C, 84.35; H, 4.72; N, 10.93. Found: C, 84.16; H, 4.61; N, 10.89. MS (CI) for C$_{18}$H$_{13}$N$_2$ [M+H]$^+$: m/z 257.2.

5.4.5 Data for the isoquinolines
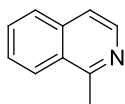
1-Methylisoquinoline (5b):[46] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.39 (d, J = 5.7 Hz, 1H), 8.12 (d, J = 8.3 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.67 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.59 (ddd, J = 8.3, 7.0, 1.2 Hz, 1H), 7.51 (d, J = 5.8 Hz, 1H), 2.97 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 159.0, 142.2, 136.3, 130.3, 127.9, 127.6, 127.4, 126.0, 119.7, 22.8. Anal. calc. for C$_{10}$H$_9$N (%): C, 83.88; H, 6.34; N, 9.78. Found: C, 83.46; H, 6.52; N, 9.54. MS (CI) for C$_{10}$H$_{10}$N [M+H]$^+$: m/z 144.2.
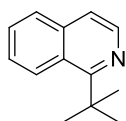

1-Isopropylisoquinoline (5c):[47] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.49 (d, J = 5.6 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.65 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 7.58 (ddd, J = 8.4, 6.8, 1.2 Hz, 1H), 7.48 (d, J = 5.6 Hz, 1H), 3.96 (septet, J = 6.8 Hz, 1H), 1.45 (d, J = 6.4 Hz, 6H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 166.7, 142.3, 136.8, 129.9, 127.9, 127.2, 126.7, 125.2, 119.4, 31.4, 22.6. Anal. calc. for C$_{12}$H$_{13}$N (%): C, 84.17; H, 7.65; N, 8.18. Found: C, 84.41; H, 7.84; N, 8.10. MS (CI) for C$_{12}$H$_{14}$N [M+H]$^+$: m/z 172.2.
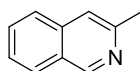
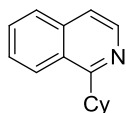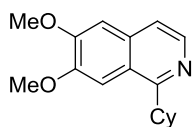***3-Methylisoquinoline (5d)***:[48] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 9.19 (s, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.66-7.62 (m, 1H), 7.54-7.48 (m, 2H), 2.71 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 152.4, 152.0, 137.0, 130.7, 127.9, 127.2, 126.7, 126.3, 118.9, 24.6. Anal. calc. for C$_{10}$H$_9$N (%): C, 83.88; H, 6.34; N, 9.78. Found: C, 84.00; H, 6.33; N, 9.70. MS (CI) for C$_{10}$H$_{10}$N [M+H]$^+$: m/z 144.0.

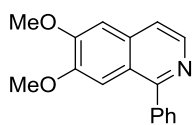***1-(tert-Butyl)isoquinoline (5e)***:[49] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.53 (d, J = 8.8 Hz, 1H), 8.44 (d, J = 5.6 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.62 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 7.54 (ddd, J = 8.4, 6.8, 1.6 Hz, 1H), 7.50 (d, J = 5.6 Hz, 1H), 1.67 (s, 9H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 167.8, 141.0, 137.8, 129.2, 128.7, 127.7, 126.6, 126.1, 120.2, 40.3, 31.6. Anal. calc. for C$_{13}$H$_{15}$N (%): C, 84.28; H, 8.16; N, 7.56. Found: C, 84.87; H, 8.14; N, 7.29. MS (CI) for C$_{13}$H$_{16}$N [M+H]$^+$: m/z 186.2.

1-Cyclohexylisoquinoline (5f):[50] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.47 (d, J = 5.6 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.64 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 7.58 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.47 (d, J = 5.6 Hz, 1H), 3.56 (tt, J = 11.6, 3.2 Hz, 1H), 2.01-1.76 (m, 7H), 1.60-1.34 (m, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 166.1, 142.4, 136.8, 129.9, 127.9, 127.2, 126.7, 125.1, 119.3, 42.0, 33.0, 27.3, 26.7. Anal. calc. for C$_{15}$H$_{17}$N (%): C, 85.26; H, 8.11; N, 6.63. Found: C, 85.94; H, 8.37; N, 6.63. MS (CI) for C$_{15}$H$_{18}$N [M+H]$^+$: m/z 212.4.

***1-Cyclohexyl-6,7-dimethoxyisoquinoline (5g)***: [^1]H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.36 (d, J = 5.6 Hz, 1H), 7.40 (s, 1H), 7.34 (d, J = 5.6 Hz, 1H), 7.06 (s, 1H), 4.05 (s, 3H), 4.02 (s, 3H), 3.39 (tt, J = 11.4, 3.1 Hz, 1H), 2.10-1.22 (m, 10H). [^13]C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 163.6, 152.7, 150.2, 141.5, 133.6, 122.3, 118.1, 106.0, 103.6, 56.4, 42.2, 32.8, 27.3, 26.7. Anal. calc. for C$_{17}$H$_{21}$NO$_2$ (%): C, 75.25; H, 7.80; N, 5.16. Found: C, 75.00; H, 7.98; N, 5.06. MS (CI) for C$_{17}$H$_{22}$NO$_2$ [M+H]$^+$: m/z 272.4.

6,7-Dimethoxy-1-phenylisoquinoline (5h):[51] [^1]H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.48 (d, J = 5.6 Hz, 1H), 7.71 (dd, J = 6.8, 1.6 Hz, 2H), 7.55-7.46 (m, 4H), 7.38 (s, 1H), 7.13 (s, 1H), 4.05 (s, 3H), 3.86 (s, 3H). [^13]C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 158.7, 153.1, 150.4, 141.8, 140.5, 134.2, 130.0, 128.8, 122.9, 119.1, 106.0, 105.4, 56.5, 56.3. Anal. calc. for C$_{17}$H$_{15}$NO$_2$ (%): C, 76.96; H, 5.70; N, 5.28. Found: C, 76.28; H, 5.72; N, 5.18. MS (CI) for C$_{17}$H$_{16}$NO$_2$ [M+H]$^+$: m/z 266.3.
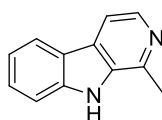
1-Methyl-9H-pyrido[3,4-b]indole (5i):[52] [^1]H NMR (d^6-Acetone, 400 MHz, 300 K) δ (ppm): 10.69 (bs, 1H), 8.27 (d, J = 5.2 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 5.2 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.52 (ddd, J = 8.2, 7.2, 1.0 Hz, 1H), 7.25 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 2.79 (s, 3H). [^13]C NMR (d^6-Acetone, 400 MHz, 300 K) δ (ppm): 143.5, 141.9, 139.4, 136.1, 129.1, 128.8, 123.1, 122.8, 120.7, 113.7, 113.1, 21.0. MS (CI) for C$_{12}$H$_{11}$N$_2$ [M+H]$^+$: m/z 183.3.
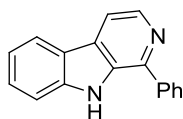

1-Phenyl-9H-pyrido[3,4-b]indole (5j):[52] [^1]H NMR (d^6-DMSO, 400 MHz, 300 K) δ (ppm): 11.60 (s, 1H), 8.47 (d, J = 5.2 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H), 8.13 (d, J =

5.2 Hz, 1H), 8.06-8.03 (m, 2H), 7.67-7.51 (m, 5H), 7.27 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H). ^{13}C NMR (d^6-DMSO, 400 MHz, 300 K) δ (ppm): 142.5, 141.5, 138.8, 133.4, 129.5, 129.1, 128.9, 128.7, 128.5, 122.0, 121.2, 119.9, 114.3, 112.8. MS (CI) for C$_{17}$H$_{13}$N$_2$ [M+H]$^+$: m/z 245.3.

5.4.5 Data for the indoles
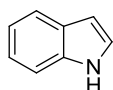
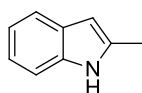***1H-indole (8a)***:[53] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.1(bs, 1H), 7.65 (dd, J = 7.9, 0.7 Hz, 1H), 7.40 (dd, J = 8.1, 0.8 Hz, 1H), 7.23-7.17 (m, 2H), 7.15-7.09 (m, 1H), 6.58-6.54 (m, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 136.2, 128.3, 124.6, 122.4, 121.2, 120.3, 111.5, 103.0. Anal. calc. for C$_8$H$_7$N (%): C, 82.02; H, 6.02; N, 11.96. Found: C, 81.82; H, 6.00; N, 11.91. MS (CI) for C$_8$H$_8$N [M+H]$^+$: m/z 118.0.
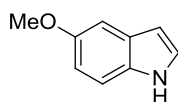
5-Methoxy-1H-indole (8b):[53] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.09 (bs, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.20 (t, J = 2.8 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 8.8, 2.5 Hz, 1H), 6.54-6.51 (m, 1H), 3.90 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 154.6, 131.4, 128.7, 125.3, 112.8, 112.2, 102.8, 102.7, 56.3. Anal. calc. for C$_9$H$_9$NO (%): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.35; H, 6.17; N, 9.57. MS (CI) for C$_9$H$_{10}$NO [M+H]$^+$: m/z 148.2.
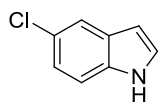
5-Chloro-1H-indole (8c):[54] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.15 (bs, 1H), 7.61 (d, J = 2.1 Hz, 1H), 7.30 (d, J = 8.7 Hz, 1H), 7.22 (t, J = 2.8 Hz, 1H), 7.14 (dd, J = 8.6, 2.0 Hz, 1H), 6.51-6.48 (m, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 134.5, 129.4, 125.9, 125.8, 122.7, 120.5, 112.4, 102.9. Anal. calc. for C$_8$H$_6$ClN (%): C, 63.38; H, 3.99; N, 9.24. Found: C, 63.55; H, 3.89; N, 9.24. MS (CI) for C$_8$H$_7$ClN [M+H]$^+$: m/z 151.9.

2-Methyl-1H-indole (8d):[55] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.61(bs, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.22-7.17 (m, 1H), 7.12-7.03 (m, 2H), 6.19 (s, 1H), 2.35 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 136.5, 135.6, 129.5, 121.4, 120.1, 110.7, 100.8, 14.1. Anal. calc. for C$_9$H$_9$N (%): C, 82.41; H, 6.92; N, 10.68. Found: C, 82.10; H, 6.73; N, 10.49. MS (CI) for C$_9$H$_{10}$N [M+H]$^+$: m/z 132.1.
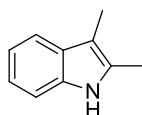
2,3-Dimethyl-1H-indole (8e):[56] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.62 (bs, 1H), 7.55 (d, J = 6.9 Hz, 1H), 7.28 (dd, J = 6.7, 1.8 Hz, 1H), 7.22-7.13 (m, 2H), 2.39 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 135.6, 131.1, 129.9, 121.3, 119.4, 118.4, 110.5, 107.5, 11.9, 8.9. Anal. calc. for C$_{10}$H$_{11}$N (%): C, 82.72; H, 7.64; N, 9.65. Found: C, 82.58; H, 7.63; N, 9.64. MS (CI) for C$_{10}$H$_{12}$N [M+H]$^+$: m/z 146.2.
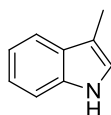
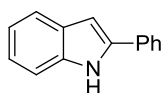***3-Methyl-1H-indole (8f)***:[57] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.72 (bs, 1H), 7.58 (d, J = 6.8 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 7.0 Hz, 1H), 7.12 (t, J = 6.8 Hz, 1H), 6.90 (s, 1H), 2.32 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 136.7, 128.7, 122.3, 122.1, 119.6, 119.3, 112.1, 111.4, 10.1. Anal. calc. for C$_9$H$_9$N (%): C, 82.41; H, 6.92; N, 10.68. Found: C, 82.45; H, 6.91; N, 10.64. MS (CI) for C$_9$H$_{10}$N [M+H]$^+$: m/z 132.1.

2-Phenyl-1H-indole (8g):[58] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.36 (bs, 1H), 7.68 (dd, J = 8.2, 1.0 Hz, 3H), 7.47 (t, J = 7.6 Hz, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.24 (td, J = 7.2, 1.2 Hz, 1H), 7.18 (td, J = 7.4, 0.8 Hz, 1H), 6.87 (d, J = 1.2 Hz, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 138.3, 137.2, 132.8, 129.7, 129.5, 128.2, 125.6, 122.8, 121.1, 120.7, 111.4, 100.4. Anal. calc. for

C$_{14}$H$_{11}$N (%): C, 87.01; H, 5.74; N, 7.25. Found: C, 86.90; H, 5.73; N, 7.21. MS (CI) for C$_{14}$H$_{12}$N [M+H]$^+$: m/z 194.3.

5.4.6 Data for the quinoxalines
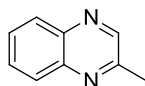
2-Methylquinoxaline (10a):[59] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.73 (s, 1H), 8.06 (dd, J = 8.1, 1.5 Hz, 1H), 8.00 (dd, J = 8.2, 1.4 Hz, 1H), 7.75-7.67 (m, 2H), 2.77 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 156.2, 148.5, 144.5, 143.4, 132.5, 131.6, 131.4, 131.1, 25.1. Anal. calc. for C$_9$H$_8$N$_2$ (%): C, 74.98; H, 5.59; N, 19.43. Found: C, 75.04; H, 5.58; N, 19.29. MS (CI) for C$_9$H$_9$N$_2$ [M+H]$^+$: m/z 145.0.
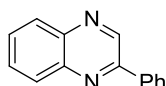
2-Phenylquinoxaline (10b):[60] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 9.35 (s, 1H), 8.22-8.13 (m, 4H), 7.83-7.75 (m, 2H), 7.61-7.52 (m, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 152.3, 143.8, 142.7, 142.0, 137.2, 130.8, 130.6, 130.05, 130.01, 129.6, 129.5, 128.0. Anal. calc. for C$_{14}$H$_{10}$N$_2$ (%): C, 81.53; H, 4.89; N, 13.58. Found: C, 80.88; H, 4.98; N, 13.24. MS (CI) for C$_{14}$H$_{11}$N$_2$ [M+H]$^+$: m/z 207.2.
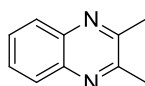
2,3-Dimethylquinoxaline (10c):[61] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.99 (dd, J = 6.3, 3.5 Hz, 2H), 7.67 (dd, J = 6.4, 3.5 Hz, 2H), 2.74 (s, 6H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 153.9, 141.5, 129.2, 128.7, 23.6. Anal. calc. for C$_{10}$H$_{10}$N$_2$ (%): C, 75.92; H, 6.37; N, 17.71. Found: C, 75.97; H, 6.25; N, 17.77. MS (CI) for C$_{10}$H$_{11}$N$_2$ [M+H]$^+$: m/z 159.1.
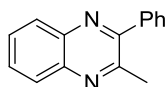
2-Methyl-3-phenylquinoxaline (10d):[61] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.15-8.12 (m, 1H), 8.09-8.06 (m, 1H), 7.78-7.71 (m, 2H), 7.69-7.66 (m, 2H),

7.57-7.48 (m, 3H), 2.80 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 155.3, 152.9, 141.6, 141.4, 139.4, 130.2, 129.7, 129.6, 129.4, 129.3, 129.0, 128.7, 24.8. Anal. calc. for C$_{15}$H$_{12}$N$_2$ (%): C, 81.79; H, 5.49; N, 12.72. Found: C, 81.42; H, 5.68; N, 12.62. MS (CI) for C$_{15}$H$_{13}$N$_2$ [M+H]$^+$: m/z 221.1.
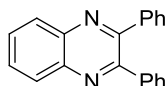
2,3-Diphenylquinoxaline (10e):[62] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.23-8.20 (m, 2H), 7.82-7.78 (m, 2H), 7.57-7.54 (m, 4H), 7.41-7.34 (m, 6H), 2.62 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 153.9, 141.6, 139.5, 130.4, 130.3, 129.6, 129.2, 128.7. Anal. calc. for C$_{20}$H$_{14}$N$_2$ (%): C, 85.08; H, 5.00; N, 9.92. Found: C, 84.68; H, 5.00; N, 9.83. MS (CI) for C$_{20}$H$_{15}$N$_2$ [M+H]$^+$: m/z 283.1.
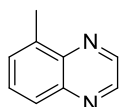
5-Methylquinoxaline (10f):[63] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.87 (dd, J = 6.7, 1.7 Hz, 2H), 7.98 (d, J = 8.4 Hz, 1H), 7.71-7.63 (m, 2H), 2.83 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 145.0, 144.1, 143.6, 142.7, 138.1, 130.5, 130.3, 127.8, 17.8. Anal. calc. for C$_9$H$_8$N$_2$ (%): C, 74.98; H, 5.59; N, 19.43. Found: C, 74.49; H, 5.68; N, 19.13. MS (CI) for C$_9$H$_9$N$_2$ [M+H]$^+$: m/z 145.2.
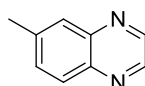
6-Methylquinoxaline (10g):[64] ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.81 (d, J = 8.3 Hz, 2H), 8.01 (d, J = 8.6 Hz, 1H), 7.89 (s, 1H), 7.63 (dd, J = 8.6, 1.6 Hz, 1H), 2.62 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 145.3, 144.5, 143.5, 141.9, 141.1, 132.8, 129.4, 128.7, 22.3. Anal. calc. for C$_9$H$_8$N$_2$ (%): C, 74.98; H, 5.59; N, 19.43. Found: C, 74.51; H, 5.72; N, 19.10. MS (CI) for C$_9$H$_9$N$_2$ [M+H]$^+$: m/z 145.2.

5.4.7 Synthesis of papaverine

N-(3,4-Dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)acetamide. The amide was prepared from the corresponding amine and acid according to the literature method

with some modification.[65] A mixture of 3,4-dimethoxyphenylacetic acid (2.5 mmol, 500 mg) and 3,4-dimethoxyphenethylamine (2.5 mmol, 477 mg) in a test vial was heated at 150 ^{o}C for 30 min under microwave irradiation. After cooling to ambient temperature, the solidified mixture was dissolved in DCM (100 mL) followed by washing sequentially with 10% KOH aq (10 ml), 5% HCl aq (10 mL) and brine (10 mL). The organic layer was dried over MgSO$_4$, filtered and concentrated under reduced pressure to give a pale-yellow solid (880 mg, 98% yield). ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 6.80 (d, J = 8.0 Hz, 1H), 6.72-6.68 (m, 3H), 6.62 (d, J = 1.6 Hz, 1H), 6.52 (dd, J = 8.0, 2.0 Hz, 1H), 5.44 (bs, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83 (s, 6H), 3.48 (s, 2H), 3.44 (q, J = 6.8 Hz, 2H), 2.68 (t, J = 7.0 Hz, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 171.6, 149.7, 149.4, 148.7, 148.0, 131.4, 127.6, 122.0, 121.0, 112.8, 112.1, 111.8, 111.5, 56.30, 56.26, 56.24, 56.22, 43.9, 41.1, 35.4. MS (CI) for C$_{20}$H$_{26}$NO$_5$ [M+H]$^+$: m/z 360.4.

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline *(3,4-dihydropapaverine).* The cyclic imine was prepared from the corresponding amide according to the literature.[66] To a solution of *N*-(3,4-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)acetamide (2.0 mmol, 701 mg) in toluene (40 mL), POCl$_3$ (4.0 mmol, 0.4 mL) was introduced dropwise at room temperature. The mixture was refluxed for 5 h and evaporated to remove toluene after cooling. The resulting residue was basified with an aqueous solution of Na$_2$CO$_3$ followed by extraction with DCM (5×30 mL). The combined organic extracts were evaporated to dryness before running a short column (silica gel, EtOAc/MeOH) to obtain the desired imine (slightly yellow solid, 614 mg, 90% yield). ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.00 (s, 1H), 6.87-6.84 (m, 2H), 6.79-6.77 (m, 1H), 6.66 (s, 1H), 3.98 (s, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H), 3.73 (t, J = 7.6 Hz, 2H), 2.65 (t,

J = 7.6 Hz, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 166.0, 151.1, 149.5, 148.1, 147.6, 132.2, 131.0, 122.0, 121.1, 112.1, 111.7, 110.87, 110.1, 56.4, 56.32, 56.27, 56.22, 47.6, 43.5, 26.2. MS (CI) for C$_{20}$H$_{24}$NO$_4$ [M+H]$^+$: m/z 342.4.

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline (Papaverine):[67] The reaction conditions were the same as for the general dehydrogenation except for using 1 mol% catalyst under 12 h. The product was obtained in 88% yield as a slightly yellow solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 8.37 (d, J = 5.6 Hz, 1H), 7.43 (d, J = 5.6 Hz, 1H), 7.35 (s, 1H), 7.05 (s, 1H), 6.83-6.81 (m, 2H), 6.77-6.75 (m, 1H), 4.53 (s, 2H), 4.00 (s, 3H), 3.91 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 300 K) δ (ppm): 158.2, 152.8, 150.2, 149.4, 147.9, 141.5, 133.9, 132.7, 123.4, 120.9, 119.1, 112.3, 111.6, 105.7, 104.6, 56.4, 56.27, 56.26, 56.21, 42.7. MS (CI) for C$_{20}$H$_{22}$NO$_4$ [M+H]$^+$: m/z 340.2.

5.4.8 Synthesis of harmine

7-Methoxy-1-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole

(Tetrahydroharmine). The tetrahydroharmine was prepared by Pictect-Spengler reaction according to a modified literature method.[68] 6-Methoxytryptamine (2.0 mmol, 381 mg) was added to an aqueous solution (25 mL) of H$_2$SO$_4$ (conc., 2.4 mmol, 240 mg). After introducing acetaldehyde (16.0 mmol, 0.9 mL), the mixture was heated for 20 min at 110 ^{o}C and then cooled to room temperature. The mixture was extracted with DCM (4×20 mL) after being basified with an aqueous solution of KOH. The combined organic extracts were evaporated to dryness before passing a short column (silica gel, DCM/MeOH) to afford the desired product (pale-yellow solid, 272 mg, 63% yield). ^{1}H NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 7.76 (bs, 1H), 7.35 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 1.2 Hz, 1H), 6.77 (dd, J = 8.4, 1.6 Hz, 1H),

4.15 (q, J = 6.6 Hz, 1H), 3.83 (s, 3H), 3.36 (dt, J = 12.8, 4.2 Hz, 1H), 3.04 (ddd, J = 13.1, 8.5, 4.9 Hz, 1H), 2.78-2.66 (m, 2H), 1.88 (bs, 1H), 1.44 (d, J = 6.4 Hz, 3H). ^{13}C NMR (CDCl$_3$, 400 MHz, 300 K) δ (ppm): 156.6, 136.8, 136.2, 122.4, 119.0, 109.2, 108.7, 95.4, 56.2, 48.6, 43.2, 23.1, 21.2. MS (CI) for C$_{13}$H$_{17}$N$_2$O [M+H]$^+$: m/z 217.2.

7-Methoxy-1-methyl-9H-pyrido[3,4-b]indole (Harmine):[69] The reaction conditions were the same as for the general dehydrogenation except for using 1 mol% catalyst under 30 h. The product was obtained in 91% yield as a slightly yellow solid. ^{1}H NMR (d$_6$-DMSO, 400 MHz, 300 K) δ (ppm): 11.40 (bs, 1H), 8.15 (d, J = 5.2 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 5.2 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 8.6, 2.2 Hz, 1H), 3.87 (s, 3H), 2.72 (s, 3H). ^{13}C NMR (d$_6$-DMSO, 400 MHz, 300 K) δ (ppm): 160.4, 142.3, 141.6, 138.1, 134.9, 127.6, 123.0, 115.2, 112.3, 109.4, 94.9, 55.7, 20.7. MS (CI) for C$_{13}$H$_{13}$N$_2$O [M+H]$^+$: m/z 213.3.

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Chapter 6

Regioselective Acceptorless Dehydrogenative Coupling of *N*-Heterocycles

6.1 Introduction

Circumventing the use of stoichiometric oxidants, acceptorless dehydrogenation reactions have recently become a rapidly growing area of research.[1] These reactions can be performed under mild conditions, with the only byproduct being H_2, which is a valuable feedstock itself and energy carrier.[2] Not only can such reactions be applied to the synthesis of unsaturated compounds, they also allow for easy bond formation, giving rise to novel coupling reactions, which require no prefunctionalisation of the coupling partners. Indeed, the last few years have witnessed the application of this acceptorless dehydrogenative coupling (ADC) strategy to the synthesis of many value-added compounds in a manner that is more straightforward and economic and greener than the conventional methods.[1,3] In the vast majority of the reported cases, an alcohol is first dehydrogenated, generating an electrophilic carbonyl species that can react with a common nucleophile (Scheme 6.1). Examples are seen in the ADC of alcohols with amines to form amides,[4] imines,[5] and *N*-heterocycles,[6] and of alcohols to form esters,[7] polyesters,[8] or lactones.[9]
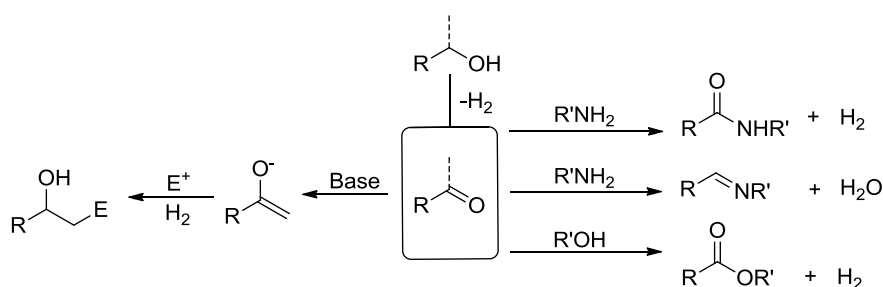
Scheme 6.1: General modes of ADC reactions reported in the literature.

Dehydrogenation of alcohols has also been harnessed to make C-C bonds. Thus, an alcohol is dehydrogenated to an electrophilic carbonyl, or a nucleophilic enolate in the presence of a base, which subsequently reacts with a carbon nucleophile or an

electrophile to generate an unsaturated bond that is reduced in situ by the H_2 borrowed from the initial dehydrogenation step (Scheme 6.1).[10,11]

Acceptorless dehydrogenation of *N*-heterocycles is rare in the literature, however, and ADC of *N*-heterocycles is even rarer. To the best of our knowledge, there appears to be only one report where an *N*-phenyl tetrahydroisoquinoline was alklylated with carbon nucleophiles at the 1-position,[12] whilst the simultaneous activation of an amine to generate an enamine to allow for C-C coupling remains unknown in the context of ADC.[13] Although a number of excellent examples have been demonstrated in the cross dehydrogenative coupling of *N*-heterocycles with various nucleophiles, these reactions generally necessitate the use of stoichiometric oxidants, such as ^{t}BuOOH, rather than releasing the hydrogen as H_2.[14]

It was successfully demonstrated in Chapter 5 that when the dehydrogenation of 2-methyl tetrahydroquinoline was carried out using cyclometalated iridium complex in TFE-d_3, the reaction led to extensive H-D exchange at the α and β positions. This suggested that the dehydrogenation leads to the generation of an imine, which isomerises to an enamine at these positions (Scheme 6.2). Therefore, it was envisioned that this nucleophilic intermediate might be intercepted by a carbon-based electrophile, thus affording C-C bond formation at α-methyl and consequently functionalisation of quinolines.[15,16] This chapter will cover our efforts in showing that the same cyclometalated iridium complexes can be exploited for this new strategy. Not only does the ADC enables the coupling of the sp^3 carbon with a range of electrophiles, but it can also be cascaded with Friedel-Crafts addition at sp^2 carbons and with reduction to generate novel saturated *N*-heterocycles (Scheme 6.2).
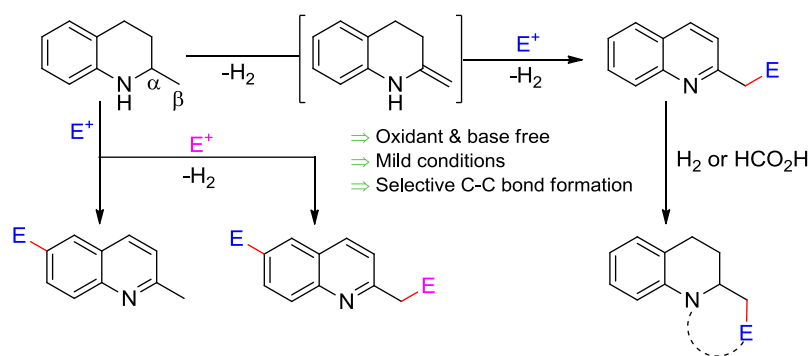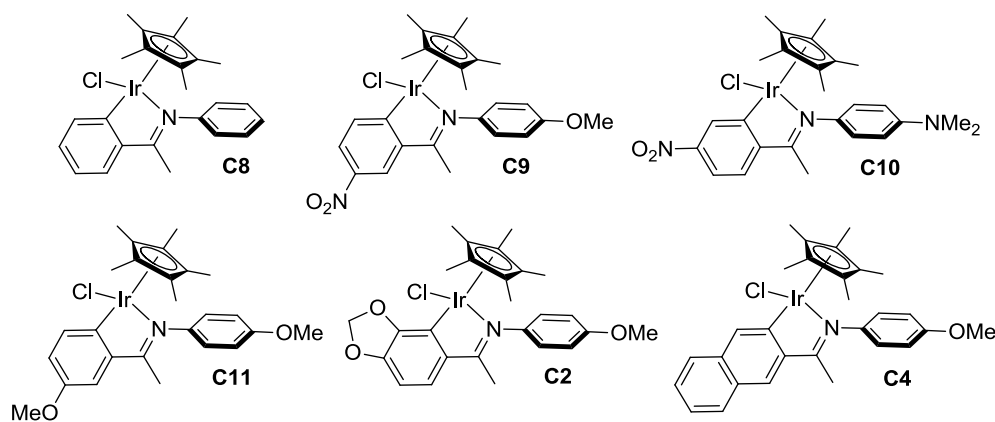
Scheme 6.2: ADC, Friedel-Crafts-ADC, and ADC-reduction reactions.

## 6.2 Results and discussion

6.2.1 Optimisation of reaction conditions

The study was initiated by testing various cyclometalated iridium complexes (Iridicycles **C**; Scheme 6.3) for the ADC of 2-methyl-1,2,3,4-tetrahydroquinoline (**1a**) with ethyl 3,3,3-trifluoropyruvate (TFP) as an electrophile.

Scheme 6.3: Cyclometalated iridium complexes.

As expected, in the absence of a catalyst, formation of **2a** was not detected in 2,2,2-trifluoroethanol (TFE) after 2 h stirring at 30 ℃, although **2a2** was obtained in a high yield (Table 6.1, entry 1). [Cp*IrCl$_2$]$_2$ without the ligand was also ineffective (Table 6.1, entry 2).

Table 6.1: Optimisation of reaction conditions
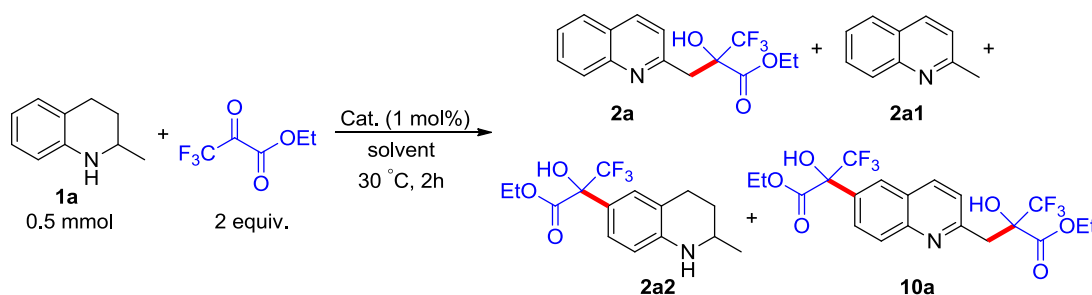
Entry[a]	Catalyst	Solvent	2a[b]	2a1[b]	2a2[b]	10a[b]
1	none	TFE	-	-	<95	-
2	[Cp*IrCl$_2$]$_2$	TFE	<2	<1	<90	-
3	**C8**	TFE	61	28	<3	<1
4	**C9**	TFE	38	16	5	<2
5	**C10**	TFE	46	14	4	<2
6	**C11**	TFE	64	31	<1	<2
7	**C2**	TFE	63	30	<1	<2
8	**C4**	TFE	58	20	<1	<2
9	**C11**	H$_2$O	8	6	-	-
10	**C11**	MeOH	-	18	10	4
11	**C11**	^{i}PrOH	-	-	11	-
12	**C11**	Toluene	-	-	62	-
13	**C11**	EtOAc	-	6	48	-
14[c]	**C11**	TFE	40	56	<1	<2
15[d]	**C11**	TFE	71	24	<1	<2
16[e]	**C11**	TFE	78	16	<1	4
17[f]	**C11**	TFE	77	12	<1	8
18[g,h]	**C11**	TFE	60	2	<1	24
19[e,i]	**C11**	TFE	78	16	<1	4
20[e,j]	**C11**	TFE	76	15	<1	4

[a] See experimental section for details. [b] Conversion (%) determined by ^{1}H-NMR spectroscopy. [c] 1.0 equivalent of 3,3,3-trifluoropyruvate (TFP) used. [d] 2.5 equiv. of TFP used. [e] 2.8 equiv. of TFP used. [f] 3.0 equiv. of TFP used. [g] 4.0 equiv. of TFP used. [h] Some other unidentified byproducts observed by ^{1}H-NMR spectroscopy. [i] Under N$_2$. [j] Under Air.

After screening a variety of iridicycles (Table 6.1, entries 3-8), electron-rich complexes were found to give a higher activity compared with electron-poor, with **C11** furnishing the desired product **2a** in 64% yield in just 2 h (Table 6.1, entries 6). ADC proceeds best in TFE, compared to other solvents that were screened (Table 6.1, entries 9-13). Variation of electrophile ratio revealed that the optimal yield was achieved when 2.8 equivalents of electrophile was used in the reaction (Table 6.1, entries 6 and 14-20). The excess amount of electrophile was necessary to inhibit the dehydrogenation of **1a** to **2a1**. Formation of H_2 was confirmed by GC-MS analysis. The hydrogenation of TFP by **C11** was not observed.

6.2.2 ADC of 2-methyl tetrahydroquinolines

Using the optimal conditions established, the ADC of various tetrahydroquinolines **1a-v** with TFP was explored. In each case, the corresponding products **2a-v** was obtained in good to excellent isolated yields, with the C-C coupling taking place almost exclusively at the β position (Table 6.2). These quaternary trifluoromethyl hydroxyl compounds are highly valuable in pharmaceuticals due to their biological activities.[16,17] A variety of functionalities were tolerated, demonstrating the utility of the protocol in practice. Thus, substrates bearing either electron-donating or -withdrawing groups all gave excellent yields regardless of their positions (Table 6.2, entries 2-5 and 11-12). Hydrogenation-labile aromatic halides, with the substituent at different positions, afforded the coupling products **2f-j** in more than 70% yield (Table 6.2, entries 6-10). Whilst ester and amide moieties are typically employed in *ortho*-directing C-H functionalisation, regioselective ADC took place when **1m-p** were coupled with TFP, furnishing excellent yields for the expected **2m-p** (Table 6.2, entries 13-16). Delightfully, thiophene- and pyridine-containing substrates underwent the ADC without poisoning the catalyst (Table 6.2, entries 18 and 19).
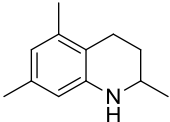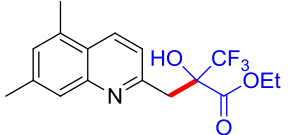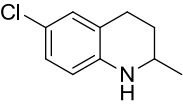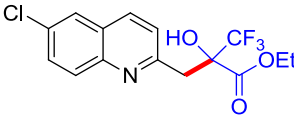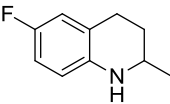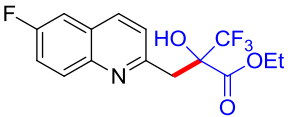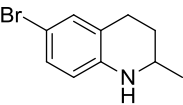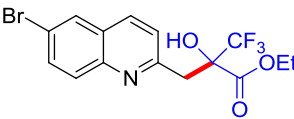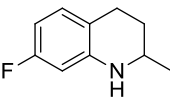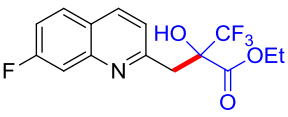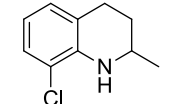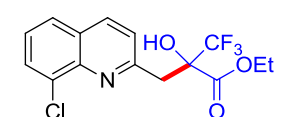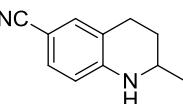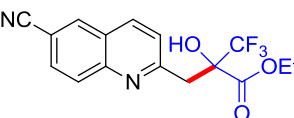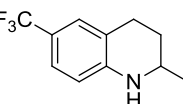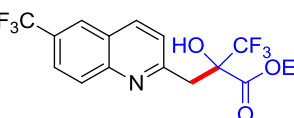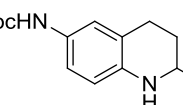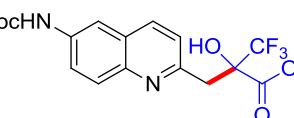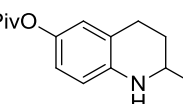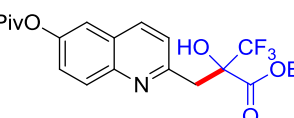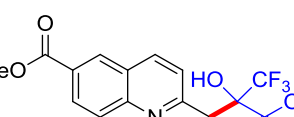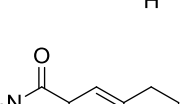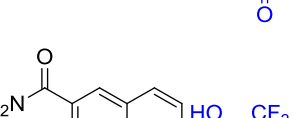
However, when the furan derivative **1t** was subjected to the ADC, competitive Friedel-Crafts alkylation was observed at the furan ring, leading to a highly functionalised product **2t** (Table 6.2, entry 20). It is known that furan can undergo electrophilic aromatic substitution at the 2-position in acidic media.[18] Further to our delight, substrates containing boronic acid pinacol ester and an allyl ether group were also well tolerated, furnishing corresponding products in good yields (Table 6.2, entries 21 and 22). Aryl boronic esters can readily undergo transition metal catalysed reaction and have in fact often been applied in cross coupling reactions as one of the coupling partners.[19] Likewise, allylic ether groups are prone to aromatic Claisen rearrangement and can give rise to allylic substitution.[20]

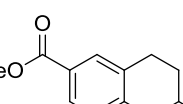**Table 6.2**: Regioselective dehydrogenative sp^3 C-H functionalisation of 2-methyl tetrahydroquinolines
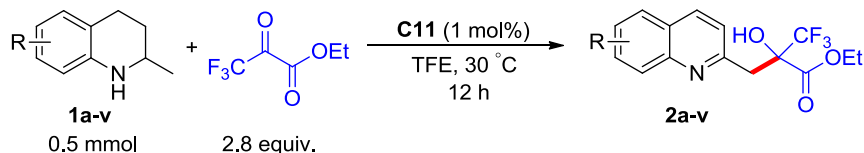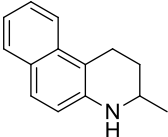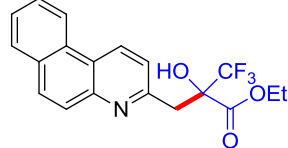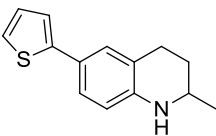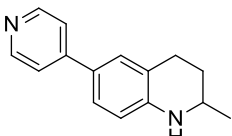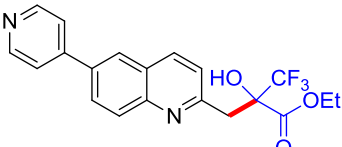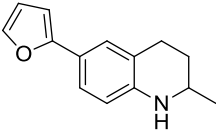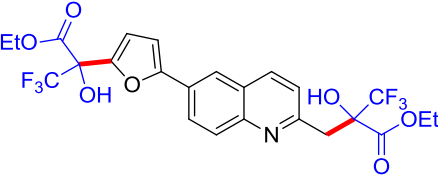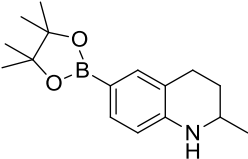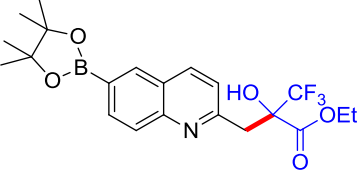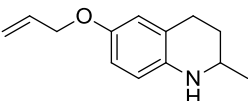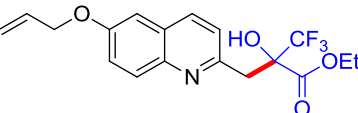
Entry[a]	Substrate	Product		Yield (%)[b]
1			**2a**	76
2			**2b**	78
3			**2c**	87
4			**2d**	89

5			**2e**	80
6			**2f**	86
7			**2g**	90
8[c]			**2h**	70
9			**2i**	79
10			**2j**	82
11			**2k**	89
12			**2l**	82
13[c]			**2m**	82
14			**2n**	86
15			**2o**	81
16			**2p**	88

17			**2q**	84
18			**2r**	85
19			**2s**	64
20			**2t**	90
21			**2u**	78
22			**2v**	55

[a] See experimental section for details. [b] Yield of isolated product. [c] Yield determined by ^{1}H-NMR spectroscopy.

Remarkably, the coordinating **3a-b** could be selectively mono- or di-alkylated, affording **4a-b** in a good yield (Scheme 6.4). The exclusive mono-functionalisation of **3a** suggests that the ADC proceeds via dehydrogenation rather than a direct C-H functionalisation at the 2-methyl position. Selective di-alkylation or mono-alkylation of 2-methyl phenanthrolines is challenging and is typically performed under harsh conditions.[21] Clearly, the current protocol offers an alternative route to these functionalised phenanthrolines.
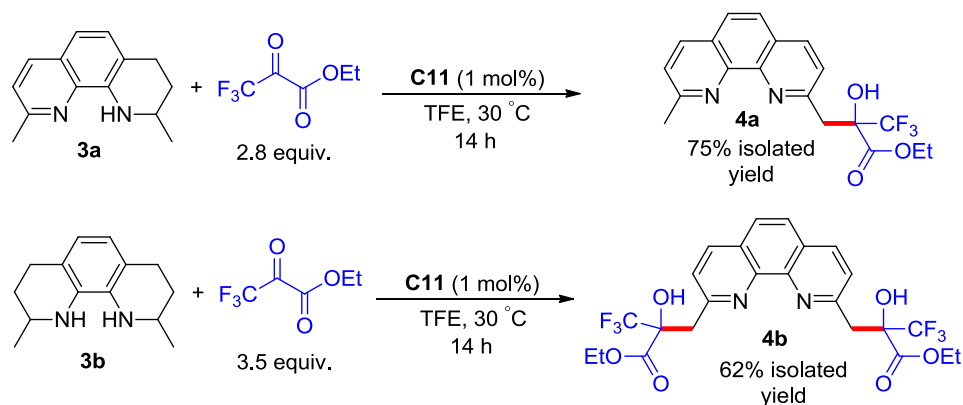
Scheme 6.4: Regioselective dehydrogenative sp^3 C-H functionalisation of tetrahydro- and octahydro-phenanthroline.

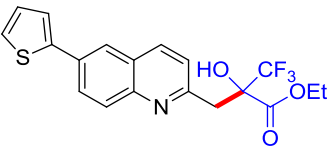### 6.2.3 ADC of 2-methyl tetrahydroquinolines with other electrophiles

To further demonstrate the utility of our protocol, ADC using different electrophiles was investigated. As can be seen from Table 6.3, the transformation occurred; however, the product yield varied with both the electrophiles and nucleophiles. In particular, low yields were obtained with 1,1,1-trifluoroacetone and pentafluoro-benzaldehyde (Table 6.3, entries 7 and 8), presumably as a result of their lower electrophilicity. Also, the electrophile 1,1,1-trifluoroacetone can interact with protic solvents, leading to addition products.[22] Disappointedly, ADC did not proceed when imine electrophiles were used under the present conditions (Table 6.3, entries 9 and 10).

Table 6.3: Dehydrogenative sp^3 C-H functionalisation of **1** with other electrophiles

Entry[a]	Substrate	Electrophile	Product		Yield (%)[b]
1	**1a**			**5a**	74
2	**1n**			**5b**	52
3	**1c**			**5c**	62
4	**1a**			**5d**	65
5	**1f**			**5e**	28
6	**1c**			**5f**	42
7[c]	**1a**			**5g**	22
8[c]	**1a**			**5h**	18
9[d]	**1a**		-	**-**	n.r.
10[d]	**1a**		-	**-**	n.r.

[a] See experimental section for details. [b] Yield of isolated product. [c] Yield determined by ^{1}H-NMR spectroscopy. [d] No reaction observed

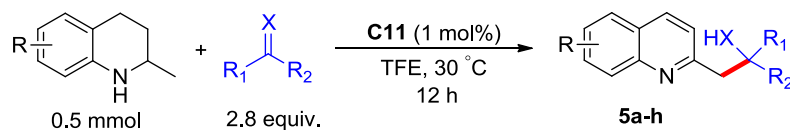## 6.2.4 One-pot synthesis of 6-alkylated quinolines

It is known that tetrahydroquinolines can undergo Friedel-Crafts reactions at the 6-position.[23,24] Indeed, 2-methyl-1,2,3,4-tetrahydroquinoline **1a** was alkylated with TFP at this position when they were mixed in TFE in the absence of **C11** (Table 6.1, entry 1). Following the Friedel-Crafts reaction, introduction of **C11** should trigger dehydrogenation, leading to one-pot synthesis of 6-alkylated quinolines. This would provide a simple way of generating these products which are traditionally synthesised by using stoichiometric organometallic species, such as Grignard, organozinc or organolithium reagents.[25] Satisfactorily, reacting **1a** and **6a-e** with TFP for 2 h followed by adding the catalyst **C11** afforded **7a-f** in excellent yields, regardless of the position of the substituents on the *N*-containing ring (Table 6.4, entries 1-6). Furthermore, functionalised indoles could also be obtained in good yields (Table 6.4, entries 7 and 8). Friedel-Crafts addition at the 5-position of indoles is challenging, as the 3-position is more reactive.[24] As maybe expected, Friedel-Crafts reaction did not proceed when 2-methyl quinoline, instead of **1a** or **6**, was used under the present conditions.

Table 6.4: Sequential Friedel-Crafts and dehydrogenative functionalisation of *N*-heterocycles

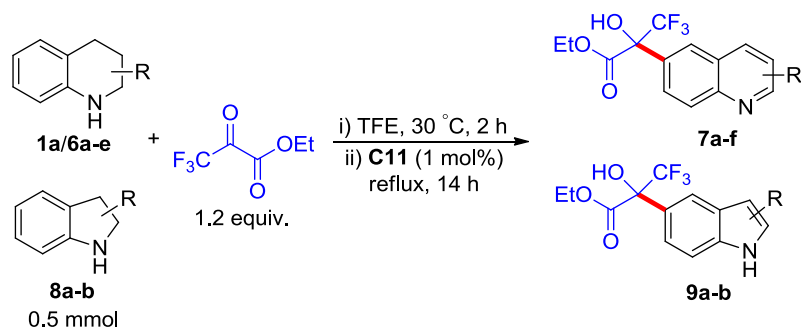| Entry[a]	Substrate	Product		Yield (%)[b]
1[c]			**7a**	72
2			**7b**	89
3			**7c**	92
4			**7d**	91
5			**7e**	86
6			**7f**	90
7[c]			**9a**	68
8			**9b**	89

[a] See experimental section for details. [b] Yield of isolated product. [c] Yield determined by ^{1}H-NMR spectroscopy.

6.2.5 One-pot sequential Friedel-Crafts-dehydrogenative sp^2 and sp^3 C-H functionalisation of 2-methyl-1,2,3,4-tetrahydroquinoline

More interestingly, double functionalisation of tetrahydroquinolines becomes possible when the Friedel-Crafts reaction is cascaded with the ADC. Scheme 6.5 presents the unprecedented, one pot sequential Friedel-Crafts addition and ADC reactions, allowing the functionalisation of both 6-position and α-methyl of **1a** to give **10a** in excellent yield. Two different electrophiles can also be introduced into the nucleophile in this one-pot strategy, as demonstrated by the synthesis of the highly functionalised **11a** and **12a**.
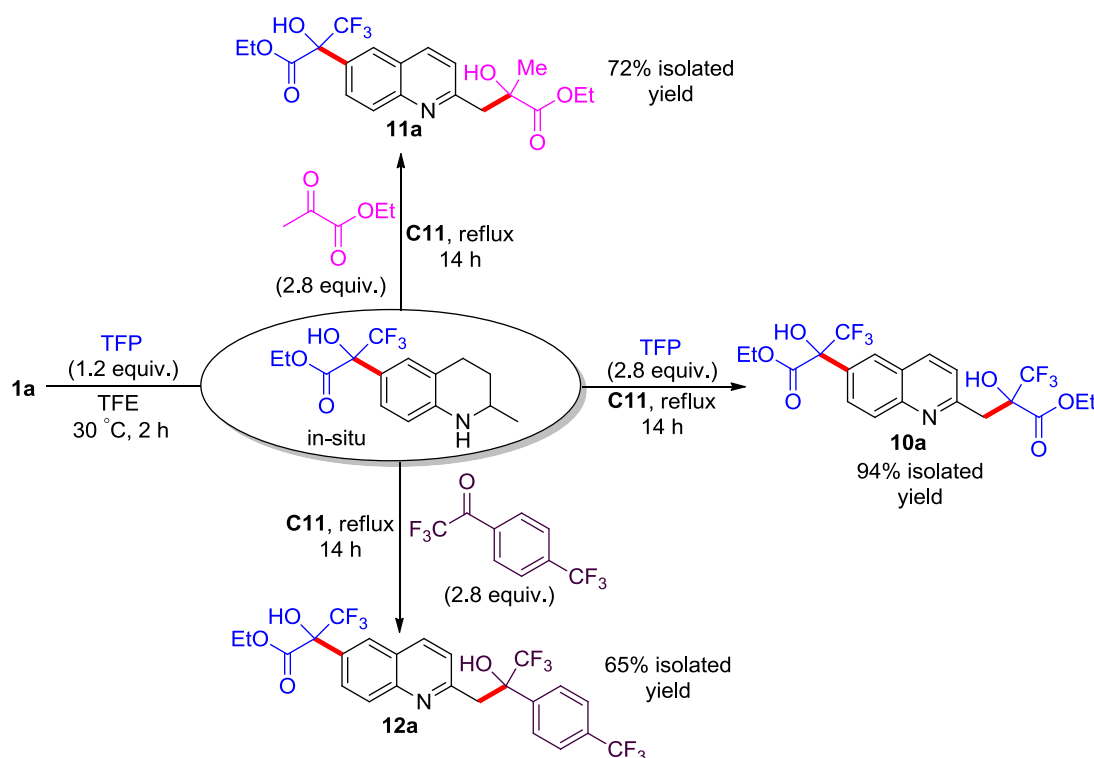
Scheme 6.5: One-pot sequential Friedel-Crafts-dehydrogenative C-H functionalisation of **1a**.

6.2.6 Saturated *N*-heterocycles by in situ reduction

Our group had previously reported that the Iridicycles are capable of catalysing both hydrogenation and transfer hydrogenation.[26] Thus, we postulated that saturated

functionalised *N*-heterocycles could also be obtained in a one pot fashion by combining ADC and reduction. Indeed, hydrogenating **2a** with H$_2$, in situ generated from **1a** by ADC, afforded **14a** in 74% yield at 30℃ (Scheme 6.6). Surprisingly, a novel compound **13a** was isolated in 71% yield when the reductant was switched from H$_2$ to HCO$_2$H. Most likely, the high reaction temperature together with the acidic reaction condition employed in the transfer hydrogenation promoted the formation of the lactam product. These reactions further demonstrate the versatility of **C11** in both dehydrogenation and hydrogenation reactions.
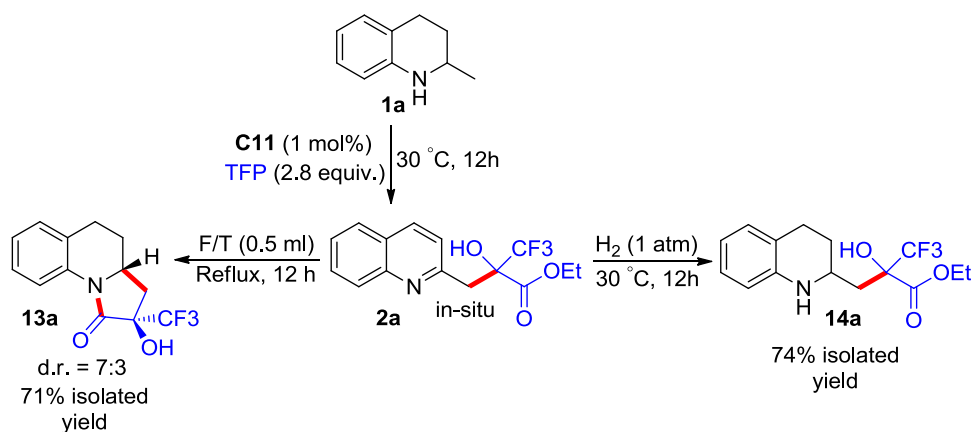
Scheme 6.6: Saturated *N*-heterocycles by in situ reduction of **2a** in a one-pot fashion using **C11**.

6.2.7 Mechanistic consideration

Based on the mechanism proposed in Chapter 5 for the dehydrogenation of 2-methyl tetrahydroquinoline, a plausible reaction pathway is proposed in Scheme 6.7. In the presence of **C11** in TFE (pK$_a$ 12.5), **1a** is in equilibrium with the imino intermediate **I**, which is probably protonated by or hydrogen-bonded with the medium. Isomerisation of **I** generates the active enamine nucleophile **III** that attacks an electrophile, thus resulting in **IV.** The intermediate **IV** can equilibrate with **V**, which probably hydrogenates **II,** resulting in the formation of **VI** and **1a**. Control

experiments shown in Scheme 6.8 also suggest that sp^3 C-H functionalisation of **1a** is favoured by the ADC pathway over alkylation catalysed by **C11**.
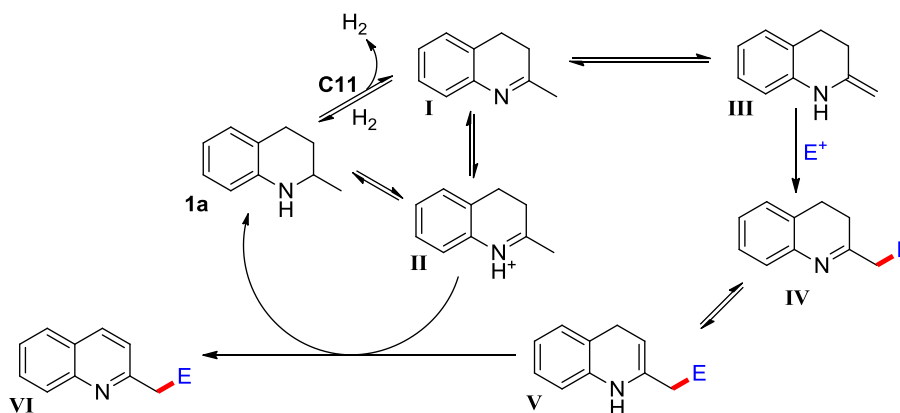
Scheme 6.7: A plausible reaction pathway.
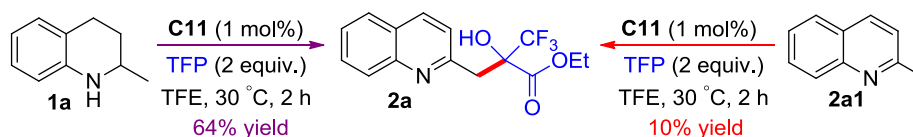
Scheme 6.8: Control experiments.

6.3 Conclusion

In conclusion, this chapter describes the development of a new protocol for the oxidant- and base-free functionalisation of *N*-heterocycles to afford novel quinoline, phenanthroline and indole derivatives under mild conditions. The core strategy is the ADC chemistry, which enables acceptor-less dehydrogenation of the *N*-heterocycles and site-selective C-C bond formation thereafter. The ADC catalyst also allows the dehydrogenated product to be saturated under either hydrogenation or transfer hydrogenation conditions, giving rise to structurally diverse products.

6.4 Experimental

6.4.1 General information

Unless otherwise specified, all reagents and solvents were purchased commercially and used as received. 2-Methyl quinolines were prepared according to the literature procedure reported by Yoshida,[27] Mahadevan[28] and Marsden.[29] Substrates **1b-v**, **3a** and **6b-e** were prepared by the reduction of the corresponding quinolines according to the method reported in Chapter 3. Substrate **3b** was prepared by the hydrogenation of neocuproine using 5 mol% Adam's catalyst in DCM (40 bar H_2, 35 °C, and 36 h). NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer unless otherwise specified. Elemental Analysis and Mass Spectrometry analysis were carried out at the Microanalysis Centre of University of Liverpool. IR spectra were recorded on a Bruker Alpha FT-IR spectrometer.

6.4.2 Representative procedure for the regioselective dehydrogenative sp^3 C-H functionalisation of 2-methyl tetrahydroquinoline (1a)

1a (73.6 mg, 0.5 mmol) was dissolved in TFE (1 mL) in a carousel tube. Meanwhile in separate vials **C11** (3.1 mg, 5×10^{-3} mmol) was dissolved in TFE (1 mL) and ethyl 3,3,3-trifluoropyruvate (238.1 mg, 0.19 mL, 1.4 mmol) was dissolved in TFE (1 mL), respectively. The solution of **C11** was then injected into the solution of **1a** in a carousel tube. The tube was shaken once and the solution of ethyl 3,3,3-trifluoropyruvate was then added slowly while shaking the tube gradually. The reaction mixture was then stirred at 30 °C under N_2 for 12 h (carousel reactor was pre-heated to 30 °C). The solvent was removed under vacuum and the resulting crude mixture was purified using flash chromatography to give the corresponding product **2a** as a white solid (119.1 mg, 76% yield).

Note: *it is important that the tube is shaken prior to the addition of ethyl 3,3,3-trifluoropyruvate in order to inhibit the side Friedel-Crafts alkylation.*

The same procedure was followed when other electrophiles were used. Products **2a**, **2b**, **2g**, **2h**, **2i**, **2j**, **2q** and **5a** are known compounds and their NMR spectra are consistent with the literature. All the other products are unknown.

6.4.3 Representative procedure for the sequential Friedel-Crafts and dehydrogenative functionalisation of 1a

1a (73.6 mg, 0.5 mmol) was dissolved in TFE (2 mL) in a carousel tube and ethyl 3,3,3-trifluoropyruvate (102.1 mg, 0.080 mL, 0.6 mmol) was added. The mixture was stirred at 30 °C under N_2 for 2 h. A freshly prepared solution of **C11** (3.1 mg, 5×10^{-3} mmol in 1 mL of TFE) was then added and the reaction was heated to reflux for 14 h. The reaction mixture was cooled to room temperature and the solvent was removed under vacuum. The resulting crude mixture was purified using flash chromatography to give the corresponding product **7f** as a light yellow solid (141.0 mg, 90% yield).

The same procedure was followed when indolines were used as substrates.

6.4.4 Representative procedure for one pot sequential Friedel-Crafts-dehydrogenative sp^2 and sp^3 C-H functionalisation of 1a to 11a

1a (73.6 mg, 0.5 mmol) was dissolved in TFE (1 mL) in a carousel tube and ethyl 3,3,3-trifluoropyruvate (102.1 mg, 0.080 ml, 0.6 mmol) was added. The mixture was stirred at 30 °C under N_2 for 2 h. A solution of **C11** (3.1 mg, 5×10^{-3} mmol in 1 mL of TFE) was then added followed by a solution of ethyl pyruvate (162.6 mg, 0.156 ml, 1.4 mmol in 1 mL of TFE). The reaction mixture was heated to reflux for 14 h. The

reaction mixture was cooled to room temperature and the solvent was removed under vacuum. The resulting crude mixture was then purified using flash chromatography to give the corresponding product **11a** as a yellow liquid (154.6 mg, 72% yield).
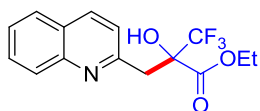
6.4.5 Data for 2a-v

Ethyl 3,3,3-trifluoro-2-hydroxy-2-(quinolin-2-ylmethyl)propanoate, 2a:[16] White solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.06 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.3 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 6.77 (bs, 1H), 4.16 (q, J = 6.9 Hz, 2H), 3.68 (d, J = 15.3 Hz, 1H), 3.45 (d, J = 15.4 Hz, 1H), 1.10 (t, J = 6.9 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -78.5. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 168.9, 156.4, 146.6, 137.3, 130.1, 128.5, 127.7, 127.0, 126.7, 122.2, 122.0 (q, J = 285.7 Hz), 78.3 (q, J = 29.0 Hz), 62.8, 38.4, 13.9. IR (neat, cm^{-1}): 3049, 2989, 2941, 1747, 1600, 1295, 1202, 1161, 1111, 1000, 750. Anal. Calc. for C$_{15}$H$_{14}$F$_3$NO$_3$ (%): C, 57.51; H, 4.50; N, 4.47. Found: C, 57.25; H, 4.45; N, 4.34. HRMS for C$_{15}$H$_{15}$F$_3$NO$_3$ [M+H]$^+$: m/z calc., 314.1004; found, 314.1011
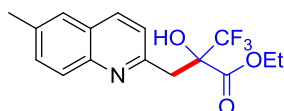
Ethyl 3,3,3-trifluoro-2-hydroxy-2-((6-methylquinolin-2-yl)methyl)propanoate, 2b:[16] Yellow liquid. ^{1}H NMR (CDCl$_3$, 400 MHz, 293 K) δ (ppm): 8.05 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.56-7.53 (m, 2H), 7.29-7.26 (m, 1H), 7.03 (bs, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.72 (d, J = 15.4 Hz, 1H), 3.50 (d, J = 15.4 Hz, 1H), 2.53 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 293 K) δ (ppm): -78.4. ^{13}C NMR (CDCl$_3$, 100 MHz, 293 K) δ (ppm): 168.8, 155.4, 145.2, 136.7, 132.4, 128.1, 127.0, 126.5, 124.8 (q, J = 286.0 Hz), 122.1, 78.1 (q, J = 29.2 Hz), 62.7, 38.3, 21.6, 13.9, 1 C is not observed. IR (neat, cm^{-1}): 3495, 2984, 2940, 1737, 1600, 1503, 1302, 1232, 1176, 1137, 1066, 828. Anal. Calc. for C$_{16}$H$_{16}$F$_3$NO$_3$ (%): C, 58.71; H, 4.93; N, 4.28. Found: C, 58.67; H, 4.92; N, 4.13. HRMS for C$_{16}$H$_{17}$F$_3$NO$_3$ [M+H]$^+$: m/z calc., 328.1155; found, 328.1165.
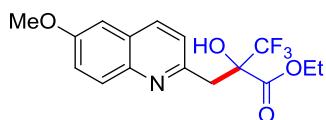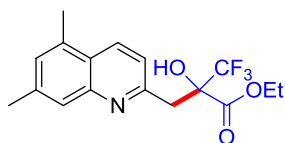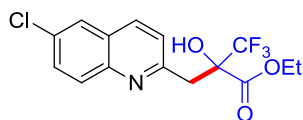
Ethyl 3,3,3-trifluoro-2-hydroxy-2-((6-methoxyquinolin-2-yl)methyl)propanoate,
2c: Light red solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 293 K) δ (ppm): 8.03 (d, J = 8.3 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H), 7.36 (dd, J = 9.2, 2.8 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.06 (d, J = 2.7 Hz, 1H), 6.91 (bs, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.93 (s, 3H), 3.70 (d, J = 15.2 Hz, 1H), 3.48 (d, J = 15.4 Hz, 1H), 1.18 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 293 K) δ (ppm): -78.4. ^{13}C NMR (CDCl$_3$, 100 MHz, 293 K) δ (ppm): 168.9, 157.9, 153.6, 142.7, 136.0, 129.9, 128.1, 122.9, 122.5, 122.0 (q, J = 286.4 Hz), 105.1, 78.1 (q, J = 29.1 Hz), 62.8, 55.6, 38.2, 13.9. IR (neat, cm^{-1}): 3443, 3382, 3001, 2949, 1737, 1625, 1602, 1504, 1297, 1224, 1173, 1132, 1015, 831, 705. Anal. Calc. for C$_{16}$H$_{16}$F$_3$NO$_4$ (%): C, 55.98; H, 4.70; N, 4.08. Found: C, 55.97; H, 4.69; N, 3.97. HRMS for C$_{16}$H$_{17}$F$_3$NO$_4$ [M+H]$^+$: m/z calc., 344.1104; found, 344.1117.
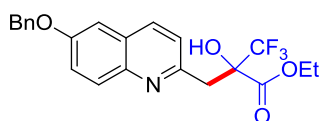
Ethyl 2-((6-(benzyloxy)quinolin-2-yl)methyl)-3,3,3-trifluoro-2-hydroxypropanoate,
2d: White solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 293 K) δ (ppm): 8.01 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 9.2 Hz, 1H), 7.49-7.34 (m, 6H), 7.26 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 2.7 Hz, 1H), 6.88 (bs, 1H), 5.18 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 3.70 (d, J = 15.3 Hz, 1H), 3.48 (d, J = 15.3 Hz, 1H), 1.18 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 293 K) δ (ppm): -78.4. ^{13}C NMR (CDCl$_3$, 100 MHz, 293 K) δ (ppm): 168.9, 157.0, 153.8, 142.8, 136.3, 136.1, 130.0, 128.7, 128.3, 128.0, 127.6, 123.2, 122.5, 122.0 (q, J = 286.0 Hz), 106.5, 78.1 (q, J = 29.2 Hz), 70.3, 62.8, 38.2, 13.9. IR (neat, cm^{-1}): 3151, 2970, 2899, 1743, 1626, 1602, 1506, 1454, 1385, 1207, 1187, 1147, 1066, 1017, 834, 752, 717. Anal. Calc. for C$_{22}$H$_{20}$F$_3$NO$_4$ (%): C, 63.00; H, 4.81; N, 3.34. Found: C, 62.52; H, 4.73; N, 3.49. HRMS for C$_{22}$H$_{21}$F$_3$NO$_4$ [M+H]$^+$: m/z calc., 420.1417; found, 420.1430.
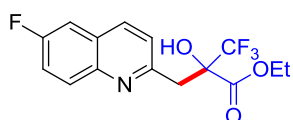
***Ethyl 2-((5,7-dimethylquinolin-2-yl)methyl)-3,3,3-trifluoro-2-hydroxypropanoate,
2e***: White solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 293 K) δ (ppm): 8.24 (d, J = 8.5 Hz,
1H), 7.57 (s, 1H), 7.27-7.20 (m, 2H), 4.22 (q, J = 7.0 Hz, 2H), 3.72 (d, J = 15.4 Hz,
1H), 3.50 (d, J = 15.4 Hz, 1H), 2.63 (s, 3H), 2.50 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H),
OH signal not observed. ^{19}F NMR (CDCl$_3$, 376 MHz, 293 K) δ (ppm): -78.4. ^{13}C
NMR (CDCl$_3$, 100 MHz, 293 K) δ (ppm): 168.9, 155.8, 147.2, 140.3, 134.2, 133.6,
129.5, 125.7, 124.5, 124.9 (q, J = 286.4 Hz), 120.9, 78.4 (q, J = 28.3 Hz), 62.7, 38.1,
21.8, 18.4, 13.9. IR (neat, cm^{-1}): 3110, 2996, 2911, 1757, 1595, 1450, 1264, 1186,
1138, 1052, 856, 703. Anal. Calc. for C$_{17}$H$_{18}$F$_3$NO$_3$ (%): C, 59.82; H, 5.32; N, 4.10.
Found: C, 59.73; H, 5.24; N, 3.97. HRMS for C$_{17}$H$_{19}$F$_3$NO$_3$ [M+H]$^+$: m/z calc.,
342.1312; found, 342.1308.

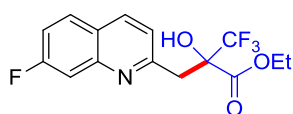***Ethyl 2-((6-chloroquinolin-2-yl)methyl)-3,3,3-trifluoro-2-hydroxypropanoate, 2f***:
Light yellow solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.04 (d, J = 8.5 Hz,
1H), 7.88 (d, J = 9.0 Hz, 1H), 7.78 (d, J = 2.3 Hz, 1H), 7.63 (dd, J = 9.0, 2.3 Hz, 1H),
7.35 (d, J = 8.5 Hz, 1H), 6.15 (bs, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.76 (d, J = 15.4 Hz,
1H), 3.51 (d, J = 15.4 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz,
298 K) δ (ppm): -78.5. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 168.8, 156.5,
145.1, 136.2, 132.4, 131.0, 130.1, 127.6, 126.3, 123.2, 121.9 (q, J = 286.6 Hz), 78.0
(q, J = 29.2 Hz), 63.0, 38.7, 13.9. IR (neat, cm^{-1}): 3465, 3010, 2950, 1733, 1601,
1494, 1309, 1220, 1190, 1145, 1075, 953, 880, 825, 696, 628, 420. Anal. Calc. for
C$_{15}$H$_{13}$ClF$_3$NO$_3$ (%): C, 51.81; H, 3.77; N, 4.03. Found: C, 51.75; H, 3.72; N, 3.82.
HRMS for C$_{15}$H$_{14}$ClF$_3$NO$_3$ [M+H]$^+$: m/z calc., 348.0609; found, 348.0614.

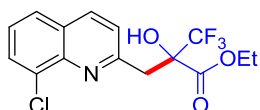***Ethyl 3,3,3-trifluoro-2-((6-fluoroquinolin-2-yl)methyl)-2-hydroxypropanoate,
2g***:[16] Light brown solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.09 (d, J =
8.4 Hz, 1H), 7.94 (dd, J = 9.1, 5.3 Hz, 1H), 7.50-7.42 (m, 2H), 7.35 (d, J = 8.4 Hz,

1H), 6.33 (bs, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.76 (d, J = 15.4 Hz, 1H), 3.52 (d, J = 15.4 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -112.9, -78.5. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 168.8, 159.2 (d, J = 248.5 Hz), 155.5 (d, J = 2.6 Hz), 143.8, 136.5 (d, J = 5.7 Hz), 130.9 (d, J = 8.9 Hz), 127.6 (d, J = 10.1 Hz), 123.0, 121.9 (q, J = 285.7 Hz), 120.2 (d, J = 26.1 Hz), 110.6 (d, J = 22.4 Hz), 78.1 (q, J = 29.3 Hz), 63.0, 38.6, 13.9. IR (neat, cm^{-1}): 3273, 3073, 2989, 1737, 1606, 1508, 1300, 1201, 1171, 1109, 1004, 828, 714, 469. Anal. Calc. for C$_{15}$H$_{13}$F$_4$NO$_3$ (%): C, 54.39; H, 3.96; N, 4.23. Found: C, 54.40; H, 3.89; N, 4.10. HRMS for C$_{15}$H$_{14}$F$_4$NO$_3$ [M+H]$^+$: m/z calc., 332.0904; found, 332.0907.
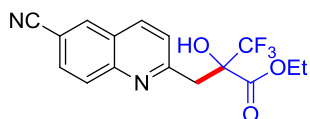

Ethyl 3,3,3-trifluoro-2-((7-fluoroquinolin-2-yl)methyl)-2-hydroxypropanoate, 2i:[30] Brown solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.13 (d, J = 8.4 Hz, 1H), 7.80 (dd, J = 8.9, 6.0 Hz, 1H), 7.56 (dd, J = 9.8, 1.8 Hz, 1H), 7.36-7.27 (m, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.76 (d, J = 15.3 Hz, 1H), 3.51 (d, J = 15.3 Hz, 1H), 1.22 (t, J = 7.1 Hz, 3H), OH signal not observed. ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -108.4, -78.5. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 168.8, 162.1 (d, J = 251.3 Hz), 157.4, 147.6 (d, J = 12.5 Hz), 137.1, 129.7 (d, J = 10.2 Hz), 124.0, 122.0 (q, J = 286.8 Hz), 121.6 (d, J = 2.5 Hz), 117.1 (d, J = 24.8 Hz), 112.2 (d, J = 20.3 Hz), 78.1 (q, J = 29.1 Hz), 63.0, 38.7, 13.9. IR (neat, cm^{-1}): 3076, 2971, 2934, 1740, 1626, 1600, 1509, 1247, 1166, 1111, 1006, 969, 868, 630, 437. Anal. Calc. for C$_{15}$H$_{13}$F$_4$NO$_3$ (%): C, 54.39; H, 3.96; N, 4.23. Found: C, 54.79; H, 3.98; N, 4.34. HRMS for C$_{15}$H$_{14}$F$_4$NO$_3$ [M+H]$^+$: m/z calc., 332.0904; found, 332.0906.

Ethyl 2-((6-chloroquinolin-2-yl)methyl)-3,3,3-trifluoro-2-hydroxypropanoate, 2j:[16] Yellow liquid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.18 (d, J = 8.3 Hz, 1H), 7.83 (dd, J = 7.5, 1.0 Hz, 1H), 7.74 (dd, J = 8.2, 0.9 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.10 (bs, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.84 (d, J = 15.8 Hz, 1H), 3.57 (d, J = 15.8 Hz, 1H), 1.19 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -78.5. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 168.6, 157.6, 142.8, 137.8, 132.8, 130.1, 128.2, 126.7, 126.6, 123.0, 121.9 (q, J =

285.6 Hz), 78.2 (q, J = 29.2 Hz), 62.9, 38.5, 13.8. IR (neat, cm^{-1}): 3470, 2985, 1738, 1600, 1501, 1250, 1176, 1139, 1068, 833, 760, 674, 460. Anal. Calc. for C$_{15}$H$_{13}$ClF$_3$NO$_3$ (%): C, 51.81; H, 3.77; N, 4.03. Found: C, 52.05; H, 3.77; N, 3.82. HRMS for C$_{15}$H$_{14}$ClF$_3$NO$_3$ [M+H]$^+$: m/z calc., 348.0609; found, 348.0613.

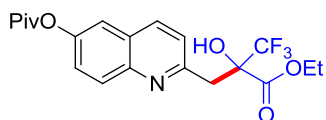***Ethyl 2-((6-cyanoquinolin-2-yl)methyl)-3,3,3-trifluoro-2-hydroxypropanoate, 2k***: Light brown solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 293 K) δ (ppm): 8.23-8.19 (m, 2H), 8.03 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 5.54 (bs, 1H), 4.32 (q, J = 7.0 Hz, 2H), 3.83 (d, J = 15.4 Hz, 1H), 3.57 (d, J = 15.4 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 293 K) δ (ppm): -78.5. ^{13}C NMR (CDCl$_3$, 100 MHz, 293 K) δ (ppm): 168.8, 159.4, 147.8, 137.2, 133.9, 130.7, 130.1, 126.3, 124.1, 121.9 (q, J = 286.3 Hz), 118.4, 110.4, 77.7 (q, J = 29.0 Hz), 63.3, 39.2, 13.9. IR (neat, cm^{-1}): 3467, 2964, 2228, 1728, 1602, 1416, 1312, 1224, 1184, 1141, 1077, 839, 703. Anal. Calc. for C$_{16}$H$_{13}$F$_3$N$_2$O$_3$ (%): C, 56.81; H, 3.87; N, 8.28. Found: C, 56.58; H, 3.89; N, 8.10. HRMS for C$_{16}$H$_{13}$F$_3$N$_2$O$_3$Na [M+Na]$^+$: m/z calc., 361.0776; found, 361.0791.
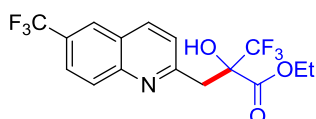
Ethyl 3,3,3-trifluoro-2-hydroxy-2-((6-(trifluoromethyl)quinolin-2-yl)methyl) propanoate, 2l: Light brown solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.24 (d, J = 8.4 Hz, 1H), 8.14 (s, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.82 (d, J = 15.4 Hz, 1H), 3.57 (d, J = 15.4 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H), OH signal not observed. ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -78.5, -62.4. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 168.8, 158.6, 147.7, 137.8, 129.8, 128.4 (q, J = 32.7 Hz), 126.0, 125.8 (q, J = 2.9 Hz), 125.6 (q, J = 4.4 Hz), 123.6, 122.5 (q, J = 272.3 Hz), 121.9 (q, J = 285.9 Hz), 77.9 (q, J = 29.3 Hz), 63.1, 39.0, 13.9. IR (neat, cm^{-1}): 3475, 2965, 1733, 1608, 1316, 1288, 1188, 1131, 1114, 1063, 840, 691, 623. Anal. Calc. for C$_{16}$H$_{13}$F$_6$NO$_3$ (%): C, 50.40; H, 3.44; N, 3.67. Found: C, 50.89; H, 3.52; N, 3.69. HRMS for C$_{16}$H$_{14}$F$_6$NO$_3$ [M+H]$^+$: m/z calc., 382.0872; found, 382.0880.

***Ethyl 3,3,3-trifluoro-2-hydroxy-2-((6-(pivaloyloxy)quinolin-2-yl)methyl) propanoate, 2n***: White solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 293 K) δ (ppm): 8.09 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 9.1 Hz, 1H), 7.52 (d, J = 1.4 Hz, 1H), 7.42 (d, J = 9.0, 1H), 7.33 (d, J = 8.4 Hz, 1H), 6.49 (bs, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.76 (d, J = 15.4 Hz, 1H), 3.52 (d, J = 15.4 Hz, 1H), 1.40 (s, 9H), 1.19 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 293 K) δ (ppm): -78.5. ^{13}C NMR (CDCl$_3$, 100 MHz, 293 K) δ (ppm): 177.1, 168.8, 156.0, 149.0, 144.6, 136.9, 129.9, 127.3, 125.4, 122.7, 121.9 (q, J = 285.9 Hz), 118.3, 78.2 (q, J = 29.1 Hz), 62.9, 39.2, 38.5, 27.1, 13.9. IR (neat, cm^{-1}): 3150, 2977, 1750, 1606, 1476, 1280, 1206, 1135, 1117, 1106, 1060, 909. Anal. Calc. for C$_{20}$H$_{22}$F$_3$NO$_5$ (%): C, 58.11; H, 5.36; N, 3.39. Found: C, 57.74; H, 5.22; N, 3.11. HRMS for C$_{20}$H$_{23}$F$_3$NO$_5$ [M+H]$^+$: m/z calc., 414.1523; found, 414.1540.
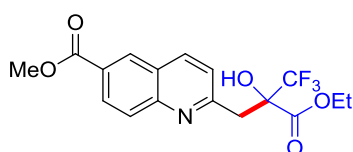
Methyl 2-(2-(ethoxycarbonyl)-3,3,3-trifluoro-2-hydroxypropyl)quinoline-6-carboxylate, 2o: White solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 293 K) δ (ppm): 8.57 (d, J = 1.7 Hz, 1H), 8.29 (dd, J = 8.9, 1.8 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.9 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 6.16 (bs, 1H), 4.28 (q, J = 7.1 Hz, 2H), 4.00 (s, 3H), 3.81 (d, J = 15.5 Hz, 1H), 3.55 (d, J = 15.5 Hz, 1H), 1.21 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 293 K) δ (ppm): -78.5. ^{13}C NMR (CDCl$_3$, 100 MHz, 293 K) δ (ppm): 168.8, 166.4, 158.6, 148.5, 138.3, 130.8, 129.6, 128.8, 128.2, 126.1, 123.1, 121.9 (q, J = 285.0 Hz), 78.0 (q, J = 29.2 Hz), 63.1, 52.5, 38.9, 13.9. IR (neat, cm^{-1}): 3466, 3408, 2960, 1734, 1715, 1696, 1625, 1601, 1439, 1281, 1233, 1179, 1136, 1095, 786, 695. Anal. Calc. for C$_{17}$H$_{16}$F$_3$NO$_5$ (%): C, 54.99; H, 4.34; N, 3.77. Found: C, 55.41; H, 4.77; N, 3.35. HRMS for C$_{17}$H$_{17}$F$_3$NO$_5$ [M+H]$^+$: m/z calc., 372.1059; found, 372.1058.
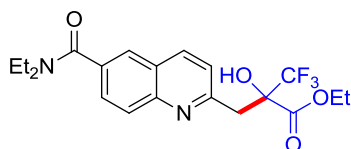
Ethyl 2-((6-(diethylcarbamoyl)quinolin-2-yl)methyl)-3,3,3-trifluoro-2-hydroxy propanoate, 2p: Yellow liquid. ^{1}H NMR (CDCl$_3$, 400 MHz, 293 K) δ (ppm): 8.16 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.84 (s, 1H), 7.69 (d, J = 8.4, 1H), 7.37 (d, J = 8.4 Hz, 1H), 4.27 (q, J = 7.0 Hz, 2H), 3.78 (d, J = 15.6 Hz, 1H), 3.60-3.52 (m, 3H), 3.29 (bs, 2H), 1.30-1.14 (m, 9H), OH signal not observed. ^{19}F NMR (CDCl$_3$, 376 MHz, 293 K) δ (ppm): -78.5. ^{13}C NMR (CDCl$_3$, 100 MHz, 293 K) δ (ppm): 170.3, 168.8, 157.2, 146.6, 137.5, 135.5, 128.9, 128.1, 126.5, 125.6, 123.0, 121.9 (q, J = 285.3 Hz), 78.1 (q, J = 29.2 Hz), 63.0, 43.4, 39.5, 38.7, 14.3, 13.9, 12.9. IR (neat, cm^{-1}): 3460, 2980, 2939, 1742, 1617, 1484, 1430, 1281, 1176, 1133, 1067, 1016, 841. Anal. Calc. for C$_{20}$H$_{23}$F$_3$N$_2$O$_4$ (%): C, 58.25; H, 5.62; N, 6.79. Found: C, 57.98; H, 5.46; N, 6.31. HRMS for C$_{20}$H$_{24}$F$_3$N$_2$O$_4$ [M+H]$^{+}$: m/z calc., 413.1688; found, 413.1697.
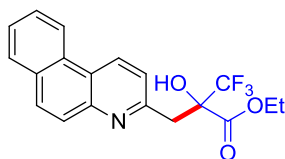
Ethyl 2-(benzo[f]quinolin-3-ylmethyl)-3,3,3-trifluoro-2-hydroxypropanoate, 2q:[16] White solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 293 K) δ (ppm): 8.92 (d, J = 8.4 Hz, 1H), 8.59 (d, J = 8.0 Hz, 1H), 7.99-7.93 (m, 2H), 7.83 (d, J = 9.0 Hz, 1H), 7.73-7.64 (m, 2H), 7.48 (d, J = 8.3 Hz, 1H), 6.87 (bs, 1H), 4.25 (q, J = 6.9 Hz, 2H), 3.79 (d, J = 15.2 Hz, 1H), 3.57 (d, J = 15.2 Hz, 1H), 1.18 (t, J = 6.9 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 293 K) δ (ppm): -78.4. ^{13}C NMR (CDCl$_3$, 100 MHz, 293 K) δ (ppm): 168.9, 155.5, 146.7, 132.0, 131.7, 131.6, 129.3, 128.8, 127.5, 127.4, 127.1, 124.2, 122.5, 122.3, 122.0 (q, J = 285.8 Hz), 78.4 (q, J = 29.1 Hz), 62.8, 38.2, 13.9. IR (neat, cm^{-1}): 3201, 2979, 2936, 1740, 1594, 1293, 1242, 1207, 1165, 1123, 1095, 1011, 829, 759. Anal. Calc. for C$_{19}$H$_{16}$F$_3$NO$_3$ (%): C, 62.81; H, 4.44; N, 3.86. Found: C, 62.42; H, 4.37; N, 3.81. HRMS for C$_{19}$H$_{17}$F$_3$NO$_3$ [M+H]$^{+}$: m/z calc., 364.1155; found, 364.1162.
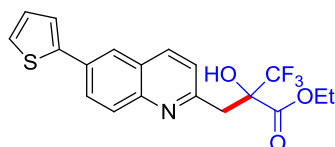
Ethyl 3,3,3-trifluoro-2-hydroxy-2-((6-(thiophen-2-yl)quinolin-2-yl)methyl) propanoate, 2r: Yellow solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 293 K) δ (ppm): 8.14 (d, J = 8.5 Hz, 1H), 7.99-7.93 (m, 3H), 7.45 (d, J = 3.6 Hz, 1H), 7.37 (d, J = 5.0 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.14 (dd, J = 5.0, 3.7 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.76 (d, J = 15.4 Hz, 1H), 3.52 (d, J = 15.4 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H), OH signal not observed. ^{19}F NMR (CDCl$_3$, 376 MHz, 293 K) δ (ppm): -78.4. ^{13}C NMR (CDCl$_3$, 100 MHz, 293 K) δ (ppm): 168.8, 156.2, 146.0, 143.2, 137.2, 132.8, 129.0, 128.6, 128.4, 127.3, 125.9, 124.2, 123.6, 122.9, 122.0 (q, J = 285.2 Hz), 78.2 (q, J = 29.1 Hz), 62.9, 38.5, 13.9. IR (neat, cm^{-1}): 3093, 2994, 1752, 1598, 1251, 1190, 1143, 1061, 830, 698. Anal. Calc. for C$_{19}$H$_{16}$F$_3$NO$_3$S (%): C, 57.72; H, 4.08; N, 3.54. Found: C, 57.52; H, 3.99; N, 3.36. HRMS for C$_{19}$H$_{17}$F$_3$NO$_3$S [M+H]$^+$: m/z calc., 396.0881; found, 396.0868.
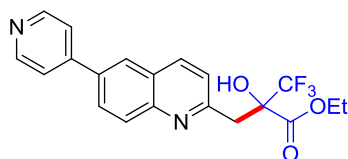
Ethyl 3,3,3-trifluoro-2-hydroxy-2-((6-(pyridin-4-yl)quinolin-2-yl)methyl) propanoate, 2s: Yellow solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 293 K) δ (ppm): 8.72-8.71 (m, 2H), 8.22 (d, J = 8.3 Hz, 1H), 8.06-8.04 (m, 2H), 7.97 (d, J = 8.8 Hz, 1H), 7.61-7.60 (m, 2H), 7.40 (d, J = 8.3 Hz, 1H), 6.49 (bs, 1H), 4.28 (q, J = 6.9 Hz, 2H), 3.80 (d, J = 15.3 Hz, 1H), 3.56 (d, J = 15.3 Hz, 1H), 1.23 (t, J = 6.9 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 293 K) δ (ppm): -78.4. ^{13}C NMR (CDCl$_3$, 100 MHz, 293 K) δ (ppm): 168.8, 157.2, 150.4, 147.3, 146.8, 137.5, 136.4, 129.5, 128.8, 127.1, 126.1, 123.1, 122.0 (q, J = 286.3 Hz), 121.8, 78.2 (q, J = 29.1 Hz), 63.0, 38.8, 14.0. IR (neat, cm^{-1}): 3050, 2985, 2811, 1741, 1598, 1491, 1307, 1254, 1189, 1149, 1060, 999, 820, 671, 612. Anal. Calc. for C$_{20}$H$_{17}$F$_3$N$_2$O$_3$ (%): C, 61.54; H, 4.39; N, 7.18. Found: C, 61.23; H, 4.35; N, 7.01. HRMS for C$_{20}$H$_{18}$F$_3$N$_2$O$_3$ [M+H]$^+$: m/z calc., 391.1270; found, 391.1277.
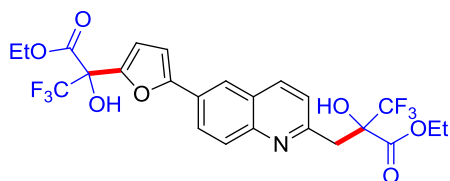
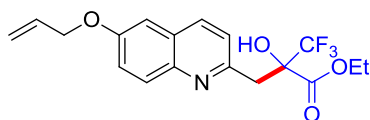***Ethyl 2-((6-(5-(3-ethoxy-1,1,1-trifluoro-2-hydroxy-3-oxopropan-2-yl)furan-2-yl)quinolin-2-yl)methyl)-3,3,3-trifluoro-2-hydroxypropanoate, 2t***: Yellow brownish crystalline solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.14 (d, J = 8.5 Hz, 1H), 8.05 (s, 1H), 7.94 (s, 2H), 7.33 (d, J = 8.5 Hz, 1H), 6.81 (d, J = 3.5 Hz, 1H), 6.74 (d, J = 3.5 Hz, 1H), 6.49 (bs, 1H), 4.52-4.44 (m, 3H), 4.26 (q, J = 7.1 Hz, 2H), 3.76 (d, J = 15.4 Hz, 1H), 3.52 (d, J = 15.4 Hz, 1H), 1.39 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -78.4, -76.1. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 168.8, 167.2, 156.5, 154.3, 146.3, 146.1, 137.3, 129.1, 128.1, 127.1, 126.4, 123.0, 122.1, 122.0 (q, J = 286.3 Hz), 120.9 (q, J = 286.3 Hz), 112.9, 107.2, 77.9 (q, J = 29.3 Hz), 75.1 (q, J = 31.9 Hz), 64.8, 62.9, 38.6, 13.9, 13.8. IR (neat, cm^{-1}): 3438, 2987, 1740, 1690, 1602, 1474, 1302, 1232, 1173, 1137, 1015, 838, 696. Anal. Calc. for C$_{24}$H$_{21}$F$_6$NO$_7$ (%): C, 52.47; H, 3.85; N, 2.55. Found: C, 52.48; H, 3.88; N, 2.46. HRMS for C$_{24}$H$_{22}$F$_6$NO$_7$ [M+H]$^+$: m/z calc., 550.1295; found, 550.1314.
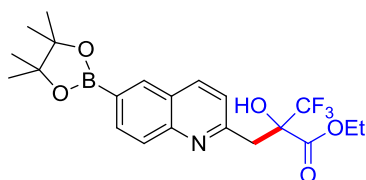
Ethyl 3,3,3-trifluoro-2-hydroxy-2-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-2-yl)methyl)propanoate, 2u: Brown solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.31 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 6.73 (bs, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.76 (d, J = 15.5 Hz, 1H), 3.52 (d, J = 15.5 Hz, 1H), 1.39 (s, 12H), 1.16 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -78.5. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 168.8, 157.4, 148.1, 137.9, 135.9, 134.9, 127.5, 126.4, 124.8 (J = 286.4 Hz), 122.2, 84.3, 78.2 (J = 29.0 Hz), 62.8, 38.6, 24.9, 13.9, one carbon signal is not observed. Anal. Calc. for C$_{21}$H$_{25}$BF$_3$NO$_5$ (%): C, 57.42; H, 5.74; N, 3.19. Found: C, 56.94; H, 5.62; N, 2.98. HRMS for C$_{21}$H$_{26}$^{10}BF$_3$NO$_5$ [M+H]$^+$: m/z calc., 439.1892; found, 439.1903 and C$_{21}$H$_{26}$^{11}BF$_3$NO$_5$ [M+H]$^+$: m/z calc., 440.1856; found, 440.1861.

Ethyl 2-((6-(allyloxy)quinolin-2-yl)methyl)-3,3,3-trifluoro-2-hydroxypropanoate,
2v: Light brown crystalline solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.01
(d, J = 8.4 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H), 7.39 (dd, J = 9.2, 2.7 Hz, 1H), 7.27 (d, J
= 5.1 Hz, 1H), 7.06 (d, J = 2.7 Hz, 1H), 6.78 (bs, 1H), 6.16-6.06 (m, 1H), 5.47 (dd, J
= 17.2, 1.3 Hz, 1H), 5.34 (dd, J = 10.5, 1.1 Hz, 1H), 4.65 (d, J = 5.2 Hz, 2H), 4.23 (q,
J = 7.1 Hz, 2H), 3.70 (d, J = 15.3 Hz, 1H), 3.48 (d, J = 15.3 Hz, 1H), 1.18 (t, J = 7.1
Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -78.4. ^{13}C NMR (CDCl$_3$, 100
MHz, 298 K) δ (ppm): 168.9, 156.8, 153.7, 142.7, 136.0, 132.7, 129.9, 128.0, 123.1,
122.5, 122.0 (q, J = 286.6 Hz), 118.1, 106.3, 78.1 (q, J = 28.9 Hz), 69.1, 62.7, 38.2,
13.9. IR (neat, cm^{-1}): 3481, 3090, 3029, 2984, 2937, 1733, 1601, 1501, 1303, 1213,
1171, 1115, 990, 833. Anal. Calc. for C$_{18}$H$_{18}$F$_3$NO$_4$ (%): C, 58.54; H, 4.91; N, 3.79.
Found: C, 58.44; H, 4.90; N, 3.68. HRMS for C$_{18}$H$_{19}$F$_3$NO$_4$ [M+H]$^+$: m/z calc.,
370.1261; found, 370.1268.

6.4.6 Data for 4a and 4b
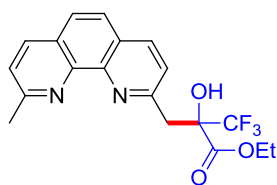
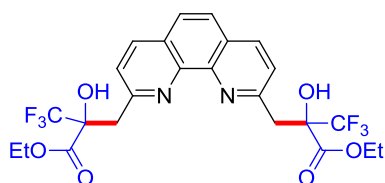***Ethyl 3,3,3-trifluoro-2-hydroxy-2-((9-methyl-1,10-phenanthrolin-2-yl)methyl)***
propanoate, 4a: Light brown solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 293 K) δ (ppm):
8.21 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.75-7.68 (m, 2H), 7.55-7.48 (m,
2H), 4.27-4.24 (m, 2H), 3.86 (d, J = 14.6 Hz, 1H), 3.66 (d, J = 14.6 Hz, 1H), 2.88 (s,
3H), 1.17 (t, J = 6.8 Hz, 3H), OH signal not observed. ^{19}F NMR (CDCl$_3$, 376 MHz,
293 K) δ (ppm): -78.0. ^{13}C NMR (CDCl$_3$, 100 MHz, 293 K) δ (ppm): 168.9, 159.5,
155.9, 144.6, 144.4, 137.2, 136.1, 127.4, 126.9, 126.6, 124.9, 123.9, 123.8, 122.2 (q,
J = 286.8 Hz), 78.8 (q, J = 29.0 Hz), 62.7, 38.4, 25.6, 13.9. IR (neat, cm^{-1}): 3065,
2984, 2907, 1746, 1589, 1499, 1274, 1200, 1169, 1134, 1050, 859, 715. Anal. Calc.
for C$_{19}$H$_{17}$F$_3$N$_2$O$_3$ (%): C, 60.32; H, 4.53; N, 7.40. Found: C, 60.19; H, 4.36; N, 7.24.
HRMS for C$_{19}$H$_{18}$F$_3$N$_2$O$_3$ [M+H]$^+$: m/z calc., 379.1270; found, 379.1278.

Diethyl 2,2'-((1,10-phenanthroline-2,9-diyl)bis(methylene))bis(3,3,3-trifluoro-2-hydroxypropanoate), 4b: White solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.22 (d, J = 8.2 Hz, 2H), 7.77 (s, 2H), 7.64-7.56 (m, 2H), 4.34-4.21 (m, 4H), 3.90-3.82 (m, 2H), 3.71-3.59 (m, 2H), 1.16 (q, J = 7.5 Hz, 6H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -78.0. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 156.1, 144.4, 136.9, 127.7, 126.2, 126.2 (q, J = 292.4 Hz), 124.6, 63.1, 29.7, 13.8, two carbon signals not observed due to low intensity. HRMS for C$_{24}$H$_{22}$F$_6$N$_2$O$_6$Na [M+Na]$^+$: m/z calc., 571.1280; found, 571.1276.
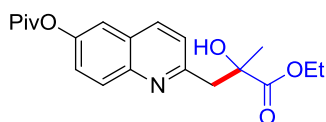
6.4.7 Data for 5a-f
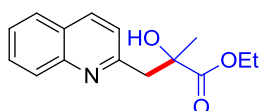
Ethyl 2-hydroxy-2-methyl-3-(quinolin-2-yl)propanoate, 5a:[30] Yellow liquid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.09 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.70-7.66 (m, 1H), 7.52-7.48 (m, 1H), 7.27 (d, J = 8.4 Hz, 1H), 6.23 (bs, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.56 (d, J = 15.4 Hz, 1H), 3.26 (d, J = 15.4 Hz, 1H), 1.58 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 176.0, 159.1, 146.9, 136.7, 129.7, 128.7, 127.5, 126.8, 126.3, 122.2, 75.1, 61.1, 46.4, 26.4, 14.1. IR (neat, cm^{-1}): 3377, 3060, 2980, 2936, 1724, 1600, 1505, 1290, 1189, 1105, 1017, 822, 752, 615. Anal. Calc. for C$_{15}$H$_{17}$NO$_3$ (%): C, 69.48; H, 6.61; N, 5.40. Found: C, 68.99; H, 6.66; N, 5.04. HRMS for C$_{15}$H$_{17}$NO$_3$Na [M+Na]$^+$: m/z calc., 282.1106; found, 282.1100.

Ethyl 2-hydroxy-2-methyl-3-(6-(pivaloyloxy)quinolin-2-yl)propanoate, 5b: Yellow liquid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.05 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 9.1 Hz, 1H), 7.50 (d, J = 2.4 Hz, 1H), 7.40 (dd, J = 9.1, 2.5 Hz, 1H), 7.29 (d, J = 8.5 Hz, 1H), 6.19 (bs, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.56 (d, J = 15.4 Hz, 1H), 3.27 (d, J = 15.4 Hz, 1H), 1.58 (s, 3H), 1.40 (s, 9H), 1.10 (t, J = 7.1 Hz, 3H). ^{13}C NMR

(CDCl$_3$, 100 MHz, 298 K) δ (ppm): 177.1, 175.9, 158.8, 148.8, 144.8, 136.4, 130.0, 127.1, 125.0, 122.7, 118.1, 75.1, 61.2, 46.3, 39.2, 27.1, 26.4, 14.1. IR (neat, cm^{-1}): 3480, 2978, 2937, 2874, 1782, 1742, 1605, 1208, 1100, 1025, 905. HRMS for C$_{20}$H$_{26}$NO$_5$ [M+H]$^+$: m/z calc., 360.1811; found, 360.1819.
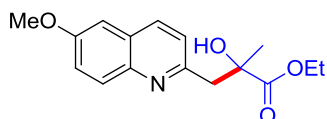
***Ethyl 2-hydroxy-3-(6-methoxyquinolin-2-yl)-2-methylpropanoate, 5c***: Yellow liquid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.98 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 9.2 Hz, 1H), 7.34 (dd, J = 9.2, 2.8 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 2.8 Hz, 1H), 6.23 (bs, 1H), 4.08 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 3.50 (d, J = 15.3 Hz, 1H), 3.22 (d, J = 15.3 Hz, 1H), 1.57 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 176.0, 157.6, 156.4, 143.0, 135.5, 130.1, 127.8, 122.5, 122.4, 105.1, 75.2, 61.1, 55.5, 46.1, 26.4, 14.1. IR (neat, cm^{-1}): 3350, 2979, 2937, 1726, 1600, 1500, 1379, 1229, 1107, 1024, 831. Anal. Calc. for C$_{16}$H$_{19}$NO$_4$ (%): C, 66.42; H, 6.62; N, 4.84. Found: C, 66.63; H, 6.70; N, 4.72. HRMS for C$_{16}$H$_{20}$NO$_4$ [M+H]$^+$: m/z calc., 290.1392; found, 290.1382.
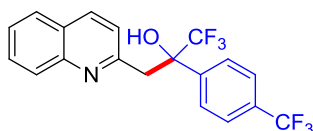
1,1,1-Trifluoro-3-(quinolin-2-yl)-2-(4-(trifluoromethyl)phenyl)propan-2-ol, 5d: White solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.73 (bs, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.3 Hz, 2H), 7.77 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 7.7 Hz, 1H), 7.57-7.51 (m, 3H), 7.24 (d, J = 8.4 Hz, 1H), 3.82 (d, J = 15.2 Hz, 1H), 3.67 (d, J = 15.2 Hz, 1H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -79.2, -62.7. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 157.2, 146.2, 142.6, 137.9, 130.4, 130.3 (q, J = 32.8 Hz), 128.3, 127.7, 127.3, 126.9, 126.8, 126.3 (q, J = 284.7 Hz), 125.1 (q, J = 3.7 Hz), 122.6 (q, J = 272.1 Hz), 122.3, 77.5 (q, J = 28.1 Hz), 39.9. IR (neat, cm^{-1}): 3086, 2920, 1600, 1509, 1431, 1327, 1156, 1119, 1103, 1069, 1040, 950, 839, 764, 623. Anal. Calc. for C$_{19}$H$_{13}$F$_6$NO (%): C, 59.23; H, 3.40; N, 3.64. Found: C, 59.34; H, 3.37; N, 3.47. HRMS for C$_{19}$H$_{14}$F$_6$NO [M+H]$^+$: m/z calc., 386.0980; found, 386.0968.
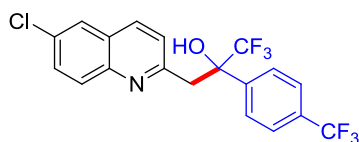
3-(6-Chloroquinolin-2-yl)-1,1,1-trifluoro-2-(4-(trifluoromethyl)phenyl)propan-2-ol, 5e: White solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.38 (s, 1H), 8.00 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 2.1 Hz, 1H), 7.63 (dd, J = 9.0, 2.1 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 3.80 (d, J = 15.4 Hz, 1H), 3.67 (d, J = 15.2 Hz, 1H), OH signal not observed. ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -79.2, -62.7. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 157.5, 144.6, 142.4, 136.9, 132.7, 131.4, 130.5 (q, J = 32.4 Hz), 129.8, 127.5, 127.2, 126.4, 125.2 (q, J = 3.9 Hz), 124.9 (q, J = 285.9 Hz), 123.9 (q, J = 271.3 Hz), 123.2, 77.3 (q, J = 28.5), 40.0. HRMS for C$_{19}$H$_{13}$ClF$_6$NO [M+H]$^+$: m/z calc., 420.0584; found, 420.0589.
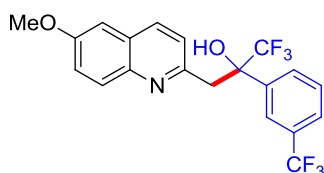
1,1,1-Trifluoro-3-(6-methoxyquinolin-2-yl)-2-(3-(trifluoromethyl)phenyl)propan-2-ol, 5f: White solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.74 (bs, 1H), 7.99 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 9.2 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.40 (t, J = 7.9 Hz, 1H), 7.32 (dd, J = 9.2, 2.7 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 2.7 Hz, 1H), 3.85 (s, 3H), 3.76 (d, J = 15.2 Hz, 1H), 3.61 (d, J = 15.4 Hz, 1H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -79.2, -62.6. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 158.0, 154.4, 142.4, 139.9, 136.5, 130.5 (q, J = 32.4 Hz), 130.2, 129.5, 128.7, 128.0, 125.1 (q, J = 3.9 Hz), 125.0 (q, J = 285.9 Hz), 124.1 (q, J = 272.0 Hz), 123.8 (q, J = 3.9 Hz), 123.3, 122.5, 105.0, 77.3 (q, J = 28.5 Hz), 55.5, 39.6. HRMS for C$_{20}$H$_{16}$F$_6$NO$_2$ [M+H]$^+$: m/z calc., 416.1080; found, 416.1077.

6.4.8 Data for 7b-f

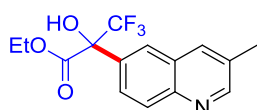***Ethyl 3,3,3-trifluoro-2-hydroxy-2-(3-methylquinolin-6-yl)propanoate, 7b***: Light yellow solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.78 (s, 1H), 8.24 (s, 1H),

8.10 (d, J = 9.1 Hz, 1H), 8.04 (d, J = 9.1 Hz, 1H), 7.97 (s, 1H), 5.06 (bs, 1H), 4.50-4.38 (m, 2H), 2.52 (s, 3H), 1.40-1.36 (m, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -76.0. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 168.7, 153.4, 146.3, 135.6, 131.3, 131.2, 129.0, 127.5, 126.6, 126.3, 121.7 (q, J = 286.5 Hz), 78.1 (q, J = 30.4 Hz), 64.5, 18.7, 13.9. IR (neat, cm^{-1}): 3070, 2984, 2745, 1742, 1505, 1446, 1247, 1155, 1145, 1116, 1029, 896, 731. Anal. Calc. for C$_{15}$H$_{14}$F$_3$NO$_3$ (%): C, 57.51; H, 4.50; N, 4.47. Found: C, 57.19; H, 4.41; N, 4.21. HRMS for C$_{15}$H$_{15}$F$_3$NO$_3$ [M+H]$^+$: m/z calc., 314.1004; found, 314.1009.
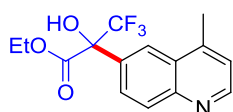
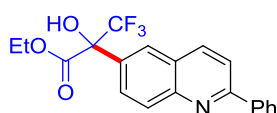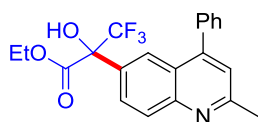***Ethyl 3,3,3-trifluoro-2-hydroxy-2-(4-methylquinolin-6-yl)propanoate, 7c***: White solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.78 (d, J = 4.4 Hz, 1H), 8.51 (d, J = 1.6 Hz, 1H), 8.17-8.10 (m, 2H), 7.27-7.26 (m, 1H), 5.39 (s, 1H), 4.51-4.37 (m, 2H), 2.73 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -76.0. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 168.7, 151.2, 147.9, 145.3, 130.9, 130.0, 127.7, 127.3, 123.0, 122.4, 121.7 (q, J = 285.7 Hz), 78.2 (q, J = 30.1 Hz), 64.4, 18.7, 13.9. IR (neat, cm^{-1}): 3060, 2983, 2686, 1747, 1593, 1240, 1162, 1128, 1017, 843, 684. Anal. Calc. for C$_{15}$H$_{14}$F$_3$NO$_3$ (%): C, 57.51; H, 4.50; N, 4.47. Found: C, 57.38; H, 4.44; N, 4.34. HRMS for C$_{15}$H$_{15}$F$_3$NO$_3$ [M+H]$^+$: m/z calc., 314.1004; found, 314.1009.

Ethyl 3,3,3-trifluoro-2-hydroxy-2-(2-phenylquinolin-6-yl)propanoate, 7d: Light yellow solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.30 (d, J = 1.7 Hz, 1H), 8.25-8.10 (m, 5H), 7.90 (d, J = 8.7 Hz, 1H), 7.54-7.44 (m, 3H), 4.59 (s, 1H), 4.53-4.38 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -76.0. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 168.7, 158.6, 148.4, 139.4, 137.5, 130.6, 129.9, 129.6, 129.2, 128.9, 127.7, 126.7, 126.5, 121.7 (q, J = 285.8 Hz), 119.6, 78.0 (q, J = 30.4 Hz), 64.7, 13.9. IR (neat, cm^{-1}): 3173, 2985, 1745, 1602, 1492, 1275, 1150, 1133, 1116, 982, 843, 763, 705. Anal. Calc. for C$_{20}$H$_{16}$F$_3$NO$_3$ (%): C, 64.00; H, 4.30; N, 3.73. Found: C, 63.87; H, 4.25; N, 3.65. HRMS for C$_{20}$H$_{17}$F$_3$NO$_3$ [M+H]$^+$: m/z calc., 376.1161; found, 376.1167.

Ethyl 3,3,3-trifluoro-2-hydroxy-2-(2-methyl-4-phenylquinolin-6-yl)propanoate, 7e:
Light yellow solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.36 (s, 1H), 8.13-8.08 (m, 2H), 7.57-7.48 (m, 5H), 7.28 (s, 1H), 4.42 (s, 1H), 4.42-4.26 (m, 2H), 2.79 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -76.2. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 168.8, 159.9, 149.1, 148.5, 137.7, 130.1, 129.5, 129.2, 128.7, 128.6, 127.4, 124.8, 124.4, 122.8, 121.5 (q, J = 286.4 Hz), 78.1 (q, J = 28.2 Hz), 64.6, 25.4, 13.7. IR (neat, cm^{-1}): 3223, 3060, 2973, 1739, 1591, 1491, 1288, 1165, 1128, 1109, 1010, 971, 847, 760, 703. Anal. Calc. for C$_{21}$H$_{18}$F$_3$NO$_3$ (%): C, 64.78; H, 4.66; N, 3.60. Found: C, 64.60; H, 4.48; N, 3.32. HRMS for C$_{21}$H$_{19}$F$_3$NO$_3$ [M+H]$^+$: m/z calc., 390.1312; found, 390.1324.
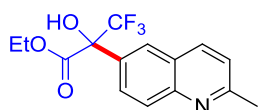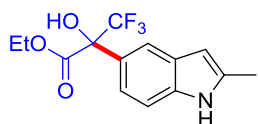

Ethyl 3,3,3-trifluoro-2-hydroxy-2-(2-methylquinolin-6-yl)propanoate, 7f: Light yellow solid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.26 (s, 1H), 8.10-8.03 (m, 3H), 7.33 (d, J = 8.5 Hz, 1H), 4.63 (s, 1H), 4.53-4.38 (m, 2H), 2.76 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -76.1. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 168.7, 160.5, 148.0, 136.8, 130.1, 128.8, 127.4, 126.7, 125.8, 122.7, 121.6 (q, J = 285.7 Hz), 77.9 (q, J = 30.4 Hz), 64.6, 25.4, 13.9. IR (neat, cm^{-1}): 3090, 2990, 2746, 1742, 1604, 1445, 1257, 1175, 1157, 1133, 1031, 842, 730, 692. Anal. Calc. for C$_{15}$H$_{14}$F$_3$NO$_3$ (%): C, 57.51; H, 4.50; N, 4.47. Found: C, 57.39; H, 4.44; N, 4.34. HRMS for C$_{15}$H$_{15}$F$_3$NO$_3$ [M+H]$^+$: m/z calc., 314.1004; found, 314.1014.

6.4.9 Data for 9b
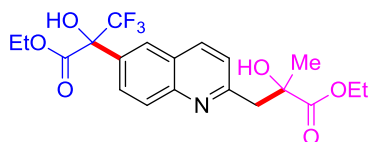

Ethyl 3,3,3-trifluoro-2-hydroxy-2-(2-methyl-1H-indol-5-yl)propanoate, 9b: Deep red viscous liquid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 7.92 (s, 2H), 7.50 (d, J = 8.6 Hz, 1H), 7.26 (d, J = 8.7 Hz, 1H), 6.24 (d, J = 0.8 Hz, 1H), 4.49-4.33 (m, 2H), 4.29 (s, 1H), 2.42 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz,

298 K) δ (ppm): -76.2. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 169.6, 136.4, 136.3, 128.9, 124.8 (q, J = 286.3 Hz), 124.1, 119.3, 118.3, 110.0, 101.0, 78.5 (q, J = 30.1 Hz), 64.1, 13.9, 13.7. IR (neat, cm^{-1}): 3460, 3401, 2986, 1732, 1625, 1500, 1477, 1234, 1160, 1131, 1100, 1013, 806, 733, 623. Anal. Calc. for C$_{14}$H$_{14}$F$_3$NO$_3$ + H$_2$O (%): C, 52.67; H, 5.05; N, 4.39. Found: C, 52.94; H, 4.78; N, 4.10. HRMS for C$_{14}$H$_{14}$F$_3$NO$_3$Na [M+Na]$^+$: m/z calc., 324.0823; found, 324.0824.

6.4.10 Data for 10a, 11a and 12a
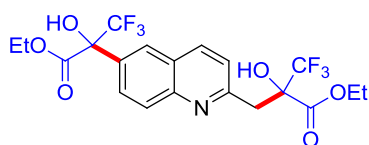
Ethyl 2-((6-(3-ethoxy-1,1,1-trifluoro-2-hydroxy-3-oxopropan-2-yl)quinolin-2-yl)methyl)-3,3,3-trifluoro-2-hydroxypropanoate, 10a: Yellow liquid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.30 (s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 9.0 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 6.38 (d, J = 2.9 Hz, 1H), 4.54-4.38 (m, 2H), 4.52 (s, 1H), 4.30-4.24 (m, 2H), 3.78 (d, J = 15.4 Hz, 1H), 3.53 (d, J = 15.4 Hz, 1H), 1.40 (t, J = 7.1 Hz, 3H), 1.25-1.20 (m, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -78.5, -76.1. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 168.8, 168.5, 157.7, 146.8, 137.9, 131.1, 128.7 (d, J = 2.4 Hz), 128.1, 126.9, 126.3, 124.8 (q, J = 286.1 Hz), 122.9, 121.5 (q, J = 286.1 Hz), 78.1 (q, J = 29.7 Hz), 77.5 (q, J = 30.5 Hz), 64.8, 63.0, 38.7, 13.9 (x2). IR (neat, cm^{-1}): 3469, 2987, 1737, 1601, 1500, 1370, 1233, 1178, 1153, 1013, 831, 703, 674. Anal. Calc. for C$_{20}$H$_{19}$F$_6$NO$_6$ (%): C, 49.70; H, 3.96; N, 2.90. Found: C, 49.25; H, 3.87; N, 2.73. HRMS for C$_{20}$H$_{19}$F$_6$NO$_6$Na [M+Na]$^+$: m/z calc., 506.1014; found, 506.1011.

Ethyl 2-(2-(3-ethoxy-2-hydroxy-2-methyl-3-oxopropyl)quinolin-6-yl)-3,3,3-trifluoro-2-hydroxypropanoate, 11a: Yellow liquid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.27 (d, J = 1.8 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 9.1 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 6.01 (d, J = 5.1 Hz, 1H), 4.57 (bs, 1H), 4.54-4.38 (m, 2H), 4.13-4.07 (m, 2H), 3.58 (dd, J = 15.5, 2.6 Hz, 1H), 3.28 (d, J = 15.4 Hz, 1H), 1.58 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H), 1.15-1.10 (m, 3H).

^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -76.1. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 175.9 (d, J = 2.2 Hz), 168.6, 160.5, 147.0, 137.4, 130.7, 128.8, 127.8, 126.8, 126.2, 122.9, 121.5 (q, J = 286.8 Hz), 77.9 (q, J = 30.3 Hz), 75.0, 64.7, 61.2 (d, J = 2.6 Hz), 46.5, 26.4, 14.1, 13.9. IR (neat, cm^{-1}): 3339, 2984, 2938, 1740, 1601, 1371, 1234, 1182, 1155, 1107, 1017, 978, 832. Anal. Calc. for C$_{20}$H$_{22}$F$_3$NO$_6$ (%): C, 55.94; H, 5.16; N, 3.26. Found: C, 55.52; H, 5.12; N, 3.05. HRMS for C$_{20}$H$_{23}$F$_3$NO$_6$ [M+H]$^+$: m/z calc., 430.1477; found, 430.1475.
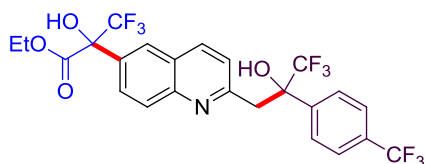
Ethyl 3,3,3-trifluoro-2-hydroxy-2-(2-(3,3,3-trifluoro-2-hydroxy-2-(4-(trifluoromethyl)phenyl)propyl)quinolin-6-yl)propanoate, 12a: Yellow liquid. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 8.50 (bs, 1H), 8.27 (s, 1H), 8.13 (d, J = 8.8 Hz, 2H), 7.99 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 7.8 Hz, 2H), 7.56 (dd, J = 8.2, 3.7 Hz, 2H), 7.28 (d, J = 8.4 Hz, 1H), 4.63 (bs, 1H), 4.53-4.34 (m, 2H), 3.83 (d, J = 15.2 Hz, 1H), 3.70 (d, J = 15.2 Hz, 1H), 1.37 (t, J = 7.1 Hz, 3H). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -79.3 (d, J = 25.1 Hz), -76.1, -62.8. ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): 168.4, 158.7, 146.3, 142.4, 138.6 (d, J = 2.8 Hz) 131.4, 130.5 (dq, J = 2.3, 32.4 Hz), 128.5 (d, J = 1.1 Hz) 128.4 (d, J = 1.6 Hz), 127.3 (d, J = 4.4 Hz), 127.0, 126.2, 125.2 (q, J = 2.3), 123.9 (q, J = 272.0 Hz), 123.0 (q, J = 285.9 Hz), 123.0 (m), 122.9, 77.7 (q, J = 30.8 Hz), 77.4 (q, J = 28.5 Hz), 64.8 (t, J = 13.9 Hz), 40.0 (t, J = 14.6 Hz), 13.8 (q, 7.7 Hz). HRMS for C$_{24}$H$_{19}$F$_9$NO$_4$ [M+H]$^+$: m/z calc., 556.1165; found, 556.1167.

6.4.11 Data for 13a and 14a

major   minor
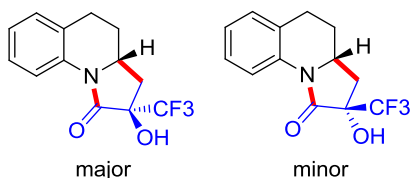
(2RS,3aRS)-2-Hydroxy-2-(trifluoromethyl)-3,3a,4,5-tetrahydropyrrolo[1,2-a]quinolin-1(2H)-one, 14a-major product and (2SR,3aRS)-2-hydroxy-2-(trifluoromethyl)-3,3a,4,5-tetrahydropyrrolo[1,2-a]quinolin-1(2H)-one, 14a-minor product, **13a**: Light off white solid. Isolated as a 7:3 mixture of isomers. ^{1}H NMR

(DMSO-d_6 with a drop of TFA, 400 MHz, 298 K) δ (ppm): 8.58 (d, J = 9.8 Hz, 1H-major), 8.50 (d, J = 8.6 Hz, 1H-minor), 7.24-7.17 (m, 2H-major and 2H-minor), 7.11-7.03 (m, 1H-major and 1H minor), 4.04 (dddd, J = 14.4, 11.3, 6.1, 2.5 Hz, 1H-major), 3.87-3.78 (m, 1H-minor), 3.00-2.88 (m, 1H-major and 1H-minor), 2.88-2.78 (m, 1H-major and 2H-minor), 2.41 (dd, J = 13.7, 6.0 Hz, 1H-major), 2.25-2.16 (m, 1H-major and 1H- minor), 2.01 (dd, J = 13.7, 8.8 Hz, 1H-major), 1.93 (dd, J = 13.8, 8.7 Hz, 1H-minor), 1.67-1.51 (m, 1H-major and 1H-minor). Signal at 7.41 (s, 1H-major and 1H-minor) exchange with TFA. ^{19}F NMR (DMSO-d_6 with a drop of TFA, 376 MHz, 298 K) δ (ppm): -78.9 (minor), -78.5 (major). ^{13}C NMR (DMSO-d_6, 100 MHz, 298 K) δ (ppm): Major: 166.8, 136.0, 130.0, 127.2, 127.0, 124.7 (q, J = 283.6 Hz), 124.7, 118.6, 76.6 (q, J = 30.1 Hz), 53.8, 35.2, 28.3, 27.2; Minor: 166.8, 135.8, 130.0, 127.4, 126.9, 125.2 (q, J = 288.2 Hz), 124.9, 119.1, 76.2 (q, J = 30.1 Hz), 53.3, 35.4, 29.2, 27.0. HRMS for $C_{13}H_{13}F_3NO_2$ [M+H]$^+$: m/z calc., 272.0893; found, 272.0890. Relative stereochemistry were assigned based on ^{1}H-^{19}F HOESY, strong correlation was observed between CF_3 and CH in the minor isomers but was absence in the major isomer.

major   minor
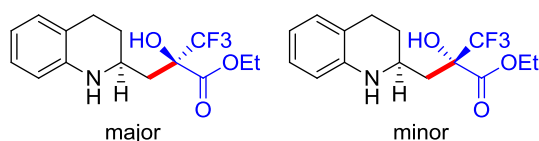
(RR)-Ethyl 3,3,3-trifluoro-2-hydroxy-2-(((SR)-1,2,3,4-tetrahydroquinolin-2-yl)methyl)propanoate and (RS)-ethyl 3,3,3-trifluoro-2-hydroxy-2-(((RS)-1,2,3,4-tetrahydroquinolin-2-yl)methyl)propanoate, 14a: Colourless oil. Isolated as a 2:1 mixture of isomers. ^{1}H NMR (CDCl$_3$, 400 MHz, 298 K) δ (ppm): 6.98-6.89 (m, 2H-major and 2H-minor) 6.64-6.57 (m, 1H-major and 1H-minor), 6.46 (d, J = 8.0 Hz, 1H-minor) 6.38 (d, J = 7.8 Hz, 1H-major), 4.66 (bs, 1H-minor), 4.39 (q, J = 7.2 Hz, 1H-major), 4.21-4.13 (m, 2H-major and 1H-minor), 3.95-3.76 (m, 2H-major and 2H-minor), 3.26 (t, J = 7.0 Hz, 1H-minor), 2.87-2.67 (m, 2H-major and 2H-minor), 2.37-2.11 (m, 1H-major and 2H-minor), 1.99 (dd, J = 14.0, 3.7 Hz, 1H-major), 1.91-1.67 (m, 2H-major and 2H-minor), 1.34 (t, J = 7.1 Hz, 3H-minor), 0.99 (t, J = 7.2 Hz, 3H-major). ^{19}F NMR (CDCl$_3$, 376 MHz, 298 K) δ (ppm): -79.3 (minor), -78.5 (major). ^{13}C NMR (CDCl$_3$, 100 MHz, 298 K) δ (ppm): Mixture of major and minor product: 48.5, 44.9 (d, J = 13 Hz), 37.0 (t, J = 6.9 Hz), 36.5 (t, J = 7.7 Hz), 29.5, 23.6 (t, J = 8.5 Hz). Major: 170.8, 142.6, 129.3 (m), 126.9 (m), 123.6 (q, J = 286.7 Hz), 120.5,

117.4 (m), 114.5 (d, J = 6.9 Hz), 76.4 (q, J = 28.5 Hz), 64.0 (m), 26.0 (m), 13.7 (q, J = 6.9 Hz). Minor: 169.5, 143.9, 129.3 (m), 126.9 (m), 123.1 (q, J = 286.7 Hz), 120.4, 117.4 (m), 114.2 (d, J = 6.9 Hz), 78.6 (q, J = 29.3 Hz), 64.0 (m), 26.0 (m), 14.0 (q, J = 6.9 Hz). HRMS for $C_{15}H_{19}F_3NO_3$ [M+H]$^+$: m/z calc., 318.1312; found, 318.1311. Strong correlation between CF_3 and CH was observed in the major product but absent in the minor product in ^{1}H-^{19}F HOESY.

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Chapter 7

Conclusion and Perspectives

7 Conclusion and perspectives

The hydrogenation of unsaturated bonds is one of the most widely studied transformations in both academia and industry. However, there are still challenges in the selective reduction of imino bonds, especially *N*-heterocycles under mild conditions. In addition, single catalysts capable of reducing multiple substrates, while tolerating an ample variety of functionalities are rare. Throughout this PhD thesis, our efforts in tacking some of the major issues affecting current reduction methods have been presented. The cyclometalated Ir(III) complexes presented herein are capable of not just reducing multiple substrates but also capable of tolerating sensitive functionalities which have been problematic in the past. Moreover, reductions could be carried out under environmentally benign reaction conditions and using user friendly reductants. Challenging substrates such as α-functionalised ketones and *N*-heterocycles were reduced in water with high yields (Scheme 7.1 and Scheme 7.2, respectively). In addition, the reductive amination of ketones with ammonium formate has also been developed with iridicycles to give direct access to primary amines which have been challenging to achieve in the past (Scheme 7.3).
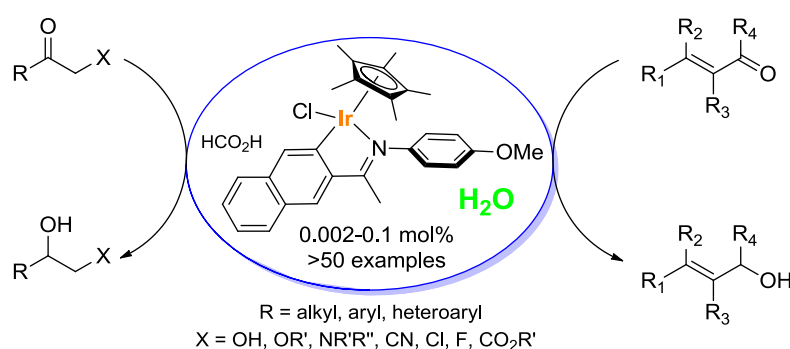
**Scheme 7.1:** Transfer hydrogenation of α-substituted ketones in water.
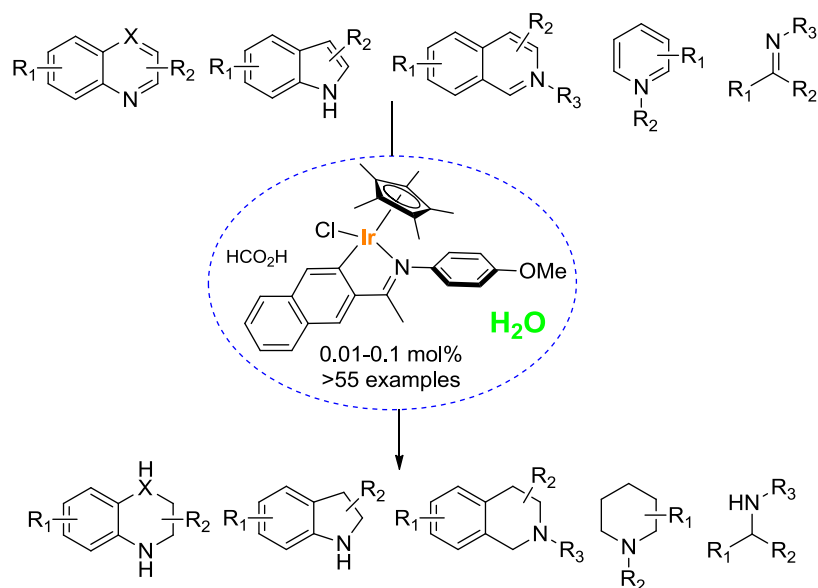
**Scheme 7.2**: Transfer hydrogenation of *N*-heterocycles in water.
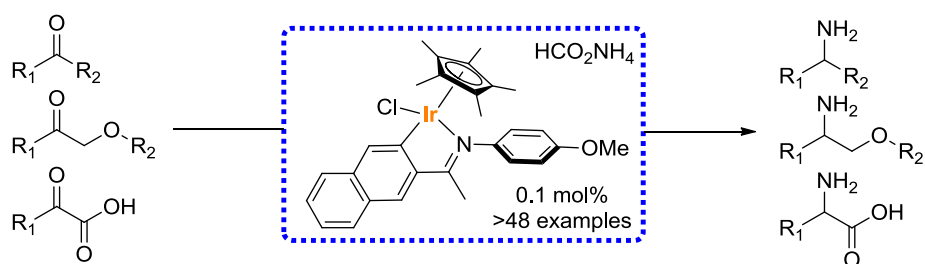
Scheme 7.3: Synthesis of primary amines by direct reductive amination of ketones.

The dehydrogenation of saturated organic molecules represents an important synthetic route towards unsaturated molecules, such as the conversion of amines to imines, or the conversion of alcohols to carbonyls. Acceptorless dehydrogenation permits such transformations in the absence of stoichiometric sacrificial hydrogen acceptors, such as benzoquinone or O_2. Molecular hydrogen that is released from the molecules is a high energy fuel. In terms of atom economy and from an industrial point of view, catalysts capable of activating such molecules to release H_2 are highly desirable. In this thesis, we have demonstrated that cyclometalated Ir(III) complexes are highly versatile for the acceptorless dehydrogenation of a range of *N*-heterocycles that have potential hydrogen storage applications. Moreover, such catalysts can also be utilised for the formation of C-C bonds leading to novel

functionalised *N*-heterocycles. This work is summarised in Scheme 7.4 and Scheme 7.5, respectively. In addition, we have also demonstrated that the reverse hydrogenation is also viable with the same catalysts for such molecules.
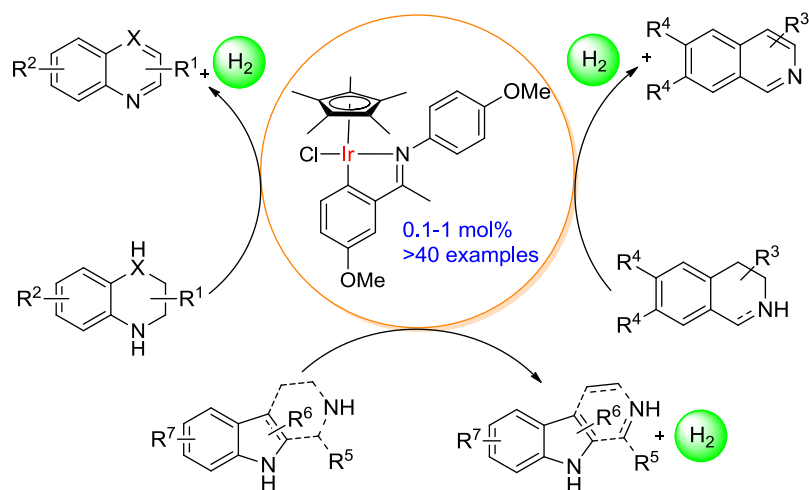

Scheme 7.4: A highly versatile cyclometalated Ir(III) complex for the acceptorless dehydrogenation of *N*-heterocycles.
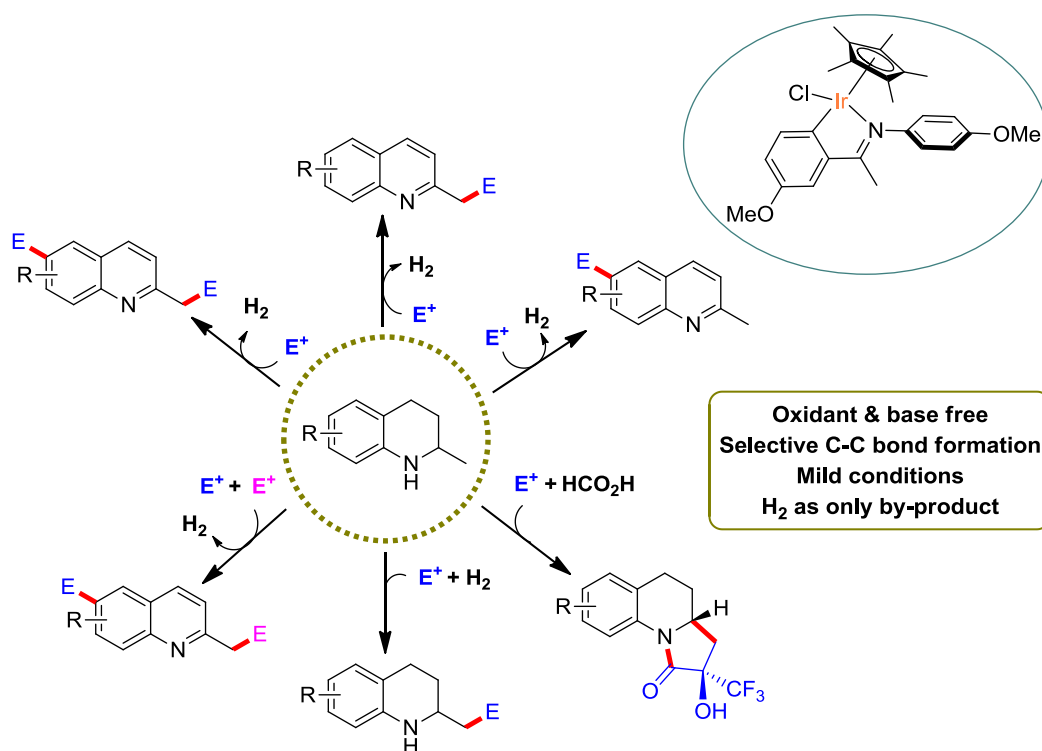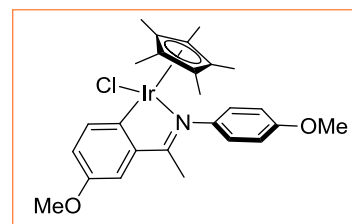

Scheme 7.5: A new acceptor-less and base free C-C bond formation strategy.

Thus, cyclometalated Ir(III) complexes are "universal" catalysts capable of hydrogenating and dehydrogenating multiple challenging substrates, rather than specialised catalysts for a particular set of substrates. Their robustness and versatility make them ideal for industrial use. Indeed, such complexes developed are now commercially available.
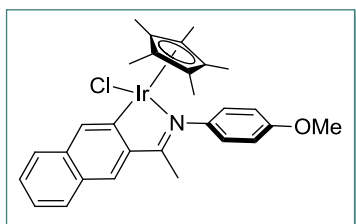
|	
✓ A robust and versatile catalyst for hydrogenation	✓ A robust and versatile catalyst for dehydrogenation
✓ Air and moisture stable	✓ Air and moisture stable
✓ Displays excellent selectivity	✓ Displays excellent selectivity
✓ Tolerates sensitive groups	✓ Tolerates sensitive groups
✓ Successful in reductive amination	✓ Wide substrate scope, with excellent yields
✓ Wide substrate scope, with excellent yields	

Scheme 7.6: Cyclometalated Ir(III) complexes for hydrogenation and dehydrogenation.

Hopefully, the work presented in this thesis opens up the door for further exciting chemistry in the future. In the area of transfer hydrogenation, a natural extension would be the development of asymmetric reduction systems with cyclometalated complexes. These complexes have also shown promise in the dehydrogenation of both primary and secondary alcohols. This work has not been included in this thesis; but preliminary results are summarised in Scheme 7.7. Future work could include developing a robust catalyst capable of such transformation with low catalyst loadings. Further, cyclometalated Ir(III) complexes could also be tested for the dehydrogenation of more challenging substrates, for instance alkanes to alkenes,

primary amines to nitriles. For acceptorless dehydrogenation coupling, chiral organocatalysts can be used together with iridicycles to induce chirality at the newly formed quaternary centres after the attack on the electrophile.
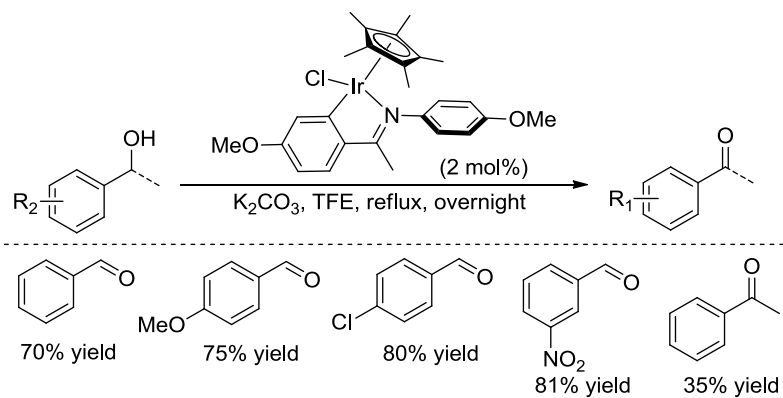
Scheme 7.7: Dehydrogenation of primary and secondary alcohols.