FROM TRANSFER HYDROGENATION TO TRANSAMINATION: NEW METHODS FOR THE PREPARATION OF *N*-HETEROCYCLES

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

by

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To my daughter Boyu Annie Wu

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ABSTRACT

Reduction of *N*-heteroaromatic compounds is a challenging and important reaction. Transfer hydrogenation using organic molecules as hydrogen donors is a safe and operationally simple alternative to hydrogenation with H_2. However, it has been underutilised and less developed. In this thesis, our contribution to the transfer hydrogenation of *N*-heteroaromatic compounds is described.

Following a brief introduction of transfer hydrogenation of *N*-heteroaromatic compounds in Chapter 1, Chapter 2 presents a novel method for the mild reduction of quinolines, isoquinolines and quinoxalines to corresponding tetrahydro products. The most significant discovery is the remarkable accelerating effect of the simple iodide ion, which acts presumably by altering the reaction mechanism.

Chapter 3 extends the above-mentioned system to the reduction of more challenging pyridines to afford not only piperidines but also the 3,4-unsaturated variants with high chemoselectivities.

Chapter 4 describes a simple, complementary system, discovered during searching for new transfer hydrogenation catalysts, which allows for the hydrogenation of *N*-heteroaromatics with H_2 using a cyclometalated iridium complex under exceptionally mild conditions (ambient temperature, 1 atm H_2) in the absence of any additives.

Chapter 5 demonstrates a new reaction for the rapid and direct preparation of various chiral piperidines from pyridines with high yields and exceptional diastereo- and enantioselectivities. Key to the success is the introduction of a chiral amine which is incorporated into the pyridine ring by transamination during the transfer hydrogenation process, presumably *via* forming previously unobtainable chiral tetrahydropyridinium intermediate *in situ*.

PUBLICATIONS

- **Highly Efficient Rhodium-Catalyzed Transfer Hydrogenation of Nitroarenes into Amines and Formanilides**

  Y. Wei, **J. Wu**, D. Xue, C. Wang, Z. Liu, Z. Zhang, G. Chen, J. Xiao, *Synlett* **2014**, st-2014-w0090-1.

- **Robust Cyclometallated 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. 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. Xiao, *Angew. Chem. Int. Ed.* **2013**, *52*, 6983–6987.

- **Efficient and Chemoselective Reduction of Pyridines to Tetrahydropyridines and Piperidines *via* Rhodium-Catalyzed Transfer Hydrogenation**

  J. Wu, W. Tang, A. Pettman, J. Xiao, *Adv. Synth. Catal.* **2013**, *355*, 35-40.

- **The Remarkable Effect of a Simple Ion: Iodide-Promoted Transfer Hydrogenation of Heteroaromatics**

  J. Wu, C. Wang, W. Tang, A. Pettman, J. Xiao, *Chem. Eur. J.* **2012**, *18*, 9525-9529.

ABBREVIATIONS

α	alpha
β	beta
δ	chemical shift
Å	amstrong
Ac	acyl
AH	asymmetric hydrogenation
Ar	aryl
ATH	asymmetric transfer hydrogenation
atm	atmosphere
Bn	benzyl
Boc	*tert*-butyl carbonate
brs	broad singlet
Bu	butyl
°C	degree Celsius
Cbz	carbobenzyloxy
CI	chemical ionisation
COD	1,5-cyclooctadiene
conv.	conversion
Cp*	pentamethylcyclopentadiene
Cy	cyclohexyl
d	doublet

DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
ddq	doublet of doublet of quartets
ddt	doublet of doublet of triplets
DPEN	1,2-diphenylethylenediamine
dq	doublet of quartets
dt	doublet of triplets
ee	enantiomeric excess
e.g.	*exempli gratia*
eq	equivalent(s)
Eq.	equation
ESI	electrospray ionisation
Et	etnyl
FT	formic acid/triethylamine azeotrope
g	gram
h	hour
HEH	Hantzsch 1,4-dihydropyridine
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
i.e.	*id est*
IPA	isopropanol

J	coupling constant value
L	levorotatory
LUMO	lowest unoccupied molecular orbital
m	multiplet
Me	methyl
mg	milligram
min	minutes
mL	mililitre
mmol	milimole(s)
m/z	mass to charge ratio
NADH	nicotinamide adenine dinucleotide hydride
NADPH	nicotinamide adenine dinucleotide phosphate hydride
NBD	norbornadiene
NHC	nitrogen heterocyclic carbenes
NMR	nuclear magnetic resonance
OAc	acetate
p-cymene	1-methyl-4-(1-methylethyl)benzene
$Pd(OAc)_2$	palladium(II) acetate
Ph	phenyl
PPh_3	triphenylphosphine
ppm	parts per million
Pr	propyl
q	quartet

r. t.	room temperature
s	singlet
S/C	substrate to catalyst ratio
SegPHOS	5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
t	triplet
TBAB	tetrabutylammonium bromide
TBAC	tetrabutylammonium chloride
TBAI	tetrabutylammonium iodide
td	triplet of doublets
TFE	2,2,2-trifluoroethanol
TH	transfer hydrogenation
THF	tetrahydrofuran
TMS	tetramethylsilane
TOF	turnover frequency
TON	turnover number
t_R	retention time
Ts	*p*-toluenesulfonyl
TsDPEN	*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine
tt	triplet of triplets
vs	*versus*

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CHAPTER 1 INTRODUCTION - TRANSFER HYDROGENATION OF *N*-HETEROAROMATIC COMPOUNDS

1.1 Introduction

Catalytic hydrogenations are amongst the largest-scale industrial processes in the world. From the hydrocracking of heavy oil in petroleum refining to pharmaceutical manufacturing with asymmetric hydrogenation processes, hydrogenation processes have fundamentally affected the daily life of human beings. Over one hundred million tonnes of ammonia are produced annually by the catalytic hydrogenation of N_2 primarily for worldwide fertilising agricultural crops. In comparison to these artificial catalytic processes, nature has developed its own catalytic system to achieve the hydrogen transfer for complex chemical transformations by oxidoreductases. The advantages of enzymatic catalysts in combination with organic molecules as hydrogen donor have been highlighted by many efficient reductions in both chemoselective and enantioselective manner.[1] For instance, in the presence of horse liver alcohol dehydrogenase, various carbonyl compounds could be enantioselectively reduced to chiral, non-racemic alcohols using NADH or NADPH as cofactors.[2] Inspired by nature, transfer hydrogenation (TH) in the presence of catalysts, using organic molecules as hydrogen donor to achieve hydrogen transfer to hydrogen acceptors (Eq. 1), has attracted much attention in the past several decades.[3]

$$DH_x + nA \xrightarrow{\text{catalyst}} nAH_x + D \qquad (1)$$

In comparison to the well-known hydrogenation with H_2, TH by using other hydrogen donors has been relatively underutilised, although it offers real and potentially benign advantages, particularly for modern synthetic chemistry. Hydrogen gas with small molecular weight, poses big challenges to safety, particularly when in its liquid form, due to its ease of diffusion and leaking, low ignition energy and extreme reactivity with oxidants. In contrast, the use of organic molecule-based hydrogen donors obviates these potential hazards and does not require the use of specialised equipment, affording a feasible alternative particularly for laboratory-scale experiments. Apart from the safer use and operational simplicity, TH is often found to enhance chemoselectivity and tolerate other reducible functionalities.[3] Thus, TH has been extensively investigated and many efficient catalysts have found their applications in organic synthesis, with the substrate scope covering almost all the reducible functionalities including alkenes, carbonyls, imines, alkynes, azo, nitro and cyano groups.[3]

Direct reduction of *N*-heteroaromatics by TH, however, has been much less developed, although the corresponding reduced heterocyclic compounds are widely found in natural products, synthetic medicines and functional materials.[4] For instance, coniine, a piperidine derivative, found

in hemlock and responsible for the death of ancient Greek philosopher Socrates, was synthesised about one hundred years ago as the first example of alkaloid synthesis.[5a] *L*-Proline, existing in human bodies, was utilised as a privileged catalyst in asymmetric catalysis in organic synthesis.[5b] Galipinine[5c] and salsolidine,[5d] as naturally occurring alkaloids, were found to exhibit diverse bioactivities and potential medicinal applications. Furthermore, synthetic drugs containing *N*-cyclic amine motifs such as Abilify[5e] and Concerta[5f] have been prescribed as the most popular pharmaceuticals for the treatment of certain diseases (Figure 1).

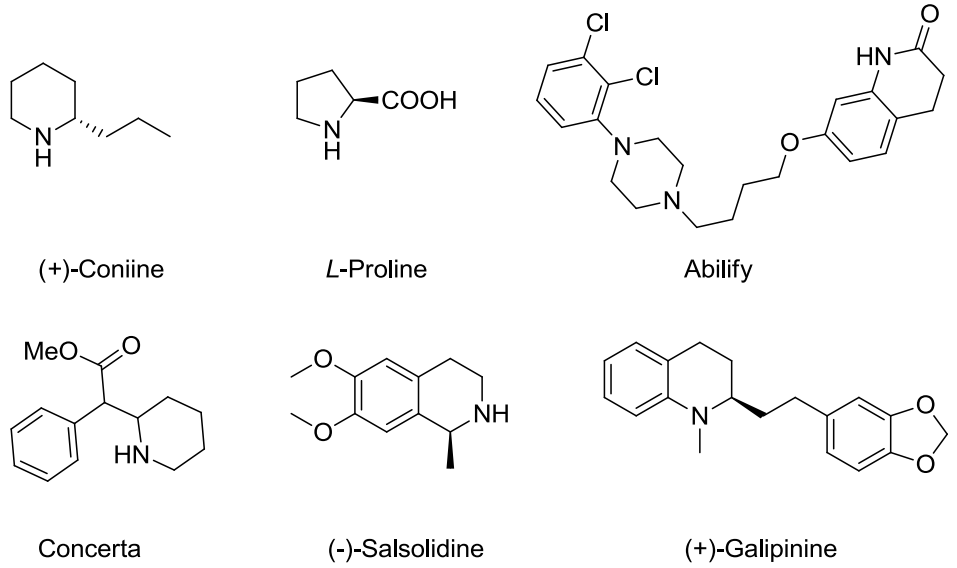


Figure 1: Representative examples of bioactive *N*-heterocyclic compounds

Due to the broad utilities of saturated *N*-heterocyclic compounds, the

reduction of various *N*-heteroaromatics has been attempted through a number of catalytic hydrogenation and TH systems, as outlined in Figure 2.

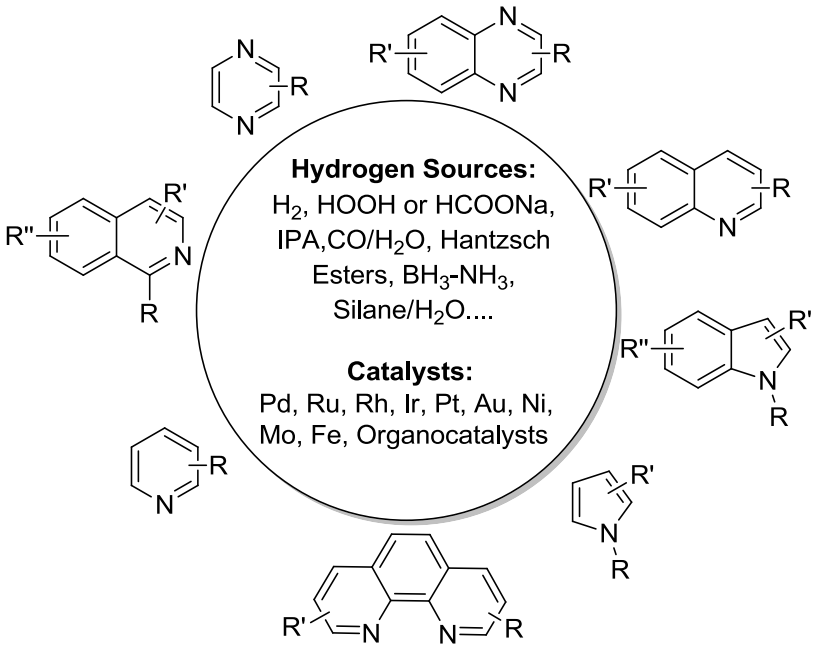


Figure 2: Catalytic hydrogenation and TH of *N*-heteroaromatics

Since Adam, Adkins and Freifelder's pioneering work,[6] transition metal catalysed heterogeneous hydrogenation of *N*-heterocycles using hydrogen gas has been extensively investigated and found tremendous application in industry. Building on Wilkinson's seminal work of homogeneous hydrogenation in the 1960's,[7] Knowles, Noyori and others have developed asymmetric hydrogenation (AH)[8] to reduce diverse prochiral functionalities in enzyme-comparable enantioselectivities, which has a far-reaching influence in the chemistry community and has

been widely adopted for the preparation of chiral compounds. In the past decade, AH of *N*-heteroaromatics to directly obtain optically active saturated cyclic amines has attracted much attention and a number of efficient hydrogenation systems have been developed.[9] However, the use of hydrogen donors rather than hydrogen gas, for example, alcohols, amines, hydrocarbons or formic acid and its derivatives, has been much less explored particularly for *N*-heterocycle reduction. In this Chapter, transfer hydrogenation (TH) with these hydrogen donors for the reduction of *N*-heterocycles by homogeneous and heterogeneous catalysis will be discussed.

1.2 TH of *N*-heteroaromatics

Since the 1980's, a variety of *N*-heteroaromatics, such as quinolines, isoquinolines, quinoxalines, indoles, pyridines and others, have been successfully reduced by TH reactions. These reactions will be briefly overviewed according to the structural differentiation.

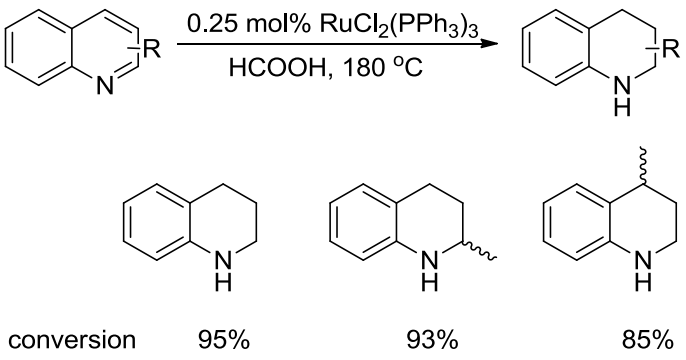
1.2.1 TH of quinolines

Transition metal catalysts and metal-free organocatalysts are generally employed in TH in the presence of commonly used hydrogen donors such as isopropanol (IPA), formic acid and its derivatives, and Hantzsch esters.[3] As many TH systems have been successfully used for the reduction of quinolines, the introduction for the TH of such

compounds will be divided on whether the metal catalyst is used.

1.2.1.1 TH of quinolines by transition-metal catalysts

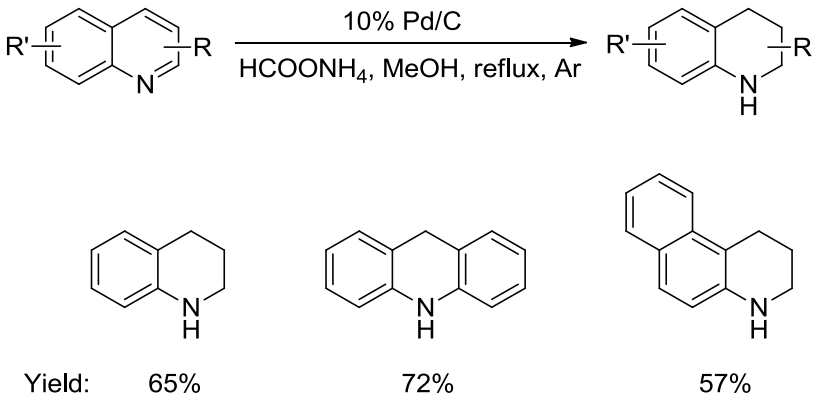
In 1984, Watanabe and co-workers reported that nitroarenes could be reduced in excellent conversions with HCOOH catalysed by $RuCl_2(PPh_3)_3$,[10] as can be seen in Scheme 1. They also demonstrated for the first time that *N*-heterocycles such as quinolines could be reduced to 1,2,3,4-tetrahydroquinolines by TH, although isoquinolines, pyridines and other aromatic compounds were inactive. Other commonly used homo- or heterogeneous Ru complexes proved of low efficiency for the reduction of quinolines. This system is presumably difficult to tolerate other functionalities, judging from the harsh conditions used (180 °C).



Scheme 1: Ru-catalysed TH of quinolines with formic acid

In the 1980's, the combination of ammonium formate and palladium on carbon was successfully applied to the reduction of

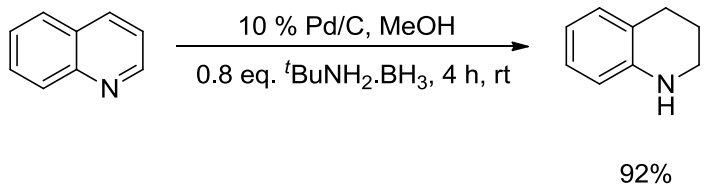
carbonyls to methylene derivatives, and nitroketals to aminoketals,[11] although no reduction of *N*-heterocycles by this method was reported until Joule and co-workers introduced it during a synthesis study in 1990. They found that in refluxing methanol, $HCOONH_4$-Pd/C could be employed for the reduction of quinolines under mild conditions (Scheme 2).[12] For instance, acridine could be hydrogenated to the 9,10-dihydro product in moderate yield at room temperature.



Scheme 2: Pd-catalysed TH of quinolines with formic acid

In 2001, Borane-amine complexes were introduced as reducing agents by Couturier and co-workers to reduce a variety of functional groups catalysed by palladium in methanol.[13] Non-substituted quinoline was tested as a representative example of *N*-heteroaromatics and a good yield was obtained (Scheme 3). In comparison to the commonly

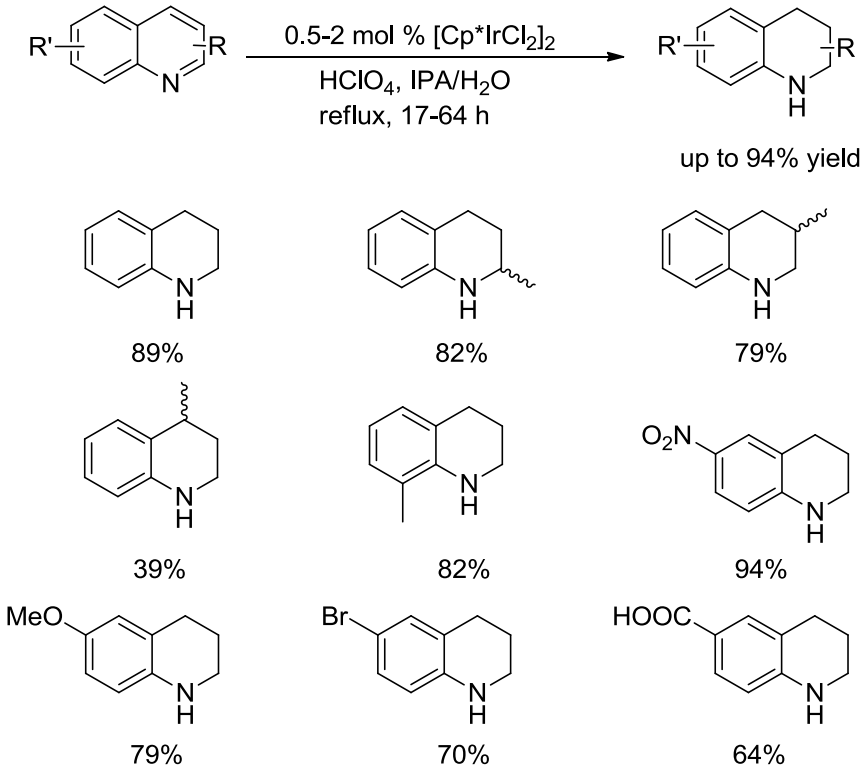
employed reduction of quinoline using pyridine-borane, this method shows more selective character and can be carried out under milder conditions.



Scheme 3: Pd-catalysed TH of quinolines with borane-amine

A breakthrough for TH of *N*-heteroaromatics using homogeneous catalysts was achieved in 2004 by Fujita and co-workers during the investigation of Cp*-Ir complexes.[14] By using IPA as hydrogen donor and $[Cp^*IrCl_2]_2$ as catalyst, a series of quinolines bearing substituents in various positions were hydrogenated to 1,2,3,4-tetrahydro products in moderate to good yields (Scheme 4). Halides, NO_2 and COOH were found to be well tolerated and common byproducts such as 5,6,7,8-tetrahydro- and decahydroquinolines found in heterogeneous hydrogenation were not detected in this system. The presence of Brønsted acid considerably enhanced the reduction, presumably through the protonation of neutral quinoline to form quinolinium, which is easier to reduce by the Ir-H. The formation of *N*-isopropyl byproduct, probably

from the reductive amination of 1,2,3,4-tehydroquinolines and *in situ* formed acetone was suppressed by the addition of H_2O. Isoquinolines and pyridines were found to be inactive in this system. A plausible mechanism is proposed by the authors, as outlined in Figure 3.



Scheme 4: Ir-catalysed TH of quinolines with IPA

The formation of iridium isopropoxide complex **A** from the reaction of the catalyst precursor $[Cp^*IrCl_2]_2$ and IPA is supposed to initiate this reduction. Then β-elimination would occur by releasing acetone to form the iridium hydride **B**, followed by the 1,2-addition of

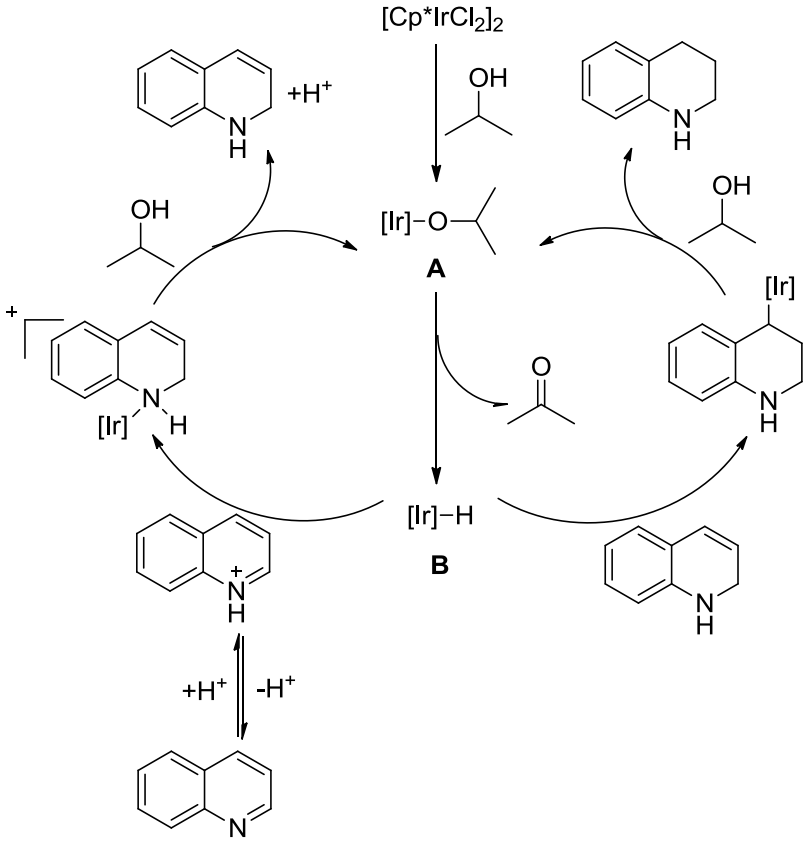
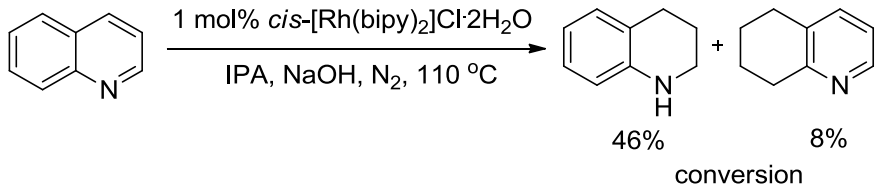


Figure 3: Proposed mechanism for TH of quinolines with IPA

such hydride complex to the protonated quinoline, which was generated *in situ* in the presence of the acidic additives. The resulting cationic iridium-1,2-hydroquinoline intermediate would decompose to 1,2-dihyroquinoline and regenerate the iridium isopropoxide **A** and consequently Ir-H. The resulting hydride and then insert into the C=C bond in the 1,2-dihyroquinoline to form the iridium-1,2,3,4-tetrahydroquinoline intermediate followed by

protonolysis with IPA to afford the desired 1,2,3,4-tetrahydroquinoline product. This proposed mechanism finds support from the reduction of a possible intermediate. Under the similar reaction conditions and without using the acids, 1,2-dihydroquinoline was hydrogenated to 1,2,3,4-tetrahydroquinoline in high yield.

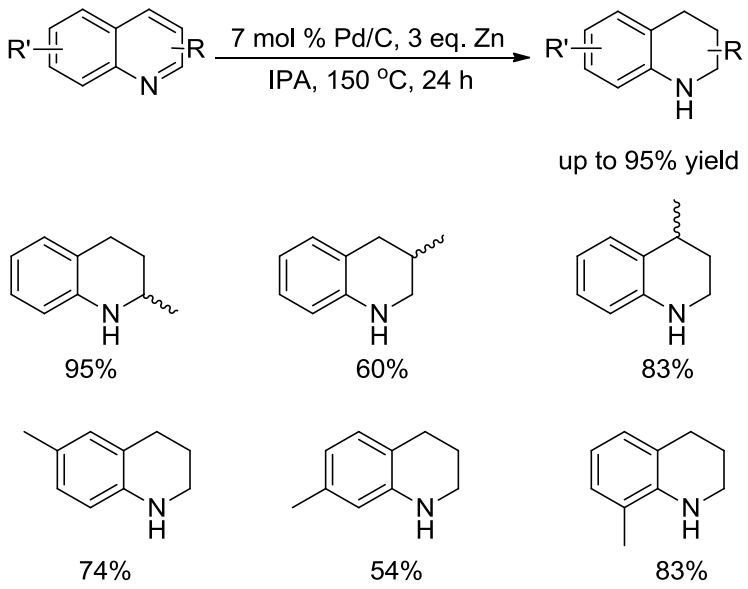
In 2006, Frediani and co-workers reported a versatile Rh-bipyridine catalyst which could hydrogenate an array of reducible functionalities, including alkenes, carbonyls and imines by using IPA as hydrogen source.[15] As can be seen in Scheme 5, this catalyst could also be applied to the reduction of *N*-heterocylces, quinoline, for example, in reasonable conversion and good selectivity.



Scheme 5: Rh-catalysed TH of quinolines with IPA

In 2010, a Pd/C/Zn combination was disclosed by Sasson and co-workers to generate hydrogen in water and was consequently applied to the reduction of carbonyl and nitro groups. Recently, this method was explored by Abarca and Ballesteros for the TH of quinolines[16] and moderate to good yields were obtained for the

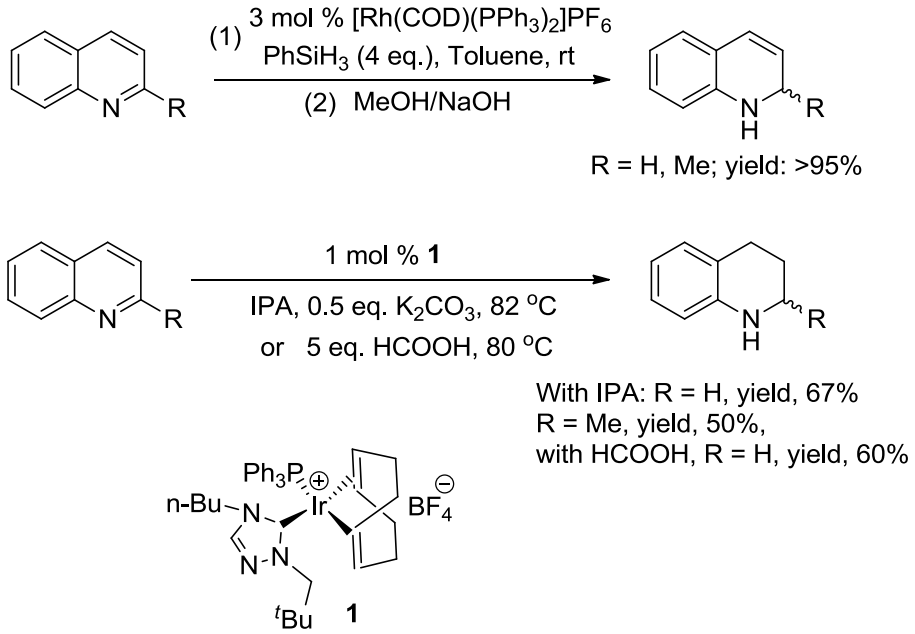
1,2,3,4-tetrahydroquinolines (Scheme 6). However, the harsh conditions, incompatibility of functionalities and the use of stoichiometric zinc restrict the potential application in synthetic chemistry.



Scheme 6: Pd-catalysed TH of quinolines with IPA

In 2008, Crabtree and co-workers developed two mild systems for catalytic hydrosilylation and transfer hydrogenation of quinolines,[17] as shown in Scheme 7. 1,2,3,4-Tetrahydroquinolines were obtained in moderate yields by using $[Ir(COD)(NHC)PPh_3]BF_4$ **1** as catalyst, with either isopropanol or formic acid as hydrogen source. It is noteworthy that the hydrosilylation of quinolines catalysed by $[Rh(NBD)(PPh_3)_2]PF_6$ in the presence of $PhSiH_3$ could afford 1,2-dihydroquinolines after a rapid

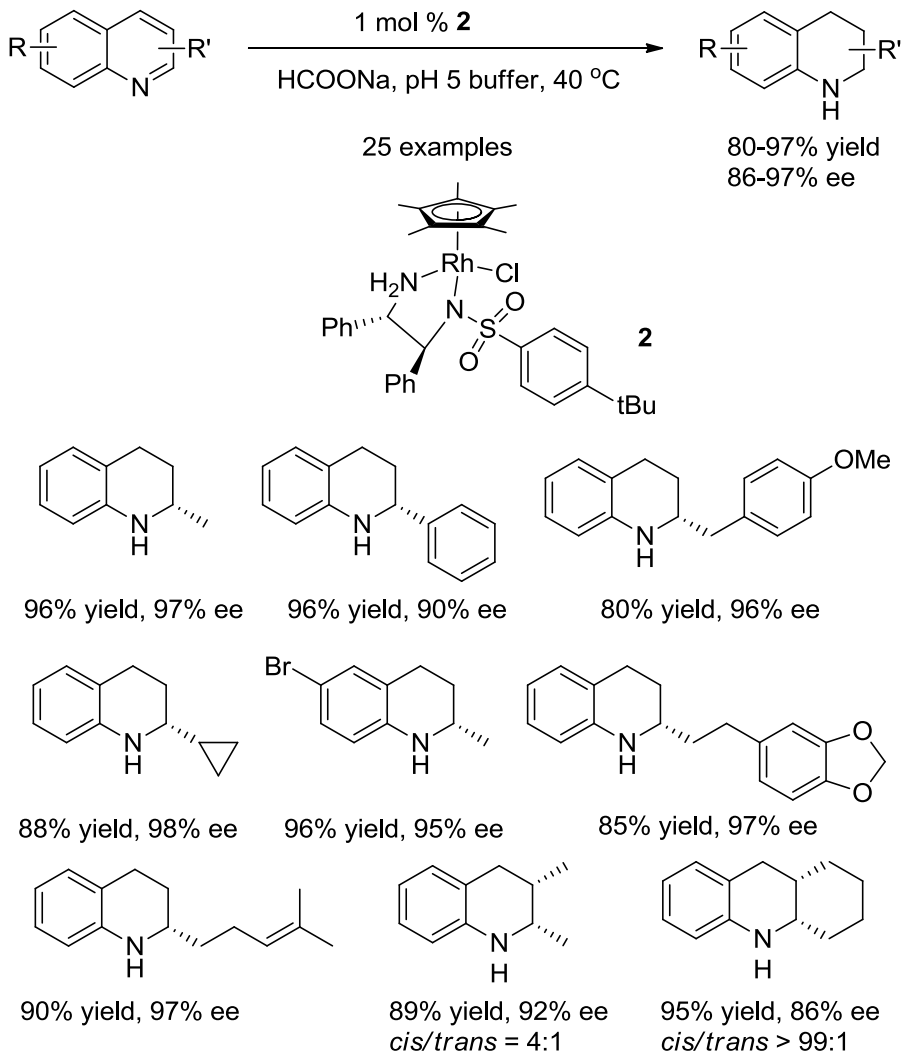
hydrolysis with base, which are not obtainable by direct hydrogenation.



Scheme 7: Rh- and Ir-catalysed hydrosilylation and TH of quinolines

Since 2003, when the first example of highly enantioselective hydrogenation of quinolines was reported by Zhou and co-workers,[18] numerous catalytic systems with transition metals, such as Ir and Ru, and diverse ligands using H_2 as hydrogen source have been developed,[19] allowing rapid and efficient preparation of a range of optically active tetrahydroquinolines. However, there are no examples of transition-metal catalysed ATH of quinolines. In 2009, Xiao and co-workers reported the first example of ATH of quinolines in water which afforded a series of 1,2,3,4-tetrahydroquinolines in excellent enantioselectivities and yields

with a Rh-TsDPEN catalyst **2**, by using formate as the hydrogen source.[20] (Scheme 8). Quinolines bearing 2-alkyl or 2-aryl substituents could be hydrogenated in good yields and excellent ee values. It is worth to note that the pH of the aqueous medium plays a crucial role for the high activity, while showing little influence on enantioselectivity.



Scheme 8: Rh-catalysed ATH of quinolines in water

As shown in Figure 4, the authors assumed that the mechanism begins with a hydride transfer to the pronated quinolines **D**, as the acidic medium is essential for the high reactivity. For the following hydride addition, there might be two options, a 1,2-, or 1,4-addition pathway. Based on the results obtained from computational calculation for the energy and distribution of LUMO orbital of 2-methylquinoline **C** and other possible intermediates, the initial 1,4-hydride addition was thought to be favored. The resulting enamine **E** was then isomerised to the iminium intermidate **F** followed by the reduction by metal hydride, generating 1,2,3,4-tetrahydroquinoline **G** as the desired product.

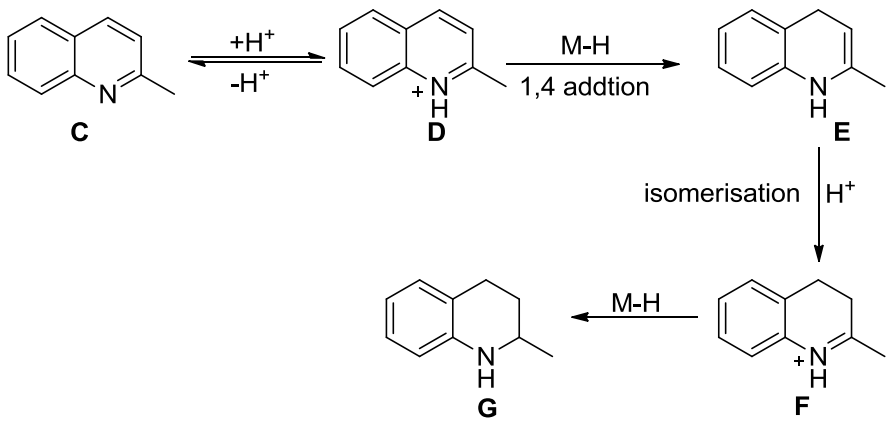
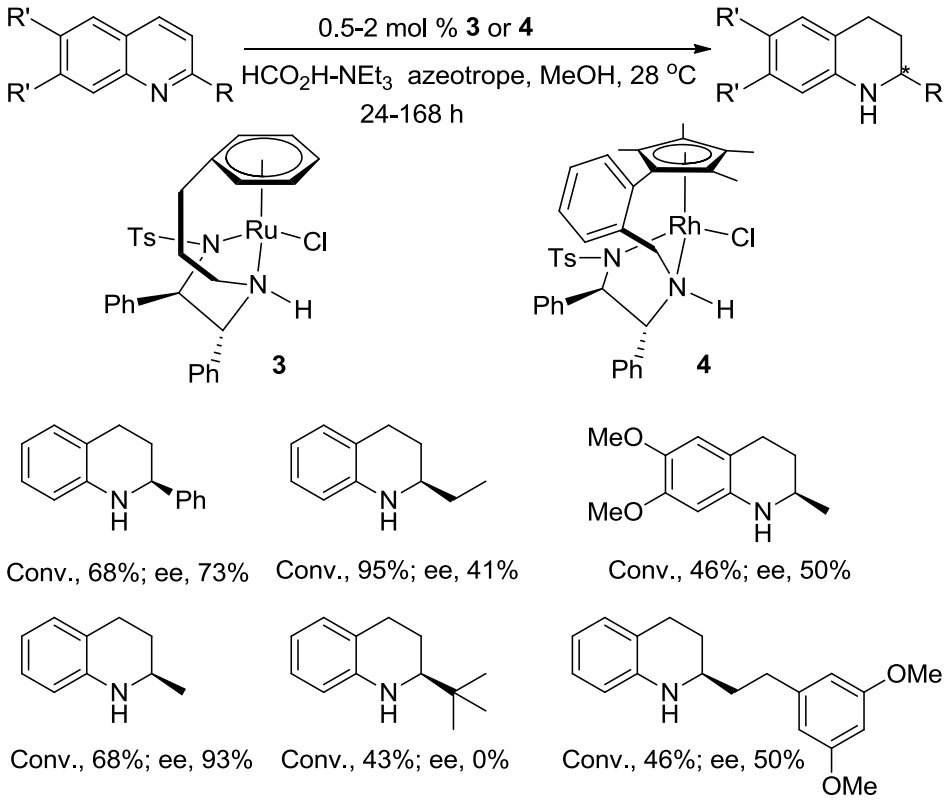


Figure 4. Proposed pathway for Rh-catalysed quinoline reduction in water

In 2010, Wills and co-workers applied their tethered ruthenium and rhodium catalysts **3** and **4,** which were excellent catalysts for ATH of

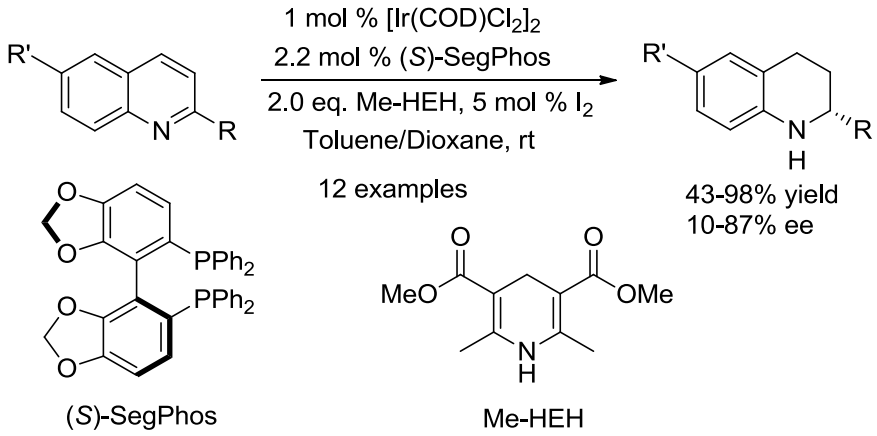
ketones, to the ATH of quinolines using formic acid as hydrogen source.[21] The reduction was found to be generally slow and satisfactory conversions were only obtained in up to 168 hours. The rhodium complex **4** displayed higher enantioselectivity than the ruthenium catalyst **3**, but significantly lower activity even with higher catalyst loading (Scheme 9).



Scheme 9: Ru- and Rh-catalysed ATH of quinolines with formic acid

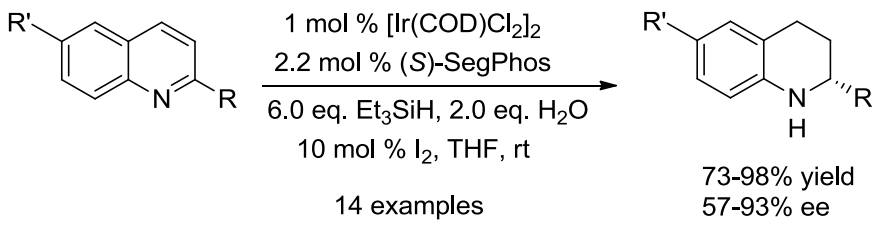
Inspired by Reuping's work on organocatalytic reduction of quinolines[22] (*vide infra*), Zhou and co-workers in 2007 introduced Hantzsch esters to replace H_2 as hydrogen source, realising ATH of quinolines under mild conditions.[23] By comparison to the results obtained

with hydrogen gas, compromised enantioselectivities were obtained in this case for 2-alkyl quinolones and this system proved less effective for 2-aryl substrates (Scheme 10).



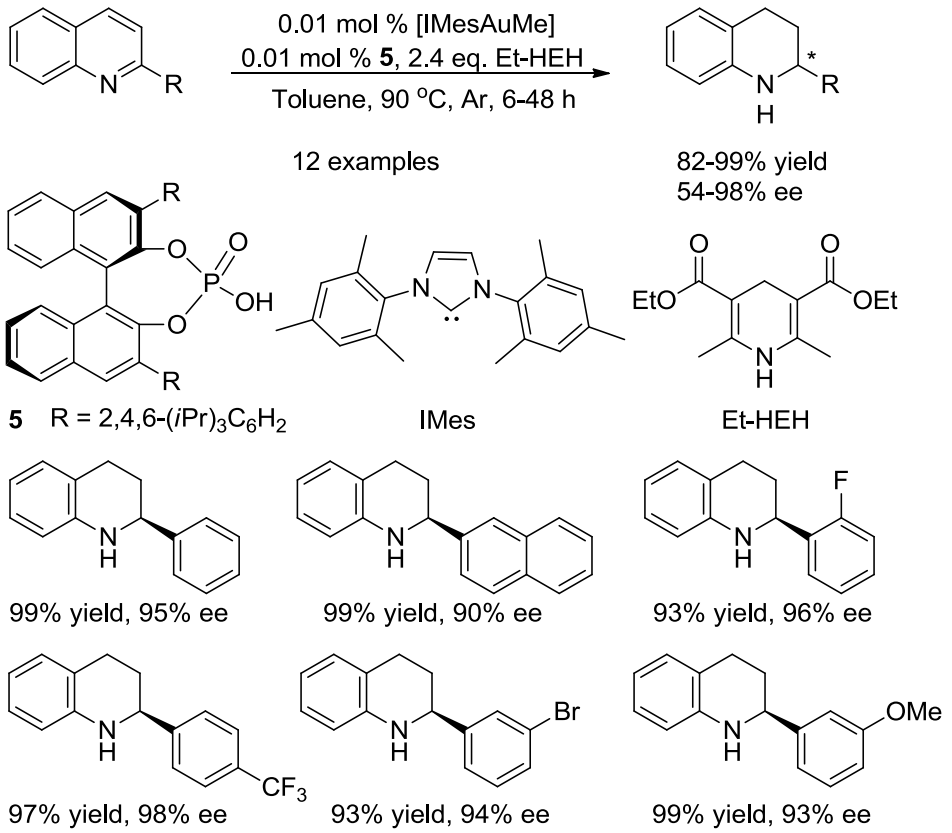
Scheme 10: Ir-catalysed ATH of quinolines with Hanzsch ester

In 2010, the same group described the first AH example using water/silane as hydrogen source and this method has been successfully applied to the ATH of quinolines to tetrahydroquinolines in good yield and enantioselectivity (Scheme 11).[24] The deuteration experiments implied that two hydrides in the hydrogenation of quinolines come from silane and another two are contributed by water.



Scheme 11: Ir-catalysed ATH of quinolines with water/silane

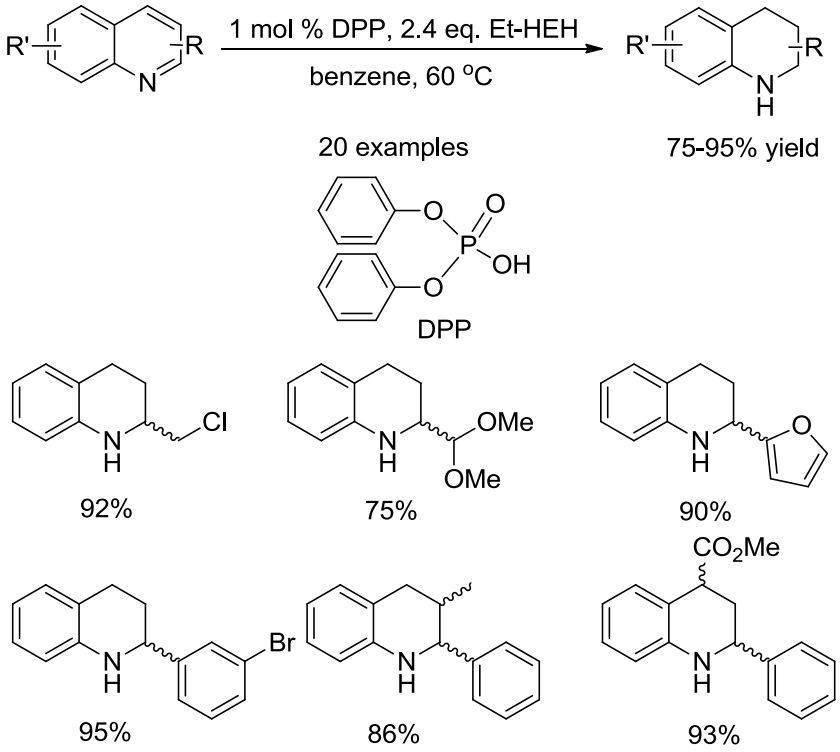
In 2012, Gong and co-workers reported an extremely active system for the ATH of 2-arylquinolines using an *in situ* formed gold phosphate complex from sterically demanding phosphate **5**.[25] With a Hanzsch ester as hydrogen donor, only 0.01 mol % of such catalyst is sufficient to reduce 2-arylquinolines in excellent yields and enantioselectivities (Scheme 12). The 10000 TON represents the best catalytic efficiency in ATH of quinolines, resulting from the tuning of the achiral ligand. However, decreased conversion and poor enantioselectivity was observed for 2-alkyl quinolines.



Scheme 12: Au-catalysed ATH of quinolines with Hantzsch ester

1.2.1.2 TH of quinolines by organocatalysts

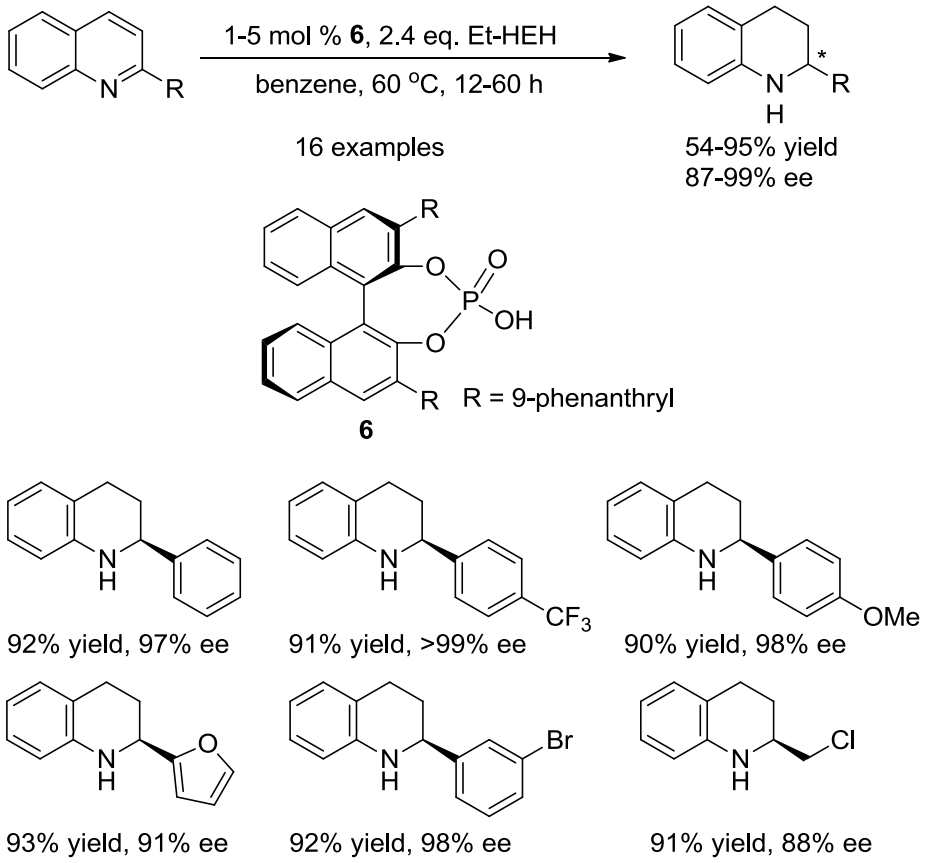
In the past decade, biomimetic, metal-free transformations using Brønsted acids as organocatalysts have attracted much attention in the synthetic community,[26] as a result of arising environmental concerns and sustainability issues. In 2006, Reuping and co-workers extended their Brønsted acid catalysed TH of imines to *N*-heterocycles employing Hantzsch esters as hydrogen source.[27] After screening various Brønsted acids, diphenyl phosphate (DPP) was found to be the most efficient organocatalyst to reduce a set of quinolines to tetrahydro products. As can be seen in Scheme 13, 1 mol % of DPP is sufficient to smoothly catalyse the reduction of quinolines possessing a range of functionalities. Better activities were observed when the reduction was carried out in non-polar solvents, such as benzene, toluene, dichloromethane and chloroform, which were also essential for higher asymmetric induction (*vide infra*).

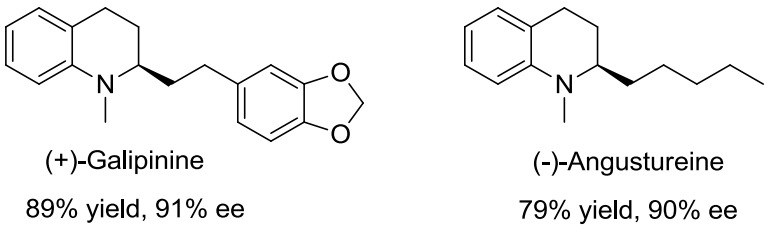


Scheme 13: Organocatalysed TH of quinolines

After successfully demonstrating the ATH of imines catalysed by chiral Brønsted acids and the observation of high activity with quinolines, it became a natural extension for Reuping and co-workers to apply the same asymmetric system to enantioselective hydrogenation of quinolines, which would represent the first example of organocatalysed reduction of heteroaromatic compounds.[22] It would also allow the prompt preparation of optically pure 1,2,3,4-tetrahydroquinolines under metal-free conditions. Based on their previous work of ATH of imines, optimised conditions for ATH of quinolines were quickly identified after systematic examination

of the reaction parameters. As can be seen in Scheme 14, the chiral sterically congested phosphoric acid **6** based on the BINOL backbone emerged as the best catalysts for hydride transfer with the Hanzsch esters, affording excellent enantioselective induction, which was in agreement with the ATH of imines. Good yields and excellent ee values were obtained for the reduction of 2-arylquinolines using 1-5 mol % catalyst, while slightly diminished enantioseletivities were observed for the reduction of 2-alkyl substrates.





Scheme 14: Organocatalysed ATH of quinolines

As shown in Figure 5, the key feature of the proposed mechanism starts with the formation of a tight ion pair, the iminium ion **H**, between the chiral Brønsted acid and quinoline, followed by the hydride transfer from the dihydropyrine to the pronated quinoline to give the pyridium salt and enamine **I**. Reacting with the Brønsted acid, such enamine undergoes isomerisation in the second cycle to produce iminium **J**. This iminium was then reduced by the hydride from the Hantzsch ester to generate chiral 1,2,3,4-tetrahydro product **K**. In both cycles, final proton transfer regenerates the chiral Brønsted acid by releasing Hantzsch pyridine as byproduct.

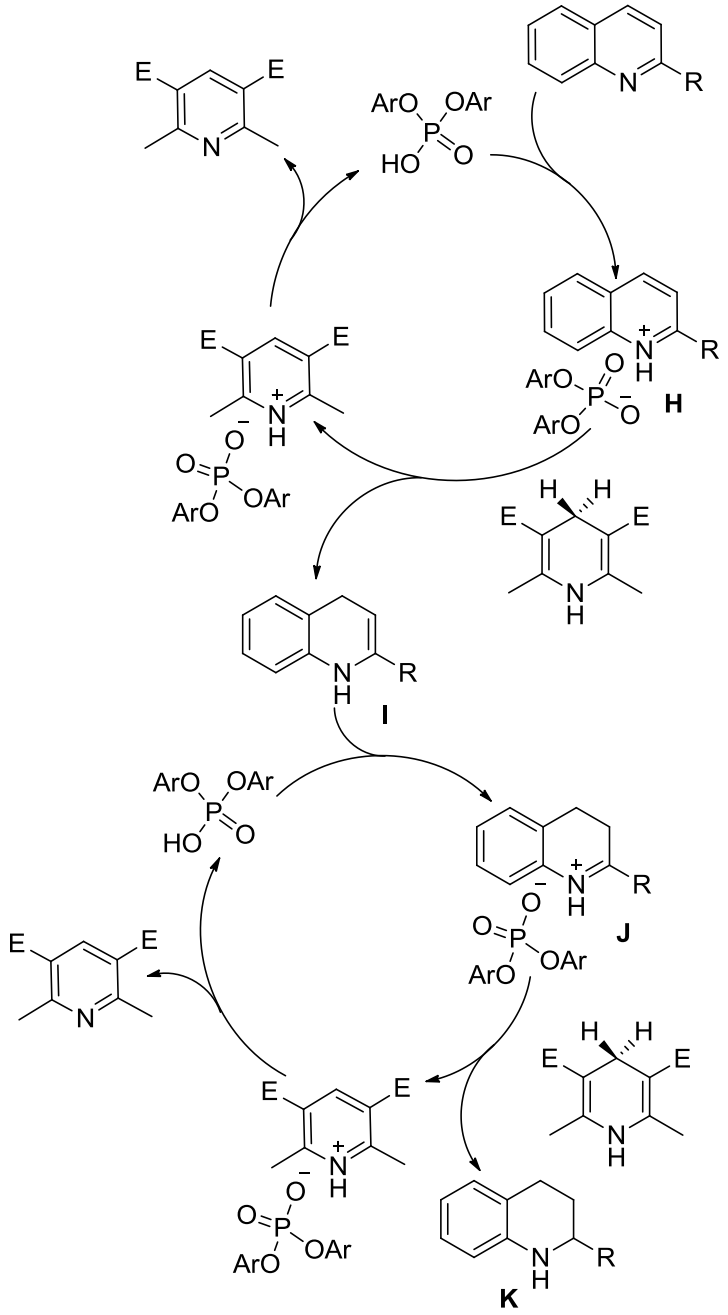
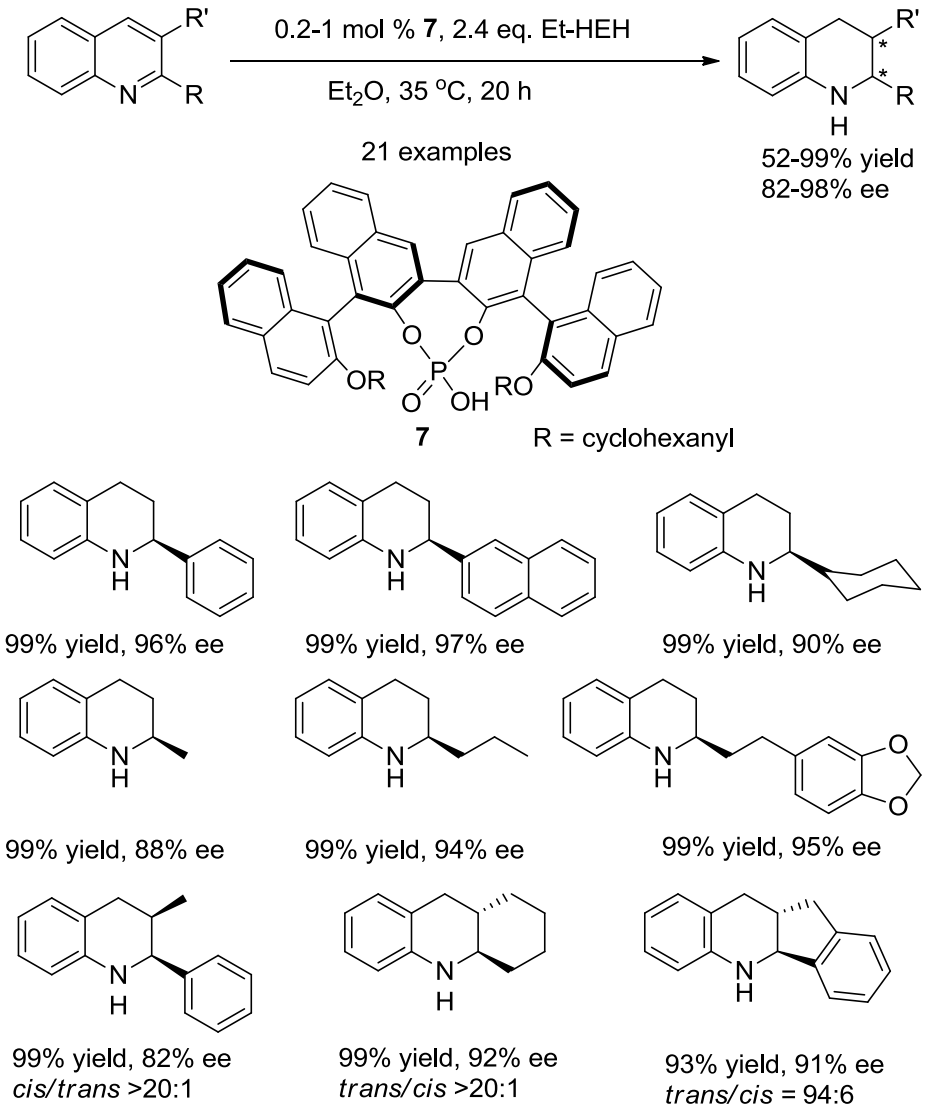


Figure 5: Proposed mechanism for organocatalysed ATH of quinolines

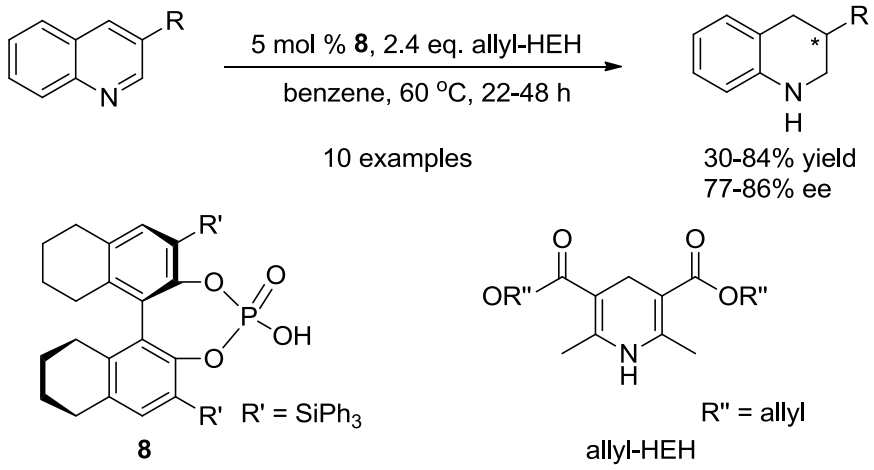
Du and co-workers next examined the same reaction by using elegantly defined chiral phosphoric acid **7** derived from bis-BINOL unit.[28] Comparable enantioselectivities and better yields were obtained

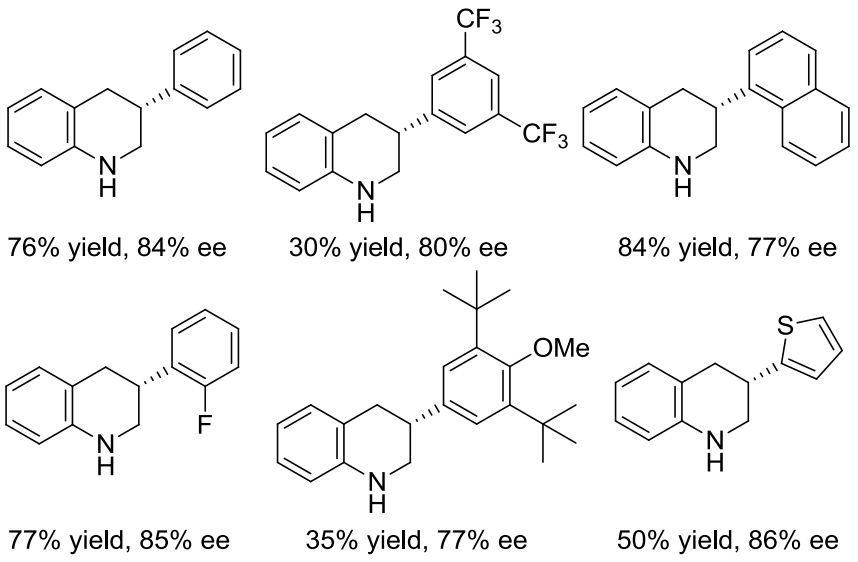
for the ATH of 2-substituted quinolines with considerably lower catalyst loading (0.2 mol %). It is worth mentioning that 2,3-disubstituted quinolines were also hydrogenated in good to excellent diastereoselectivities and enantioselectivities (Scheme 15).

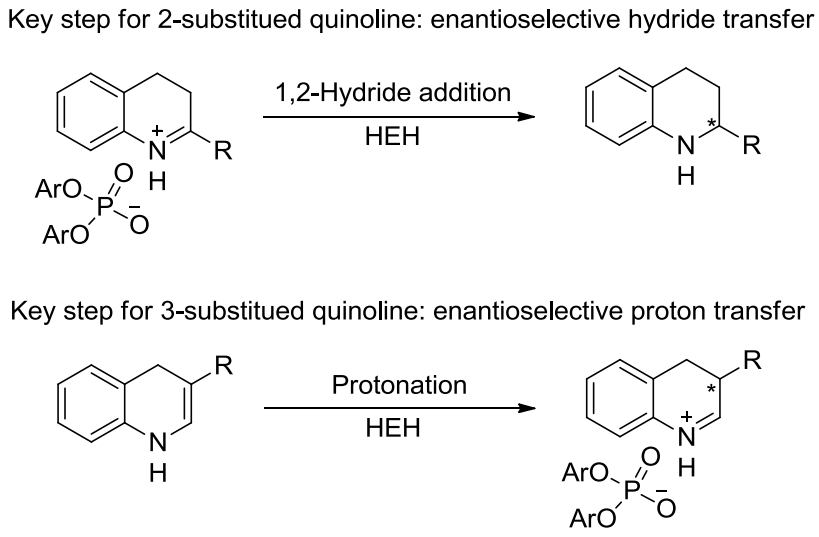


Scheme 15: Organocatalysed ATH of 2- and 2,3-substituted quinolines

In comparison with 2-substituted quinolines, 3-substituted quinolines are problematic substrates for asymmetric hydrogenation and successful examples are rare. In 2008, Reuping and co-workers reported that 3-arylquinolines could be enantioselectively hydrogenated for the first time using a H_8-BINOL derived phosphate **8** bearing a triphenylsilyl substituent as catalyst in high yields and ee values (Scheme 16).[29] In sharp contrast to the ATH of 2- or 4-substituted quinolines, in which chiral Brønsted acid catalyses an enantioselective hydride addition to the iminium intermediates, the Brønsted acid in this case plays a key role in catalysing an enantioseletive protonation process *via* a hydride-proton-hydride transfer cascade in the ATH of 3-substituted quinolines (Scheme 16).



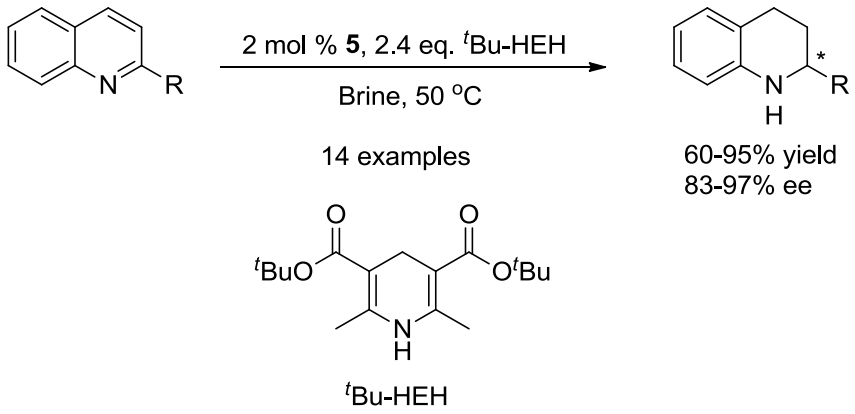




Scheme 16: Organocatalysed ATH of 3-substituted quinolines

Inspired by biological reactions, the same group later realised the first example of Brønsted acid catalysed asymmetric reduction using water as sole reaction medium, employing the principle of hydrophobic hydration.[30] Under careful scrutiny, both sterically demanding phosphoric acid and Hantzsch ester were found to be essential for the best enantioselctivity. Sodium chloride was found to slightly enhance the

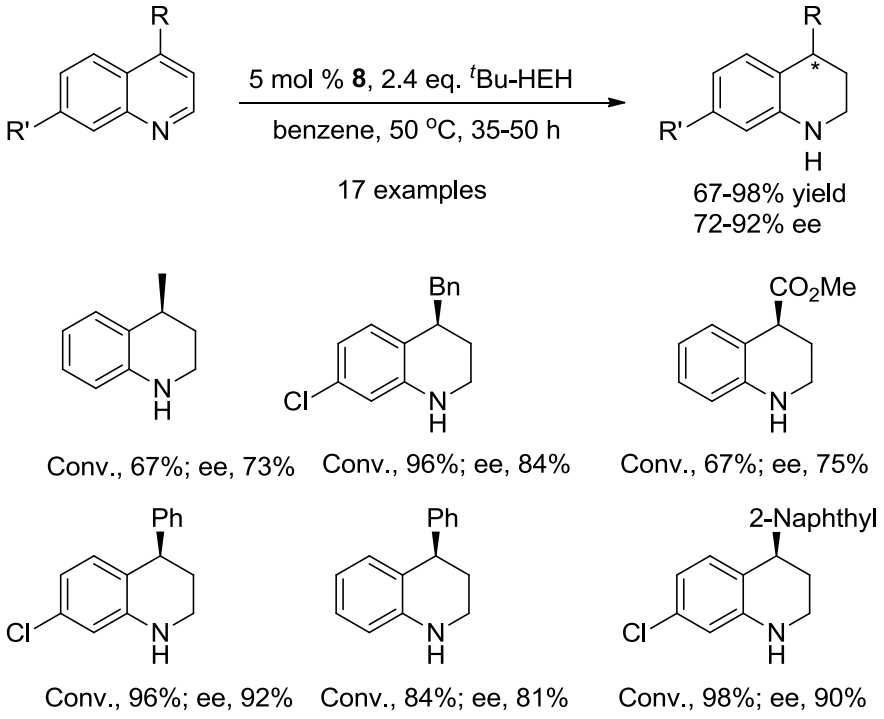
enantioselectivities. Compared to their early work using benzene as solvent, the use of aqueous medium in this process exhibits an ideal and ecologically sound system while maintaining the activity and enantioselctivity obtained in their previous work (Scheme 17).



Scheme 17: Organocatalysed ATH of quinolines in water

In 2011, the same group expanded their ATH of *N*-heterocycles catalysed by chiral phosphoric acid to more challenging and/or so-far-ignored 4-substituted quinolines.[31] Before this work, there appeared no direct asymmetric reduction routes available to prepare chiral 4-substituted-1,2,3,4-tetrahydroquinolines. A diverse collection of 4-alkyl and 4-arylsubstituted quinolines were transfer-hydrogenated by using the phosphoric acid **8** and Hanzsch ester reduction system, leading to the corresponding optically active 4-substituted tetrahydro analogues in good yields and high enantioselectivities (Scheme 18).

Chloro-containing quinolines were found to be more efficient substrates with higher yields and ee values obtained, presumably for the reason that the presence of chloro atom enhances the electrophilicity of the substrates allowing easier hydride attack.

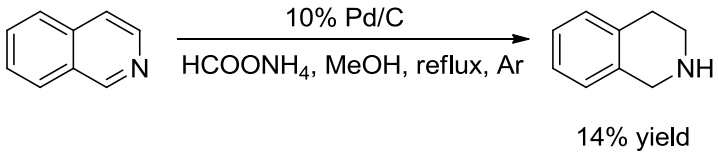


Scheme 18: Organocatalysed ATH of 4-substituted quinolines

1.2.2 TH of isoquinolines

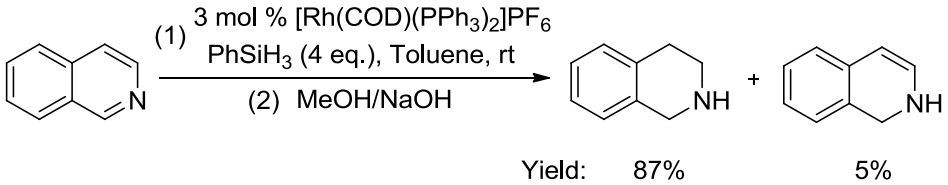
In comparison with TH of quinolines, other *N*-heterocycles including isoquinolines, quinoxalines, pyridines, indoles, etc, have been much less investigated. One of the reasons is that these compounds have stronger aromaticity than quinolines, and therefore require increased activation either of catalysts or substrates. In 1990, Joule reported the

first TH of *N*-heterocycles by employing ammonium formate as hydrogen source and Pd/C as catalyst.[12] Moderate yields could be obtained for quinolines; however, it is less efficient for isoquinolines, as can be seen in Scheme 19.



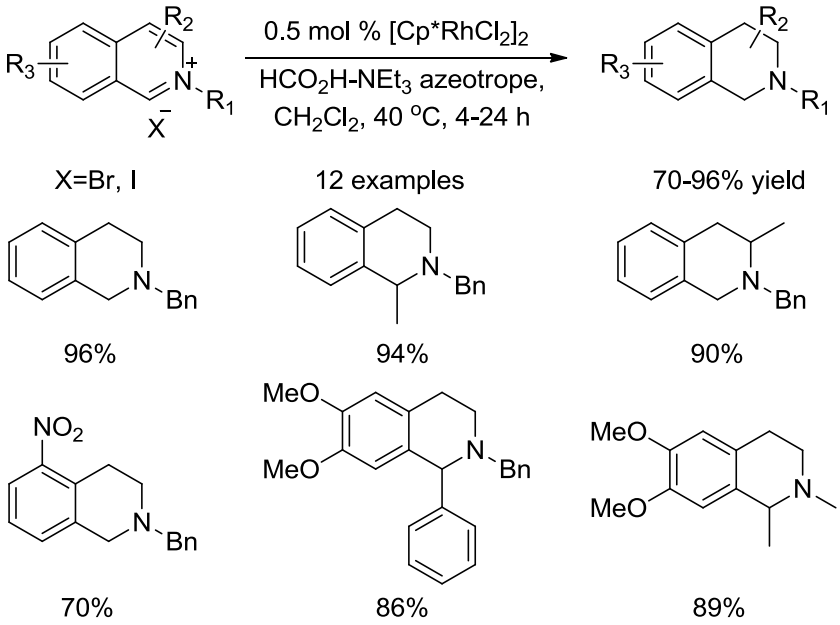
Scheme 19: Pd-catalysed TH of isoquinolines with $HCOONH_4$

Crabtree and co-workers have reported a rhodium-catalysed mild hydrosilylation of isoquinoline using silane as hydrogen source and by subsequent basic work-up, obtained tetrahydroisoquinoline as the major product (Scheme 20).[17] Key to this mild reduction was ascribed to the presence of highly active SiH_4 which was generated from initial *in situ* disproportionation of $PhSiH_3$ to Ph_2SiH_2 and SiH_4 catalysed by the same catalyst.



Scheme 20: Rh-catalysed hydrosilylation of isoquinolines

In 2006, Deng described $[Cp^*RhCl_2]_2$ catalysed TH of quaternary isoquinoline salts, an activated form of isoquinolines, using formic acid as hydrogen source under mild conditions. A range of *N*-alkyl-1,2,3,4-tetrahydroisoquinolines including naturally occurring products were obtained in good to excellent yields (Scheme 21).[32] Like the Pd-catalysed TH, debromination was also observed in this system; but nitro groups were tolerated.

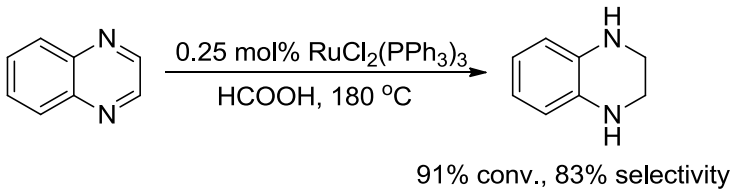


Scheme 21: Rh-catalysed TH of isoquinolinium salts

1.2.3 TH of quinoxalines

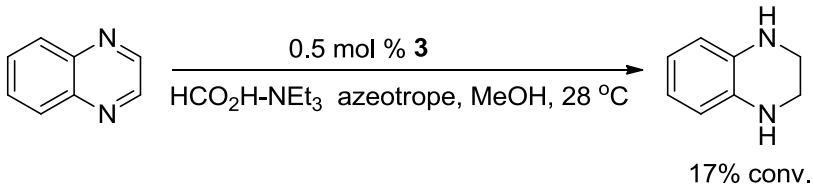
As shown in Scheme 1, the HCOOH-$RuCl_2(PPh_3)_3$ system developed by Watanabe and co-workers in 1984, could be used to transfer-hydrogenate quinolines in good yields.[10] Such system also finds utility in TH of more challenging quinoxalines in good yield and high selectivity (Scheme 22).

However, just one example was reported.



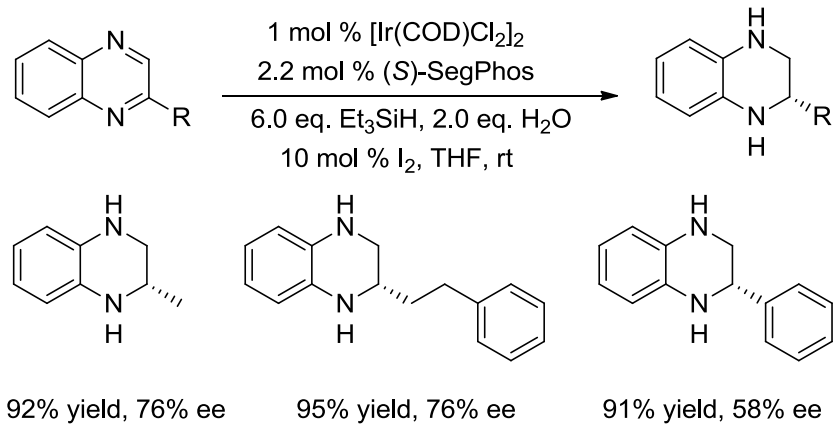
Scheme 22: Ru-catalysed TH of quinoxalines with HCOOH

In 2010, Wills and co-workers revealed that the tethered Ru-diamine complex **3** is an efficient catalyst for the TH of quinolines using HCOOH-Et_3N as hydrogen source,[21] as shown in Scheme 9. When a quinoxaline was subjected to the TH system, however, poor conversion was obtained (Scheme 23).



Scheme 23 Ru-catalysed TH of quinoxalines with HCOOH-NEt_3

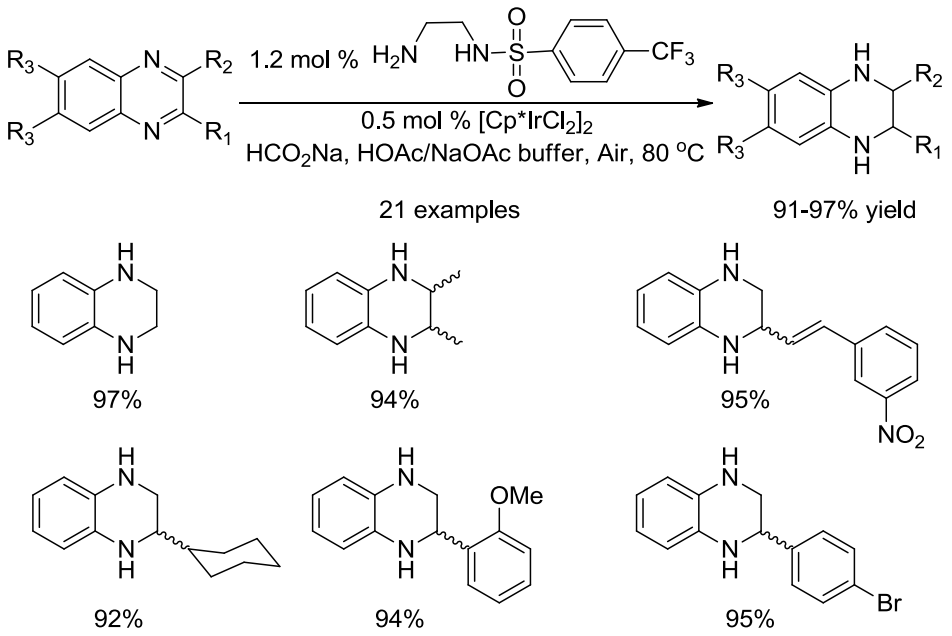
During the ATH of quinolines using water/silane as hydrogen donor,[24] Zhou and co-workers also applied the conditions to 2-substituted quinoxalines, which were reduced to tetrahydroquinoxalines in good yields and moderate enantioselectivities (Scheme 24).



Scheme 24: Ir-catalysed TH of quinoxalines with water/silane

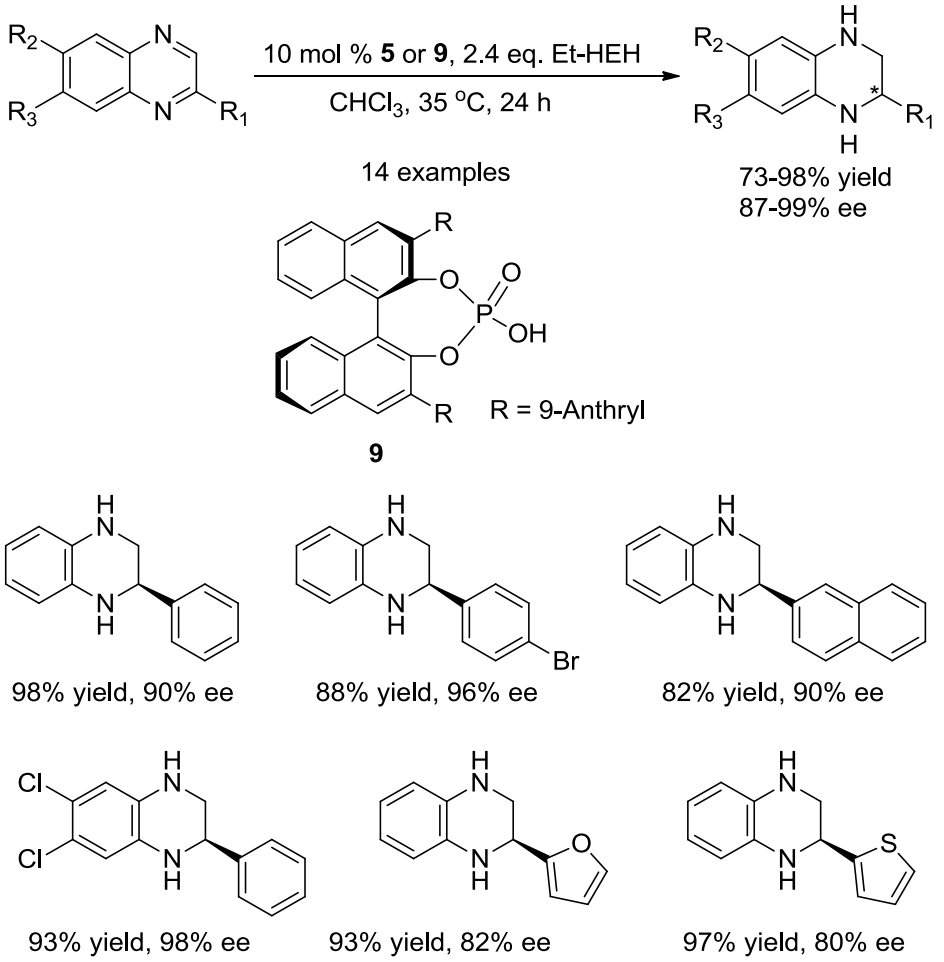
Inspired by the effect of solution pH on the TH of quinolines in water, Xu and co-workers found that a simple Ir-TsEN (TsEN = tosylated ethylene diamine) system is highly efficient for the TH of quinoxalines using aqueous formate as reducing agent.[33] A number of quinoxalines were reduced to the corresponding tetrahydro products in good to excellent yields (Scheme 25). Functional groups such as halides, nitro and conjugated alkene were observed to be well tolerated in this TH system. The HOAc/NaOAc buffer solution was found essential for good conversions by suppressing the pH fluctuation to maintain optimal pH during the entire reduction process. The ATH of quinoxalines was attempted by replacing TsEN with chiral TsDPEN which was successfully used in ATH of quinolines, only 3% ee value was obtained for the reduction of 2-methylquinoxaline, although the TH was still fast with full

conversion obtained in 2 h.



Scheme 25: Ir-catalysed TH of quinoxalines with formate in water

In 2010, Reuping and co-workers extended their organocatalytic TH of *N*-heterocycles to the prepration of chiral tetrahydroquinoxalines.[34] Employing a chiral BINOL phosphate as catalyst and Hantzsch esters as reducing agent, various 2-arylquinoxalines were reduced in good to excellent yield and enantioselectivity, which reprents the first example of highly enantioselective TH of quinoxalines (Scheme 26). Compared to the organocatalysed ATH of quinolines, the reduction of quinoxalines requires higher catalyst loading (10 mol %), and electron deficient substituents were found to enhance the enantioselectivities.

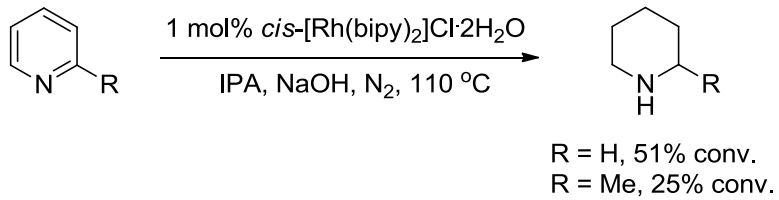


Scheme 26: Organocatalysed ATH of quinoxalines with Hantzsch esters

1.2.4 TH of pyridines

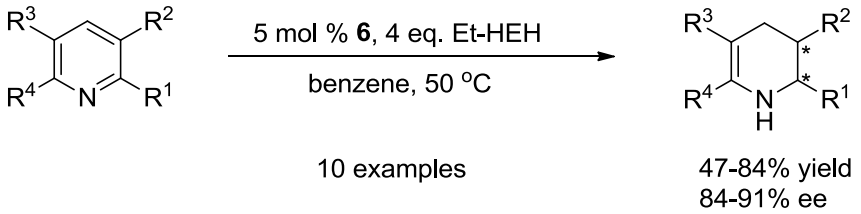
In comparison with benzo-fused *N*-heterocycles such as quinolines, isoquinolines and quinoxalines, monocyclic pyridines have much stronger aromatic stability and successful reduction often requires harsh conditions or pre-activated pyridines as substrates in order to overcome their inactive nature. As a result, there are only two examples reported for the TH of pyridines. One example was described by Frediani and co-workers in 2006 with a Rh-bipyridine catalyst and using IPA as

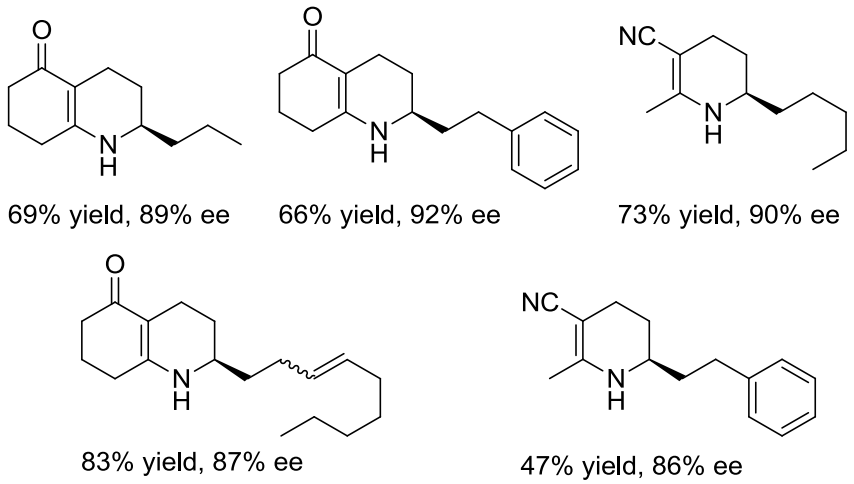
hydrogen donor.[15] Only two substrates were examined, which showed poor to moderate conversions (Scheme 27).



Scheme 27: Rh-catalysed TH of pyridines with IPA

In 2007, Reuping and co-workers disclosed the first example of ATH of pyridine derivatives adopting catalytic amount of a chiral phosphate and using Hantzsch esters as hydrogen source.[35] Several pyridines were partially reduced to the tetrahydropyridine products in moderate to high yields and moderate to good enantioselectivities (Scheme 28). The presence of EWG in the pyridine ring is crucial for the activity, enabling an easier 1,4-hydride addition.



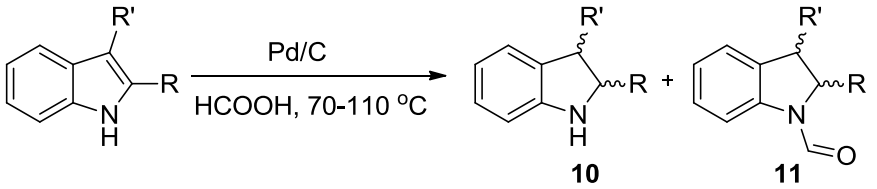


Scheme 28: Organocatalysed ATH of pyridines with Hantzsch esters

1.2.5 TH of indoles

In the 1970's, the use of formic acid as reducing agent attracted significant attention due to its use in deprotection reactions in the presence of palladium black in peptide synthesis. In 1982, Kikugawa and co-workers found that the tryptophanyl unit was reduced to its 2,3-dihydro analogue in 7% yield by using HCOOH-Pd system during the study of deprotection of the tryptophan-containing peptide. By increasing the temperature, a variety of indolines and their formylation products were obtained from TH of the corresponding indoles in reasonable to high yield,[36] as can be seen in Scheme 29. Formic acid served as hydrogen donor as well as activator by protonating the indole to form an iminium salt intermediate before reduction. The formylation was found to be enhanced when ammonium formate was introduced as

co-reductant. Given the inert nature of unprotected indoles, and the convenience of hydrolysis of formyl group, this method could be used as a practicable alternative for the preparation of indolines.

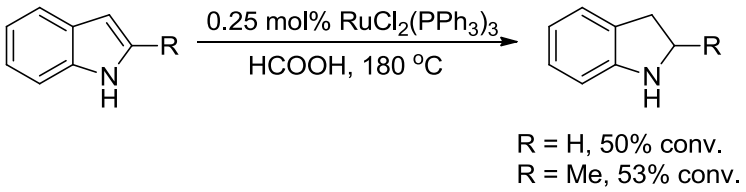


R	R'	Time [h]	Conv. of **10** [%]	Conv. of **11** [%]
H	H	0.5	31	37 (71)
CH_3	H	6	0	47
H	CH_3	1.5	0	83 (87)
$-(CH_2)_4-$		1.5	22	32 (37)
$-(CH_2)_2-NH_2Ac$		3.5	0	69 (67)
$-CH_2CH(COOEt)-NH_2Ac$		0.75	0	77 (77)

Data in parentheses were obtained by using $HCOOH/Et_3N$-HCOOH (4:1)

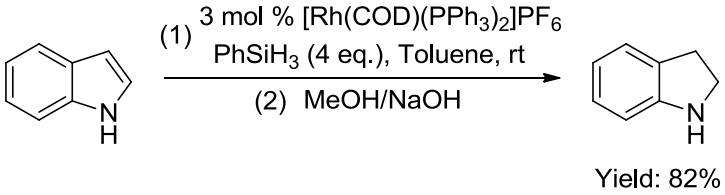
Scheme 29: Pd-catalysed TH of indoles with HCOOH

Two years later, the homogeneous catalyst $RuCl_2(PPh_3)_3$ was used to reduce indoles by Watanabe and co-workers during their extensive investigations on the TH of nitroarenes and *N*-heteroaromatic compounds.[10] Moderate conversions were obtained for two examples of indoles (Scheme 30).



Scheme 30: Ru-catalysed TH of indoles with HCOOH

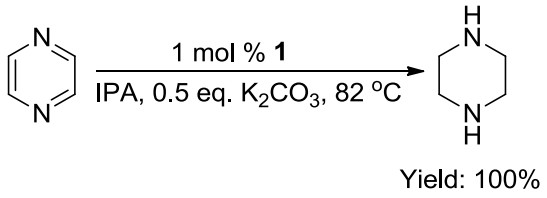
In 2008, Crabtree and co-workers observed that rhodium-catalysed hydrosilylation of indoles followed by simple hydrolysis could afford indolines in high yield (Scheme 31).[17]



Scheme 31: Rh-catalysed hydrosilylation of indoles

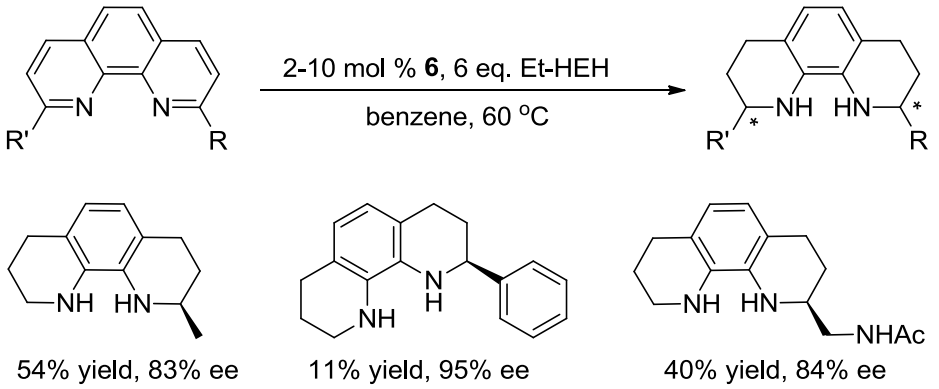
1.2.6 TH of other *N*-heteroaromatics

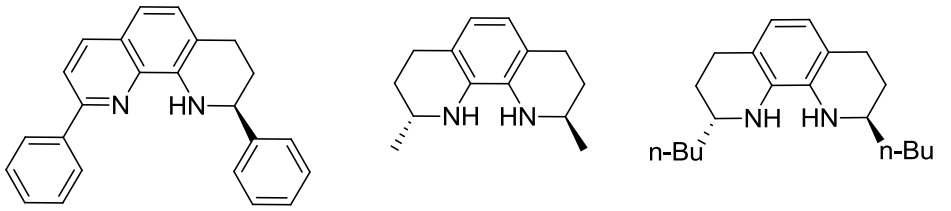
In 2008, Crabtree and co-workers realised the first example of TH of pyrazine using $[Ir(COD)(NHC)(PPh_3)]BF_4$ as catalyst and IPA as hydrogen donor (Scheme 32).[17] Although only one example was demonstrated, the full reduction observed for the inert pyrazine was still very encouraging.



Scheme 32: Ir-catalysed TH of pyrazine with IPA

In 2008, Metallinos and co-workers reported the Brønsted acid-catalysed ATH of 1,10-phenanthrolines using HEH as hydrogen source.[37] 2-Substituted and 2,9-disubstituted 1,10-phenanthrolines were successfully reduced although undesired partially reduced products were observed in a significant degree. While the reduction of 2-substituted variants occurred with poor yields but good enantioselectivity, excellent ee values were obtained for 2,9-dialkylsubstituted 1,10-phenanthrolines, albeit with poor diasteroselectivities (Scheme 33).





81% yield, 25% ee

72% yield, 99% ee
dl/meso = 3:2

88% yield, 99% ee
dl/meso = 3:2

Scheme 33: Organocatalysed TH of phenanthrolines

1.3 Conclusion and aims of the thesis

In the past several decades, the use of organic molecules, rather than H_2, as hydrogen donors in TH, has offered viable benefits for modern organic synthesis particularly in small or medium-scale processes. Appling hydrogen transfer strategy to the reduction of *N*-heteroaromatic compounds leads to the development of a number of efficient TH and ATH systems as a powerful complement to the well-established hydrogenation and emerging AH. Various *N*-heteroaromatics, such as quinolines, isoquinolines, quinoxalines, indoles and pyridines, could be transfer-hydrogenated to the corresponding saturated *N*-heterocycles with the help of many well-defined catalysts. As can be seen in Section 1.2, there are several systems currently available for the efficient TH of *N*-heteroaromatics affording multiple choices to rapidly access saturated *N*-heterocycles, particularly in their optically pure forms, which was almost impossible to imagine just ten years ago. By comparison with

hydrogenation with H_2, however, catalyst loadings for both heterogeneous and homogeneous TH are still relatively high (>1%), although gold catalysed ATH afforded comparable efficiency for some types of quinolines at 0.01% loading. Furthermore, the current ATH systems are restricted mainly to quinolines and quinoxalines, while the progress in more challenging substrates, such as isoquinolines, indoles and pyridines, has been sluggish. In addition, Hantzsch esters, which are expensive hydrogen donors (£43/gram for Et-HEH, £65/gram for ^{t}Bu-HEH, £1840/gram for Me-HEH) and of low hydrogen content (<0.8%), were predominantly used in highly enantioseletive hydrogen transfer systems, whilst much cheaper hydrogen sources, such as formic acid and IPA with much higher hydrogen content (>3.2%), have been less explored. Moreover, organocatalysed ATH commonly favors the aryl-substituted *N*-heteroaromatics while transition-metal catalysed ATH prefers the alkyl-substituted substrates. Therefore, general, efficient and economical TH and ATH methods for the reduction of *N*-heteroaromatics are still desirable.

The main aim of this thesis is to develop more efficient TH and ATH systems for *N*-heteroaromatics reduction. Chapter 2 reports a new protocol for the mild reduction of quinolines, isoquinolines and quinoxalines to corresponding tetrahydro products. The most important

discovery is the remarkable accelerating effect of the simple iodide ion, presumably by altering the reaction mechanism. Chapter 3 extends the above-mentioned system to the reduction of more challenging pyridines to afford not only piperidines but also the 3,4-unsaturated variants with high chemoselectivities. Chapter 4 presents a simple, complementary system, discovered during attempts to search for new TH catalysts, to hydrogenate *N*-heteroaromatics with H_2 using a cyclometalated iridium complex under mild conditions (ambient temperature, 1 atm H_2) without using any additives. Chapter 5 demonstrates a new reaction for the rapid preparation of various chiral piperidines from pyridines with high yields and exceptional diastereo- and enantioselectivities. Key to the reaction is the addition of a chiral amine which is incorporated into the pyridine ring by transamination during the TH process, presumably forming previously unobtainable chiral tetrahydropyridinium intermediate *in situ*.

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CHAPTER 2 IODIDE-PROMOTED TRANSFER HYDROGENATION OF *N*-HETEROAROMATIC COMPOUNDS

2.1 Introduction

Among a variety of heteroaromatics, 1,2,3,4-tetrahydro- quinolines, isoquinolines and quinoxalines are three important sub-motifs in numerous natural products, pharmaceuticals, agrochemicals, dyes and fragrances.[1] Examples are found in the naturally occurring alkaloids galipinine,[2] augustureine[2b, 3] and salsolidine,[4] the anthelmintic drug oxamniquine,[5] antiprotozoal and vomit-inducer emetine,[6] and a cholesterylester transfer protein (CETP) inhibitor (Figure 6). [7]

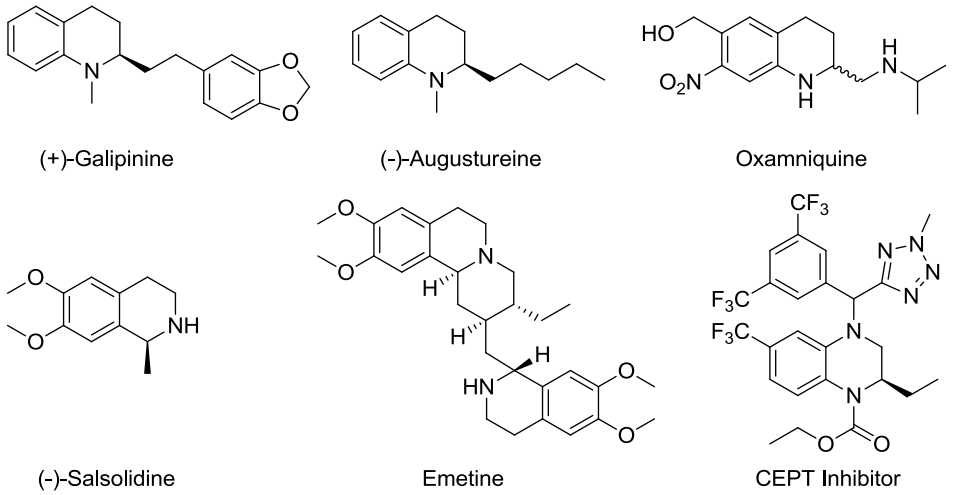
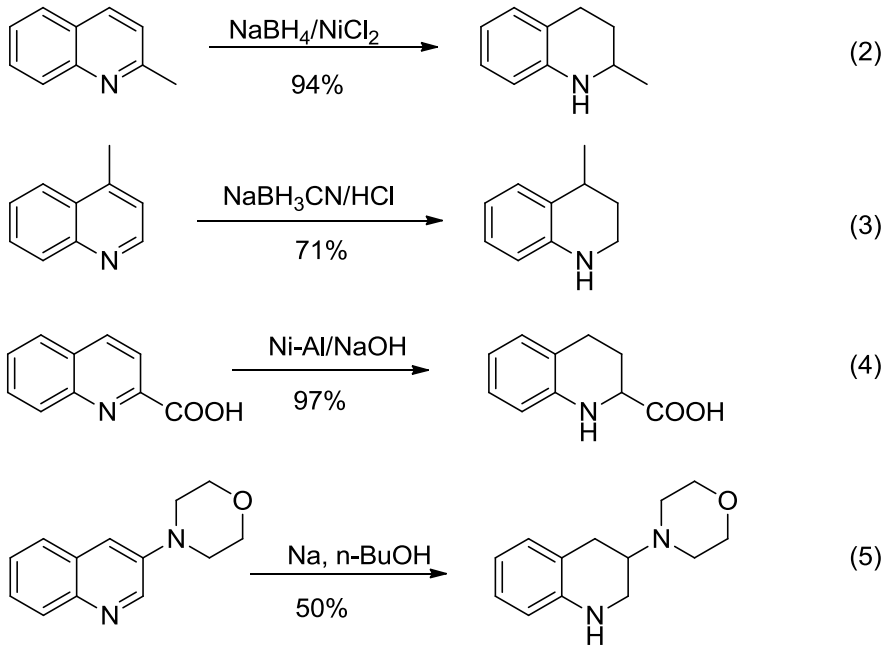


Figure 6: Examples of tetrahydro quinolines, isoquinolines and quinoxalines

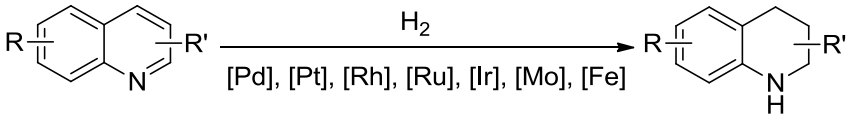
A great deal of attention has been paid to the synthesis of these compounds in both industry and academia. Considering the fact that many quinolines, isoquinolines and quinoxalines are commercially available, and there are many synthetic methods reported, their reduction would provide a general and direct method for the preparation of the

corresponding tetrahydro heterocycles. Traditionally, stoichiometric metal hydrides such as $NaBH_4$ or $NaBH_3CN$ are used as reducing reagents in the presence of Lewis or Brønsted acids (Eqs. 2 and 3). Reactive metal reagents such as Na, Ni-Al alloy (Eqs. 4 and 5) and indium have also been used for this purpose.[8] Apart from producing copious waste and using often hazardous reagents, these methods suffer from limited substrate scope, incompatibility with functionality and poor chemoselectivity.



A more attractive method is to use catalytic hydrogenation. Over the past several decades, numerous homogeneous and heterogeneous catalysts mainly based on Pt, Pd, Rh, Ru, Ir, Mo and Fe have been applied to the hydrogenation of heteroaromatics, including the asymmetric versions (Scheme 34).[9-13] The need for high catalyst loading and harsh conditions such as high H_2 pressure or high reaction

temperature, which limits the potential from industrial application, is often found for metal-catalysed hydrogenation.

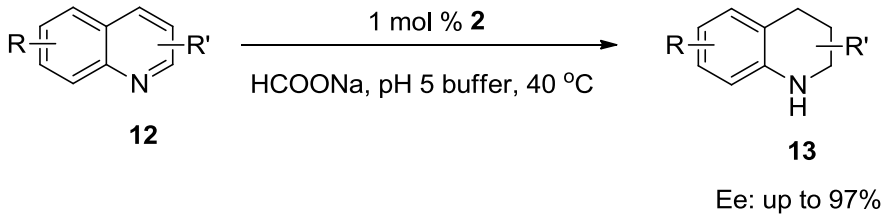


Scheme 34: Hydrogenation of quinolines with H_2

Obviating the need for hydrogen gas, which usually requires the use of specialised equipment, transfer hydrogenation (TH) offers an alternative by using isopropanol (IPA) or formate compounds. However, only a very few catalysts have been reported so far that allow for the TH of heteroaromatics, and in all cases the catalyst loading is relatively high (≥0.5 %).[14] Furthermore, in either hydrogenation or TH, there appears to be no single catalyst capable of reducing all three classes of heteroaromatics: quinolines, isoquinolines and quinoxalines. This is not surprising, as all these compounds bear a stable aromatic system which appears difficult for general TH systems to reduce. Thus, a general, efficient and mild method for TH of these heteroaromatics is highly desirable.

Our group recently reported the first example of asymmetric transfer hydrogenation (ATH) of quinolines in water with formate as the hydrogen source.[14f] Excellent enantioselectivities and yields for a variety of quinolines including some problematic substrates were obtained with a Rh-TsDPEN catalyst **2**, [Cp*RhCl(TsDPEN)][15] (TsDPEN = *N*-(p-

toluenesulfonyl)-1,2-diphenylethylenediamine)[16] under buffered aqueous conditions (Scheme 35). Further *N*-alkylating the products can afford chiral *N*-alkyl tetrahydroquinolines which structurally exist in many natural alkaloids (see Figure 1). The *N*-alkylation step is generally achieved by substitution with alkyl halides or reductive amination with aldehydes, which would afford a range of potentially bioactive analogues of the above-mentioned naturally occurring alkaloids.[2, 3] However, it would be interesting if it were possible to carry out ATH of quaternary quinoline salts so that chiral *N*-alkylated tetrahydroquinolines could be obtained directly.



Scheme 35: ATH of quinolines in water

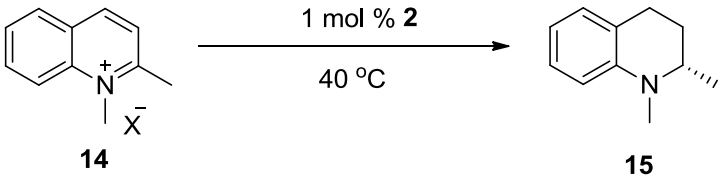
2.2 Results and Discussion

2.2.1 Discovery and further optimisation of reaction conditions

Like other common quaternary amines, *N*-alkylated quinolinium salts can be quantitatively formed by alkylation of neutral quinolines with alkyl halides. We chose the *N*-methyl-2-methylquinoline iodide salt **14a** as a benchmark substrate which can be readily prepared by alkylation of quinaldine with iodomethane. The model quaternary quinoline salt along with other substrates was purified simply by filtration and washing with

acetone. The Rh-TsDPEN which was successful for ATH of neutral quinolines was used as the catalyst (1 mol %). However, there was little reduction using sodium formate as the reductant in water at 40 °C in 24 h, under which condition quinolines were readily reduced.[14f] This was really a surprise as we believe that the quaternary form of quinoline, which is an activated form of quinoline, should be much easier to reduce. Bearing in mind the fact that the catalyst was dissolved in the top oily quinoline phase of an aqueous-organo biphasic system, we thought that the lack of reactivity for the aqueous-soluble quinoline iodide salt might be the result of insolubility of the catalyst in that system. This assumption was later proved correct. As can be seen in Scheme 36, by introducing THF as co-solvent, **14a** was successfully reduced to the corresponding *N*-methyl tetrahydro quinoline with a 69% yield. However, the product was almost racemic. We then wondered if the existence of stoichimetric iodide ion was adverse to the enantioselectivity. It was surprising to find that the ee value could be significantly improved to 73% by using *N*-methyl-2-methylquinoline SbF_6^- salt **14b** as substrate. The isolated yield also increased to 84%. The SbF_6 salt can be readily prepared by abstraction of iodide ion from the iodide substrate with $AgSbF_6$ driven by the precipitation of AgI. Other weakly coordinating anions BF_4^-, PF_6^-, $SO_3CF_3^-$ based salts were found to be efficient substrates as well, affording 53-76% ee values while maintaining the good yield. However, the cost of using stoichimetric silver salt as halide scavenger limits the

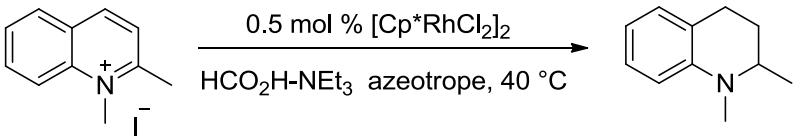
potential application of this method. Therefore, we did not continue the effort for further optimisation of the system.



HCOONa,THF/H_2O: X = I, **14a**, Ee, 5%; yield, 69%;
X = SbF_6, **14b**, Ee, 73%; yield, 84%.
HCO_2H-NEt_3 azeotrope: X = I, **14a**, Ee, 5%; yield, 95%;
X = SbF_6, **14b**, yield, <2%.

Scheme 36: ATH of quaternary quinoline salts

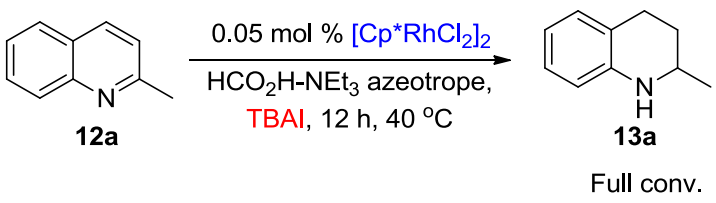
Changing the aqueous formate to the azeotropic HCO_2H/NEt_3 (ratio 2.5:1.0) mixture led to an excellent isolated yield of 95% but a very low ee value of 5% for the tetrahydro product. Somewhat surprisingly, by using the SbF_6^- salt as substrate, the reduction was totally inhibited under azeotropic HCO_2H/NEt_3 conditions (Scheme 36), which demonstrated the necessity of iodide ions for the reduction under such conditions. Noteworthy is that similar conversion was also observed under identical conditions with $[(Cp^*RhCl_2)_2]$ as catalyst, without adding the TsDPEN ligand (Scheme 37).



Scheme 37: TH of quaternary quinoline salts

Considering the significant impact on enantioselectivity when using weakly coordinating anion salts as substrates, we realised that the low ee value might result from the diamine ligand in Rh-TsDPEN being replaced by the iodide anion in the salt during the reaction. It would not be a surprise for the iodide replacement to happen as the concentration of iodide ion was 100 times greater than that of the Rh-TsDPEN catalyst **2**.

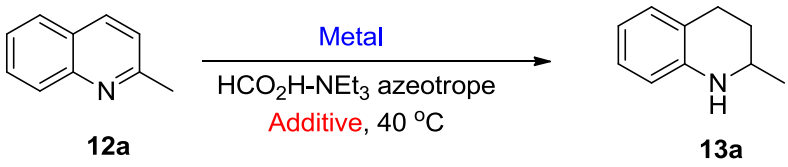
Bearing in mind the unusual effects of iodide documented in catalysis[17] and the scarcity of effective catalysts for TH of heteroaromatics,[14] we thought it would be interesting to explore whether [(Cp*$RhCl_2$)$_2$] in combination with the iodide ion would lead to a simple but highly active catalytic system. With this hypothesis in mind, we chose 2-methylquinoline **12a** (p*K*a 5.4) as a benchmark substrate, which is expected to be protonated when using formic acid (p*K*a 3.6) as the reductant. The TH was first carried out with 0.05 mol% [(Cp*$RhCl_2$)$_2$] in the azeotropic HCO_2H/NEt_3 at 40 °C. The reduction was insignificant, with only 6% yield of 2-methyl tetrahydroquinoline **13a** obtained in 12 h (Table 1, entry 2), indicating that iodide might indeed be necessary for high conversion. To our delight, in the presence of 1 or even 0.1 equivalent of an iodide salt, tetrabutylammonium iodide (TBAI), **12a** was fully converted to **13a** (Scheme 38 and Table 1, entries 3 and 4).



Scheme 38: Iodide-promoted TH of quinolines

In contrast, the analogous bromide salt TBAB is much less effective (Table 1, entry 5) and the chloride TBAC is ineffective for the acceleration of the reduction (Table 1, entry 6). The much cheaper potassium iodide KI, which is the most commercially available iodide source, was found equally effective for the TH, showing that it is the iodide anion, not the cation that promotes the catalysis (Table 1, entry 7). Remarkably, in the presence of KI, the metal loading could be further decreased to 0.01 mol % without affecting the conversion (Table 1, entry 8). Such low metal loading is rare in TH of heteroaromatics. At an even lower loading of 0.001 mol % of rhodium with 0.5 equivalent of KI added, a moderate conversion of 71% was still obtained which shows the robust nature of this catalysis, albeit in a longer reaction time (Table 1, entry 9). It yields a turnover number close to 7.1×10^4 (Table 1, entry 10), which is, to the best of our knowledge, the highest TON value ever reported in catalytic reduction of heteroaromatics. It means that 10 moles of the Rh catalyst in the presence of KI can convert about 1 million moles

Table 1. Effect of iodide on the TH of **12a**.[a]



12a **13a**

Entry	Metal, mol %[b]	Time [h]	Additive, equiv	Conv. [%][c]
1	None	12	None	NR

2	Rh, 0.1	12	None	6
3	**Rh, 0.1**	**12**	**TBAI, 1.0**	**100**
4	Rh, 0.1	15	TBAI, 0.1	100
5	Rh, 0.1	15	TBAB, 0.1	42
6	Rh, 0.1	15	TBAC, 0.1	8
7	Rh, 0.1	15	KI, 0.1	100
8	**Rh, 0.01**	**12**	**KI, 0.2**	**100**
9	Rh, 0.001	48	KI, 0.5	71
10	Ir, 0.01	12	KI, 0.2	<1
11	Ru, 0.01	12	KI, 0.2	<1
12	$RhCl_3$, 0.01	12	KI, 0.2	NR

[a] Reaction conditions: **12a** (0.5 mmol), HCO_2H-NEt_3 azeotrope (3 mL), 40 °C. [b] Rh = $[Cp^*RhCl_2]_2$, Ir = $[Cp^*IrCl_2]_2$ and Ru = $[RuCl_2(p\text{-cymene})]_2$. [c] Conversion determined by ^1H NMR of the crude reaction mixture and normalising the sum of the product and starting material integrals to 100%. NR = no reaction.

of quinolines to their tetrahydro products. However, under similar conditions, other widely used metal catalysts, $[Cp^*IrCl_2]_2$, $[RuCl_2(p\text{-cymene})]_2$ and $RhCl_3$ for example, failed to catalyse the TH (Table 1, entries 10-12).

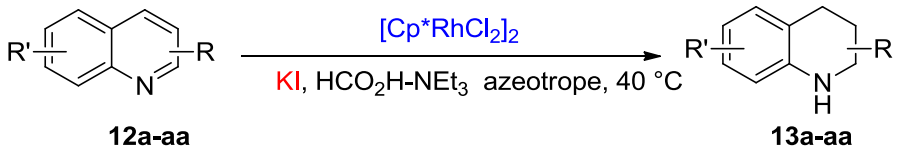
2.2.2 Substrate scope

Having identified the optimized conditions, we subjected a variety of quinoline derivatives to the TH. As can be seen from Table 2, the

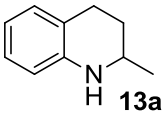
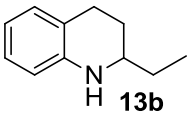
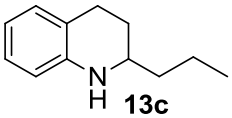
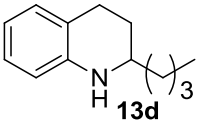
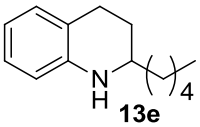
reduction affords good to excellent yields at 40 °C with 0.01-0.1 mol % catalyst. Notably, apart from the mild condition, the reaction can be carried out in air; degassing with N_2 did not show any detectable difference in yield. The reaction is not sensitive to moisture as well. Quinolines bearing various alkyl substituents at the 2-position (**12a-f**), no matter of the length of the chain, proceeded successfully to give the corresponding hydrogenated products in excellent yields (Table 2, entries 1-6). Delightedly, good to excellent yields were obtained for quinolines with bulky substituents at the 2-position (**12g-k**) (Table 2, entries 7-11), and in particular, 1,2,3,4-tetrahydro-2-*tert*-butylquinoline (**13i**) was obtained in 99% yield. In homogeneous hydrogenation, the best result previously reported for this substrate was 43% conversion after 48 hours, employing 2 mol % of a rhodium catalyst.[14g] 2,3-Disubstituted and 3-substituted quinolines (**12s**, **12t** and **12z**) (Table 2, entries 19, 20 and 26) and acridine **12u** can be smoothly reduced to 9,10-dihydroacridine **12u** (Table 2, entry 21). It is noteworthy that the isolated C=C bond in **12v**, which is often reduced in heterogeneous hydrogenation with molecular hydrogen, was well tolerated (Table 2, entry 22). A problem was encountered with the less basic 2-arylquinolines (**12w-y**) however, where good yields were only obtained with a higher metal and iodide loading as well as a longer reaction time (Table 2, entries 23-25). 4-Substituted quinolines proved problematic, affording very low conversion even with much higher catalyst loading (Table 2, entry 27). This appears to be in

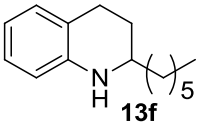
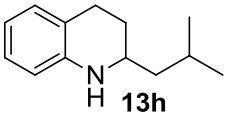
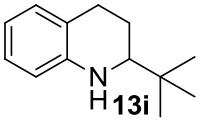
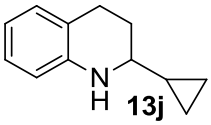
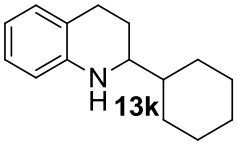
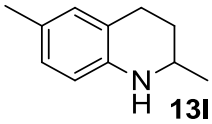
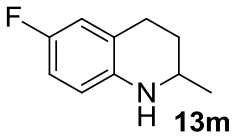
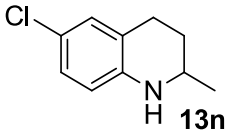
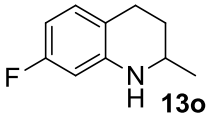
agreement with the proposed mechanism starting the reduction from 1,4-hydride addition (*vide infra*).

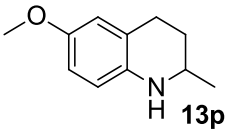
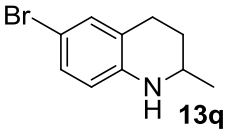
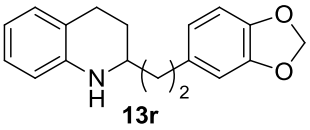
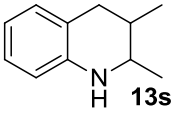
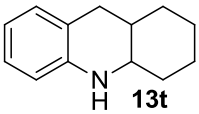
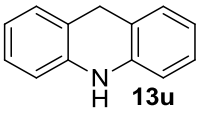
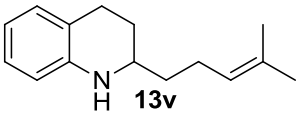
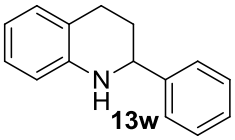
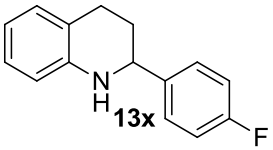
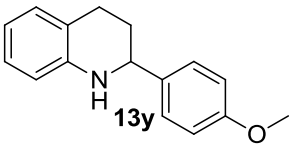
Table 2. TH of quinolines with $[Cp^*RhCl_2]_2$-KI in the HCO_2H-NEt_3 azeotrope.[a]

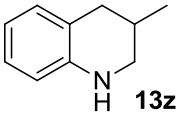
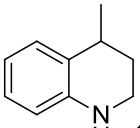


12a-aa **13a-aa**

Entry	Product	S/C[b]	Time [h]	Yield [%][c]
1	 **13a**	10000	12	91
2	 **13b**	10000	15	93
3	 **13c**	10000	12	93
4	 **13d**	10000	15	96
5	 **13e**	10000	15	84

6	 **13f**	10000	10	72
7	 **13g**	10000	15	91
8	 **13h**	10000	12	93
9	 **13i**	10000	15	99
10	 **13j**	10000	15	85
11	 **13k**	10000	11	96
12	 **13l**	10000	12	76
13	 **13m**	10000	12	74
14	 **13n**	10000	24	92
15	 **13o**	10000	12	83

16	 **13p**	10000	24	73
17	 **13q**	10000	48	83
18	 **13r**	10000	15	89
19	 **13s**	10000	20	69
20	 **13t**	10000	12	95
21	 **13u**	5000	12	98
22	 **13v**	10000	24	71
23	 **13w**	1000	48	98
24	 **13x**	1000	48	98
25	 **13y**	1000	26	94

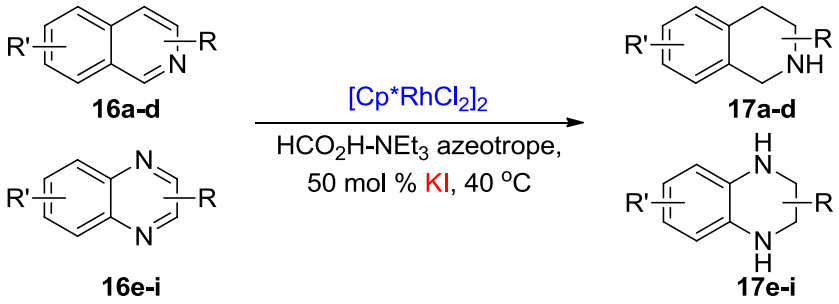
26	 **13z**	5000	12	88
27	 **13aa**	50	24	23[d]

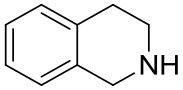
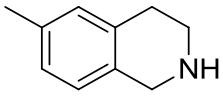
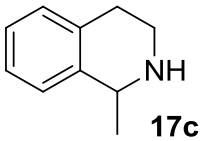
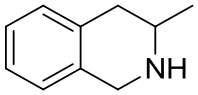
[a] Reaction conditions: **12** (0.5 mmol), $[Cp^*RhCl_2]_2$ (0.025-5 μmol), KI (0.1-0.8 mmol), HCO_2H-NEt_3 azeotrope solution (3 mL), 40 °C, 12-48 h. [b] Substrate/catalyst molar ratio. [c] Yields of isolated products. [d]Conversion determined by ^{1}H NMR of the crude reaction mixture and normalising the sum of the product and starting material integrals to 100%.

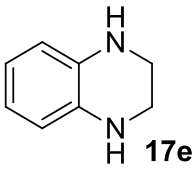
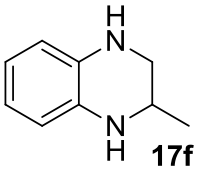
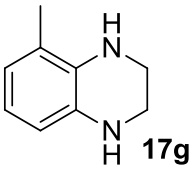
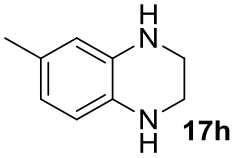
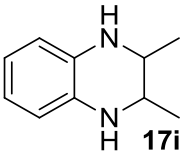
The more challenging quinoxalines and particularly isoquinolines were also attempted (Table 3). The latter has not been reduced, until now, to tetrahydroisoquinolines under TH due to their stable pyridine-like aromaticity. Higher catalyst loading was necessary for the reduction of some of these substrates, however. Thus, using 0.2 mol% rhodium loading, good to excellent yields were obtained for a range of tetrahydroisoquinolines (**17a-d**). This represents the lowest metal loading reported in any metal-catalysed hydrogenation of this class of substrates. For 2-methylisoquinoline **16c**, satisfactory yields can only be obtained by adjusting the HCOOH/Et_3N ratio from 2.5:1 to 3.5:1 (Table 3, entry 3), which demonstrated another parameter of the current system for potential optimisation. Excellent yields were also observed in the reduction of several commercially available quinoxalines (**16e-i**) (Table 3, entries 5-9) with as low as 0.02 mol % catalyst loading. The accelerating effect of

iodide was again noted. Thus, by control experiments, no reaction was observed in the TH of **16a** and **16e** when the iodide salt was omitted.

Table 3. TH of isoquinolines and quinoxalines with $[Cp^*RhCl_2]_2$-KI in HCO_2H-NEt_3.[a]

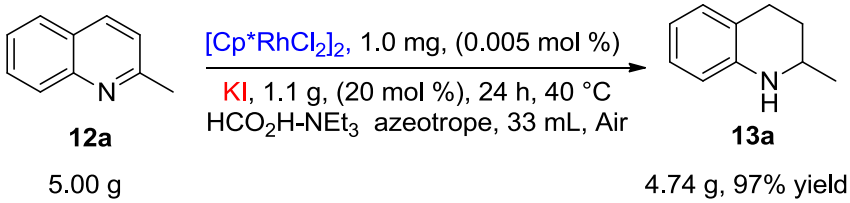


Entry	Product	S/C[b]	Time [h]	Yield [%][c]
1	 **17a**	500	24	83
2	 **17b**	500	24	95
3[d]	 **17c**	500	24	92
4	 **17d**	500	24	91

5	 **17e**	5000	12	99
6	 **17f**	5000	12	86
7	 **17g**	5000	12	92
8	 **17h**	5000	12	90
9	 **17i**	500	24	91

[a] Reaction conditions: **16** (0.5 mmol), $[Cp^*RhCl_2]_2$ (0.05-0.5 µmol), KI (0.25 mmol), HCO_2H-NEt_3 azeotrope solution (3 mL), 40 °C, 12-24 h. [b] Substrate/catalyst molar ratio. [c] Yields of isolated products. [d] HCO_2H/NEt_3 = 3.5/1.0.

To showcase the practicality of this protocol, we carried out the TH of 5 g of **12a** with 0.01 mol % rhodium (1.0 mg). The reduction afforded **13a** in 97% isolated yield in 24 h at 40 °C (Scheme 39).



Scheme 39: TH of quinoline on gram scale

2.2.3 Mechanistic investigations

The beneficial effect of iodide in asymmetric hydrogenation (AH) with H_2 has been noted in a number of instances, though the mechanistic details remain to be delineated.[11a, m, 17a, 18] In some proposed mechanisms, the presence of iodide, commonly as I_2, which is proposed to oxidise a low valent metal, Ir(I) to Ir(III) for example, was demonstrated to enhance both reactivity and enantioselectivity.[11a] The most well-known example is seen in the million tons production of (*S*)-metolachlor, an active ingredient of herbicide Dual Magnum®, which uses an Ir-Xyliphos catalyst in the presence of iodide for the AH of the imine intermediate.[19] To the best of our knowledge, no examples of iodide effect in TH are known, however.

We therefore decided to take a further insight into the rate acceleration of TH of quinolines by iodide ion. Figure 7 shows the effect of iodide concentration [I^-] on the conversion of **12a** to **13a** at 4.5 h in the HCO_2H-NEt_3 azeotrope. A dramatic increase in the reaction rate was noted when [I^-] was increased, up to 20 or 50 mol % of **12a**; thereafter the reaction rate decreased with more iodide added, suggesting that the iodide is involved in the turnover limiting step or steps prior to this step. This hypothesis finds support from the conversion-time profiles of TH of **12a** shown in Figure 8, obtained by using catalysts $[Cp^*RhCl_2]_2$, $[Cp^*RhI_2]_2$, and $[Cp^*RhCl_2]_2$ in the presence of 20 mol% KI (1 mol %

rhodium in each case). Clearly, the iodo-dimer $[Cp^*RhI_2]_2$ catalysed significantly faster TH than its chloro analogue $[Cp^*RhCl_2]_2$. More

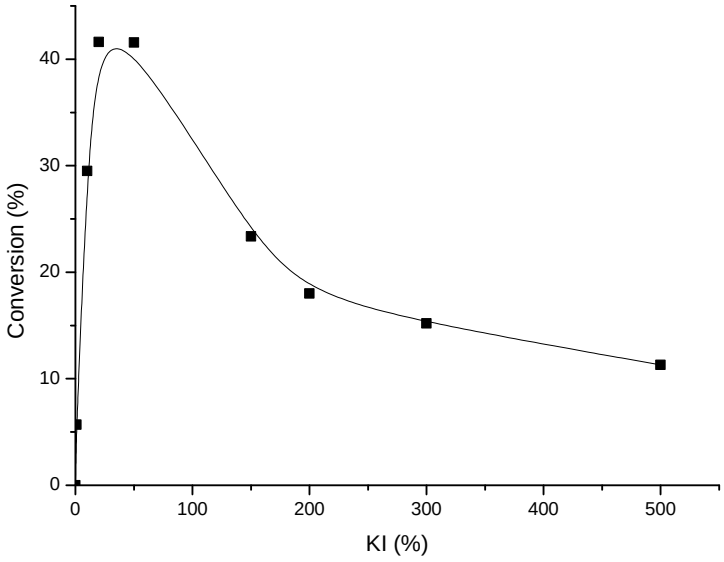


Figure 7: Effect of the concentration of iodide on the transfer hydrogenation of **12a** (0.5 mmol) catalysed by $[Cp^*RhCl_2]_2$ (0.05 mol %). Reactions were carried out in the HCO_2H-NEt_3 azeotrope (3 mL) for 4.5 h at 40 ℃.

interestingly, the kinetics for these two catalysts appears distinctively different. With the chloro catalyst, the reduction appears to be zero order in the concentration of **12a** which means decreasing [**12a**] during the reaction does not decrease the reaction rate. However, in the case of the iodo catalyst, the profile suggests a rate dependence on [**12a**]. Decreasing [**12a**] as the reaction proceeds decreases the rate. In the presence of excess I^- (20 mol % KI), the reduction became faster still, with the initial rate being ca 7 times that obtained with $[Cp^*RhI_2]_2$ and ca 40 times that with $[Cp^*RhCl_2]_2$ alone! These results suggests that in the presence of

excess I^-, an active Cp*Rh-iodo catalyst is generated in situ from $[Cp^*RhCl_2]_2$. The presence of excess I^- alters the hydrogenation kinetics, with the turnover rate limited by hydride formation with $[Cp^*RhCl_2]_2$ but more likely by hydride transfer when iodide is added.

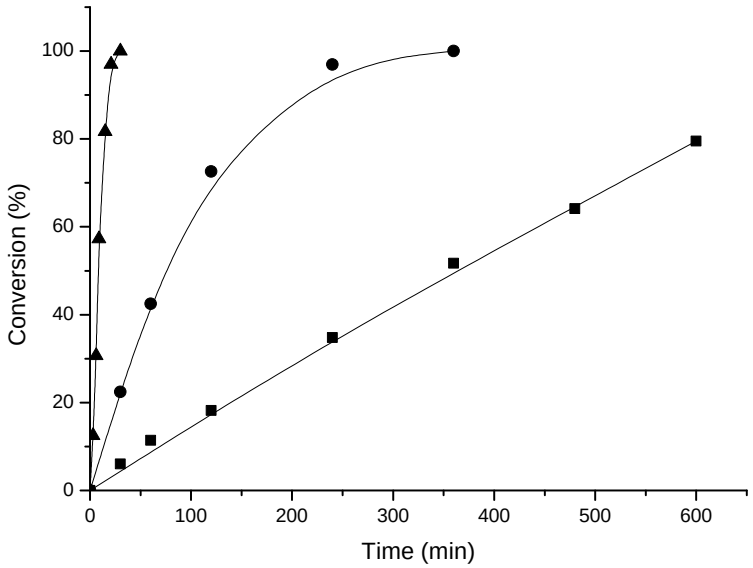
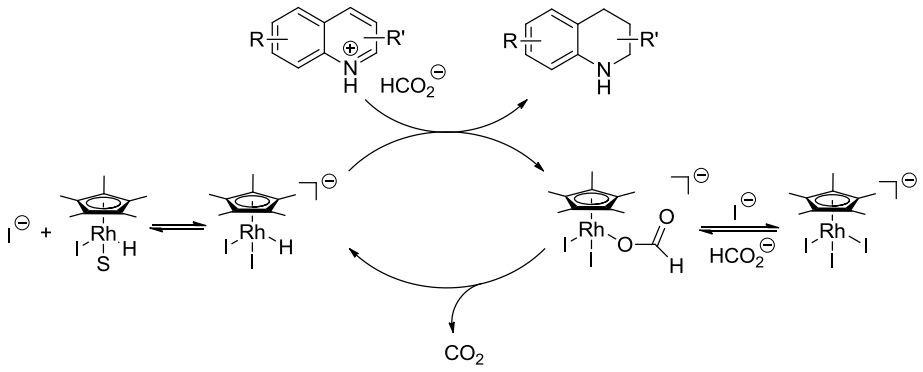


Figure 8: Effect of iodide anion on the transfer hydrogenation of **12a (**0.8 mmol) catalysed by $[Cp^*RhX_2]_2$ (0.05 mol %) (■ X = Cl, ● X = I, ▲ X = Cl plus 20 mol% KI). Reactions were carried out in the HCO_2H-NEt_3 azeotrope (5 mL) at 40 ℃.

A plausible mechanism is shown in Scheme 40. The key feature of the mechanism is that the substrate, which is most likely to be protonated under the acidic conditions, is reduced by an anionic diiodo Rh-H, probably *via* a 1,4-addition pathway as indicated by deuterium labelling. As shown in Figure 9, when using DCOOH-NEt_3, full deuteration at the C2 and C4 position of 2-methylquinoline **12a** took place. This is consistent with a 1,4-hydride addition pathway, in which the

hydride/deutride is first added to the C4 position of protonated **12a**, affording an enamine which isomerises into an iminium species under the acidic condition. Finally, addition of a second hydride/deutride at the C2 leads to the product observed. In support of this, 4-methyl quinolone was much more difficult to reduce, showing a 23% conversion of **13aa** at S/C = 50 and 50 mol % KI after 24 h reaction time (see Table 2, entry 27). The anionic charge is quite likely to make the hydride more hydridic, and this would be reinforced by the stronger bonding of the soft iodide to Rh(III) and its stronger "trans effect" than the hard chloride,[20] facilitating hydride transfer to the protonated substrate. Increasing [I^-] increases the concentration of the hydride and hence the rate; however, when [I^-] becomes too high, the equilibrium shown in Scheme 40 will favor the triiodo species formation, decreasing the concentration of active catalyst and so the rate. Therefore, a maximum is expected in the conversion-[I^-] profile seen in Figure 7.



Scheme 40: A possible mechanism for the Cp*Rh(III)-catalysed hydrogenation of quinoline promoted by iodide

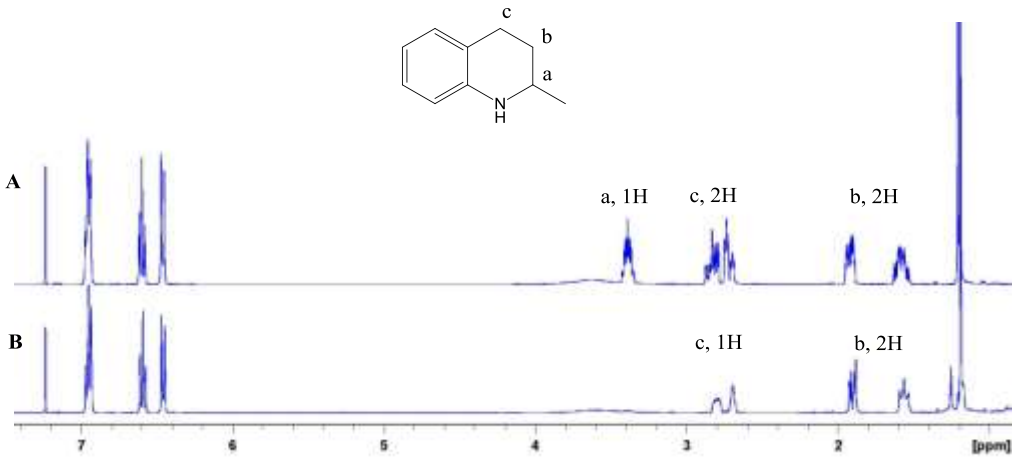
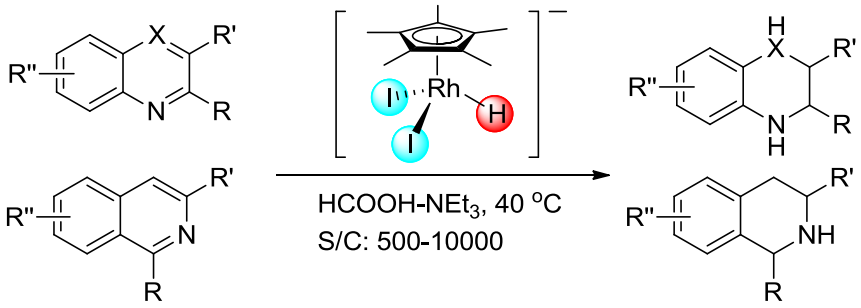


Figure 9: Deuteration experiment of iodide-promoted transfer hydrogenation of **12a** catalysed by $[Cp^*RhCl_2]_2$. (A) with HCOOH-NEt_3 azeotrope; (B) with DCOOH-NEt_3 azeotrope.

2.3 Conclusions and future work

We have developed a new protocol for the reduction of quinolines, isoquinolines and quinoxalines under mild conditions (Scheme 41). The most significant discovery is the remarkable accelerating effect of the simple iodide ion, which accelerates the TH, presumably by altering the reaction mechanism. The reduction is air and moisture stable, practical and operationally simple, providing a valuable alternative to currently used methods for heterocycle reduction. This protocol can efficiently reduce a range of *N*-heteroaromatics including 2-, 3-, 6-, 7-substituted, 2,3-disubstituted quinolines, 1-, 3-, 6-substituted isoquinolines and 2-, 5-, 6-substituted quinoxalines .



Scheme 41: Summary of iodide-promoted TH of heteroaromatics

However, for the quinolines bearing a functional group at the 2 or 8 position and 4-substituted, the reaction either became very sluggish or was almost completely inhibited. Future work may focus on the application of this iodide-promoted, highly active reduction system to more challenging *N*-heterocycles, such as pyridines and pyrazines, affording industrially valuable piperidines and piperazines. Searching a more structurally rigid chiral catalyst, which may tolerate excessive iodide ion, could lead to ATH with much lower catalyst loading than currently reported asymmetric systems.

2.4 Experimental

2.4.1 General information

Unless otherwise specified, the chemicals were obtained commercially from Aldrich, Alfa Aesar or TCI and used without further purification. Silica gel plates (GF254) were used for TLC monitoring and silica gel (230-400 mesh) was used for running column chromatography.

2-Methylquinoline **12a** was purchased from Aldrich and purified by flash column chromatography. Formic acid-triethyl amine azeotrope was distilled prior to use. NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer with TMS as the internal standard. The mass spectra were obtained by chemical ionization (CI). Quinolines **12b**-**k**, **12r**-**t**, and **12v**-**y** were prepared according to the literature.[21a] The NMR and elemental analysis data for the synthesized $[Cp^*RhI_2]_2$ were consistent with related literature.[21b] HPLC analysis was performed on Gilson UV/VIS-151 equipped with an OJ column purchased from Daicel Chemical Industries.

2.4.2 General procedure for TH of *N*-heteroaromatics

A carousel reaction tube containing a magnetic stirring bar and the $[Cp^*RhCl_2]_2$ dimer (0.0155 mg, 0.025 μmol, measured using a stock DCM solution), 2-methylquinoline (**12a**, 72 mg, 0.5 mmol) and potassium iodide (17 mg, 0.1 mmol) in 5 mL HCOOH-Et_3N azeotrope was sealed without degassing and placed in a carousel reactor. The reaction mixture was stirred at 40 °C for the time indicated, cooled to room temperature and then basified with an aqueous solution of KOH. The resulting mixture was extracted with ethyl acetate (3×5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the product was purified by flash column chromatography using hexane/ethyl acetate as eluant. For substrates **13a**, **17e** and **17i**, further hydrolysis of the *N*-formyl byproducts were performed under the

following condition according to the literature:[21c] An aqueous solution of **18** (crude, about 0.5 mmol) in 20% NaOH (5 mL) was stirred under reflux (110 °C) for 5 h. After cooling, the mixture was extracted by ethyl acetate (3×5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure before ^1H NMR analysis of the residue oil, which showed **18** was fully converted to **13a**. For substrates **13z, 17a-17d, 17f-17h,** hydrolysis of corresponding *N*-formyl byproducts were done under the following condition according to the literature:[21d] A 10% NaOH aqueous solution was introduced to a stirring crude mixture resulting from above substrates in 5 mL EtOH, the mixture was heated under the temperature and time indicated. The cooled mixture was extracted with ethyl acetate (3×5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the product was purified by flash column chromatography using hexane/ethyl acetate or dichloromethane/methanol as eluant.

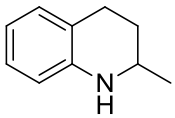
2.4.3 Deuteration experiments

In a carousel reaction tube containing a magnetic stirring bar was charged $[Cp^*RhCl_2]_2$ dimer (1.3 mg, 0.002 mmol), 2-methylquinoline **12a** (41 mg, 0.27 mmol) and potassium iodide (17 mg, 0.1 mmol). The pre-prepared DCOOH-Et_3N mixture (DCOOH, 5 mmol, 0.20 mL; Et_3N, 2 mmol, 0.28 mL) was then introduced into the reaction tube, which was placed in a carousel reactor. The reaction mixture was stirred at 40 °C for 3 h and TLC indicated that the reaction was finished. After cooling to

room temperature and basifying with an aqueous solution of K_2CO_3, the resulting mixture was extracted with ethyl acetate (3×5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to afford the pure product **13a** (27 mg), which was then analysed by ^{1}H NMR. ^{1}H NMR analysis showed indicates full deuteration at the C2 and C4 of 2-methylquinoline.

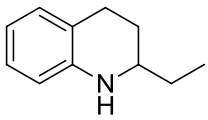
2.5 Analytical data of isolated products

All analytical data are in agreement with those previously reported in the literature, which is referenced accordingly.



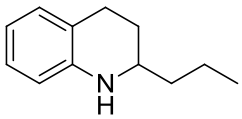
13a **2-Methyl-1,2,3,4-tetrahydroquinoline (13a):**[14f] TH of **12a**: for 0.5 mmol (72 mg) scale, 91% isolated yield and full conversion in 12 h, 20 mol % KI, S/C = 10000; for 33.7 mmol (5.00 g) scale, 97% isolated yield and full conversion in 24 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.96-6.93 (m, 2H), 6.59 (td, *J* = 7.4, 1.1 Hz, 1H), 6.46 (dd, *J* = 8.4, 1.0 Hz, 1H), 3.43-3.36 (m, 1H), 2.87-2.79 (m, 1H), 2.75-2.68 (m, 1H), 1.94-1.88 (m, 1H), 1.62-1.53 (m, 1H), 1.19 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.2, 129.7, 127.1, 121.5, 117.4, 114.5, 47.6, 30.6, 27.0, 23.1; MS (CI, *m/z*, %) 148 (100)

$[M+H]^+$; Anal. calcd. for $C_{10}H_{13}N$: C, 81.59; H, 8.90; N, 9.51; Found: C, 81.40; H, 8.94; N, 9.54.



13b

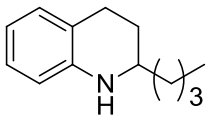
2-Ethyl-1,2,3,4-tetrahydroquinoline (13b):[14f] 93% isolated yield and full conversion in 15 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.97-6.93 (m, 2H), 6.59 (td, *J* = 7.4, 1.2 Hz, 1H), 6.48-6.45 (m, 1H), 3.71 (br, 1H), 3.16 (ddt, *J* = 12.8, 6.4, 3.3 Hz, 1H), 2.85-2.69 (m, 2H), 1.99-1.93 (m, 1H), 1.63-1.48 (m, 3H), 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.1, 129.6, 127.1, 121.9, 117.3, 114.5, 53.5, 29.8, 28.0, 26.8, 10.5; MS (CI, *m/z*, %) 162 (100) $[M+H]^+$; Anal. calcd. for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69; Found: C, 81.83; H, 9.42; N, 8.72.



13c

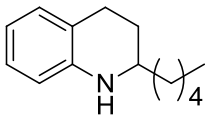
2-Propyl-1,2,3,4-tetrahydroquinoline (13c):[14f] 93% isolated yield and full conversion in 12 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.96-6.93 (m, 2H), 6.58 (td, *J* = 7.4 , 1.0 Hz, 1H), 6.45 (dd, *J* = 8.5, 1.2 Hz, 1H), 3.73 (br, 1H), 3.27-3.21 (m, 1H), 2.84-2.68 (m, 2H), 1.98-1.91 (m, 1H), 1.63-1.54 (m, 1H), 1.50-1.36 (m, 4H), 0.95 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.2, 129.7, 127.1, 121.8, 117.3, 114.5, 51.7, 39.3, 28.6, 26.9, 19.3, 14.7;

MS (CI, *m/z*, %) 176 (100) $[M+H]^+$; Anal. calcd. for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99; Found: C, 82.15; H, 9.83; N, 8.00.



13d

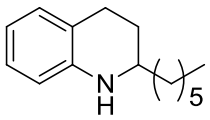
2-Butyl-1,2,3,4-tetrahydroquinoline (13d):[14f] 96% isolated yield and full conversion in 15 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.97-6.93 (m, 2H), 6.59 (td, *J* = 7.3, 1.0 Hz, 1H), 6.47 (d, *J* = 8.2 Hz, 1H), 3.74 (brs, 1H), 3.23 (ddt, *J* = 9.4, 6.4, 3.3 Hz, 1H), 2.85-2.69 (m, 2H), 1.99-1.92 (m, 1H), 1.64-1.54 (m, 1H), 1.50-1.46 (m, 2H), 1.42-1.32 (m, 4H), 0.95-0.91 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.1, 129.7, 127.1, 121.8, 117.5, 114.5, 52.0, 36.9, 28.6, 28.4, 26.9, 23.3, 14.5; MS (CI, *m/z*, %) 190 (100) $[M+H]^+$; Anal. calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40; Found: C, 82.32; H, 10.14; N, 7.43.



13e

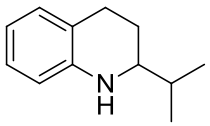
2-Pentyl-1,2,3,4-tetrahydroquinoline (13e):[14f] 84% isolated yield and 96% conversion in 15 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.96-6.93 (m, 2H), 6.58 (t, *J* = 7.3 Hz, 1H), 6.46 (d, *J* = 7.6 Hz, 1H), 3.74 (br, 1H), 3.22 (ddt, *J* = 9.4, 6.3, 3.3 Hz, 1H), 2.84-2.68 (m, 2H), 1.98-1.92 (m, 1H), 1.63-1.54 (m, 1H), 1.51-1.26 (m, 8H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.1, 129.7, 127.1, 121.8, 117.3, 114.5, 52.0, 37.1, 32.4, 28.6, 26.9, 25.8,

23.1, 14.5; MS (CI, *m/z*, %) 204 (100) $[M+H]^+$; Anal. calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89; Found: C, 82.31; H, 10.45; N, 6.90.



13f

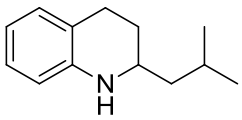
2-Hexyl-1,2,3,4-tetrahydroquinoline (13f):[14f] 72% isolated yield and 90% conversion in 10 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.97-6.93 (m, 2H), 6.59 (td, *J* = 7.4, 0.9 Hz, 1H), 6.48-6.46 (m, 1H), 3.75 (brs, 1H), 3.23 (ddt, *J* = 9.5, 6.3, 3.3 Hz, 1H), 2.85-2.69 (m, 2H), 1.98-1.92 (m, 1H), 1.64-1.54 (m, 1H), 1.51-1.26 (m, 10 H), 0.91-0.88 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 144.6, 129.1, 126.5, 121.2, 116.7, 113.9, 51.4, 36.6, 31.7, 29.4, 28.0, 26.3, 25.5, 22.5, 13.9; MS (CI, *m/z*, %) 218 (100) $[M+H]^+$; Anal. calcd. for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.44; Found: C, 82.85; H, 10.66; N, 6.39.



13g

2-Isopropyl-1,2,3,4-tetrahydroquinoline (13g):[14f] 91% isolated yield and full conversion in 15 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.97-6.93 (m, 2H), 6.58 (td, *J* = 7.4, 1.0 Hz, 1H), 6.47 (d, *J* = 8.2 Hz, 1H), 3.76 (brs, 1H), 3.03 (ddd, *J* = 9.9, 5.9, 2.9 Hz, 1H), 2.84-2.69 (m, 2H), 1.94-1.88 (m, 1H), 1.74-1.60 (m, 2H), 0.98 (dd, *J* = 10.3, 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.4, 129.6, 127.1, 121.9, 117.2, 114.4, 57.7, 32.9, 27.1, 24.9,

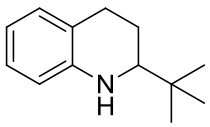
19.0, 18.7; MS (CI, *m/z*, %) 176 (100) $[M+H]^+$; Anal. calcd. for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99; Found: C, 82.24; H, 9.91; N, 7.97.



13h

2-Isobutyl-1,2,3,4-tetrahydroquinoline (13h):[14f]

93% isolated yield and full conversion in 12 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.97-6.93 (m, 2H), 6.59 (td, *J* = 7.4, 1.0 Hz, 1H), 6.48-6.45 (m, 1H), 3.74 (brs, 1H), 3.35-3.29 (m, 1H), 2.82-2.73 (m, 2H), 1.97-1.91 (m, 1H), 1.80-1.70 (m, 1H), 1.63-1.53 (m, 1H), 1.44-1.29 (m, 2H), 0.94 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.1, 129.7, 127.1, 121.8, 117.3, 114.5, 49.7, 46.3, 29.0, 26.8, 24.9, 23.6, 22.9; MS (CI, *m/z*, %) 190 (100) $[M+H]^+$; Anal. calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40; Found: C, 82.50; H, 10.09; N, 7.37.

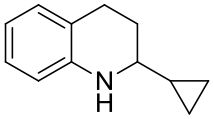


13i

2-(*tert*-Butyl)-1,2,3,4-tetrahydroquinoline (13i):[14g]

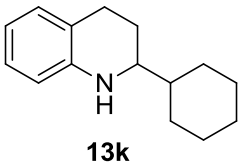
99% isolated yield and full conversion in 15 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.97-6.92 (m, 2H), 6.57 (td, *J* = 7.4, 1.1 Hz, 1H), 6.48 (d, *J* = 7.9 Hz, 1H), 3.80 (br, 1H), 2.96 (dd, *J* = 11.0, 2.6 Hz, 1H), 2.81-2.73 (m, 2H), 1.97 (ddt, *J* = 12.8, 5.4, 2.7 Hz, 1H), 1.64-1.53 (m, 1H), 0.96 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.9, 129.4, 127.1, 121.9, 117.1, 114.5, 61.4, 33.8, 27.9, 26.5, 23.6; MS

(CI, *m/z*, %) 190 (100) $[M+H]^+$; Anal. calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40; Found: C, 82.22; H, 10.09; N, 7.37.



13j

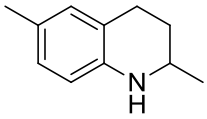
2-Cyclopropyl-1,2,3,4-tetrahydroquinoline (13j):[14f] 85% isolated yield and 95% conversion in 15 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.03-6.99 (m, 2H), 6.64 (td, *J* = 7.3, 1.1 Hz, 1H), 6.53 (d, *J* = 7.7 Hz, 1H), 4.01 (br, 1H), 2.89-2.79 (m, 2H), 2.45 (td, *J* = 9.4, 2.6 Hz, 1H), 2.16-2.10 (m, 1H), 1.89-1.79 (m, 1H), 0.99-0.90 (m, 1H), 0.62-0.53 (m, 2H), 0.33-0.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 142.7, 127.3, 124.8, 119.3, 114.9, 111.9, 55.6, 26.4, 24.8, 15.1, 1.1, 0.0; MS (CI, *m/z*, %) 174 (100) $[M+H]^+$; Anal. calcd. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.08; Found: C, 83.33; H, 8.79; N, 7.96.



13k

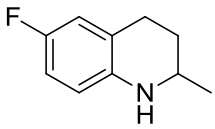
2-Cyclohexyl-1,2,3,4-tetrahydroquinoline (13k):[14f] 96% isolated yield and full conversion in 11 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.96-6.92 (m, 2H), 6.57 (td, *J* = 7.3, 0.8 Hz, 1H), 6.46 (d, *J* = 7.9 Hz, 1H), 3.79 (brs, 1H), 3.02 (ddd, *J* = 9.6, 6.2, 3.1 Hz, 1H), 2.82-2.67 (m, 2H), 1.94-1.87 (m, 1H), 1.86-1.76 (m, 4H), 1.73-1.63 (m, 2H), 1.41-1.31 (m, 1H), 1.30-0.96 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.4, 129.6, 127.1, 121.9, 117.1,

114.4, 57.0, 42.9, 29.6, 29.2, 27.1, 27.0, 26.8, 26.7, 25.0; MS (CI, *m/z*, %) 216 (100) $[M+H]^+$; Anal. calcd. for $C_{15}H_{21}N$: C, 83.67; H, 9.83; N, 6.50; Found: C, 83.65; H, 9.79; N, 6.49.



13l

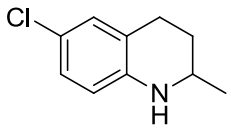
2,6-Dimethyl-1,2,3,4-tetrahydroquinoline (13l):[14f] 76% isolated yield and full conversion in 12 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.78-6.76 (m, 2H), 6.40 (d, *J* = 7.7 Hz, 1H), 3.39-3.31 (m, 1H), 2.85-2.77 (m, 1H), 2.72-2.65 (m, 1H), 2.20 (s, 3H), 1.93-1.88 (m, 1H), 1.62-1.52 (m, 1H), 1.19 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 142.9, 130.2, 127.6, 126.7, 121.6, 114.7, 47.7, 30.8, 27.0, 23.0, 20.8; MS (CI, *m/z*, %) 162 (100) $[M+H]^+$; Anal. calcd. for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69; Found: C, 81.58; H, 9.46; N, 8.26.



13m

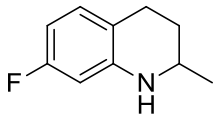
6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (13m):[14f] 74% isolated yield in 12 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.69-6.65 (m, 2H), 6.41-6.38 (m, 1H), 3.38-3.30 (m, 1H), 2.86-2.77 (m, 1H), 2.72-2.66 (m, 1H), 1.94-1.88 (m, 1H), 1.60-1.50 (m, 1H), 1.20 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 155.9 (d, J_{CF} = 233.2 Hz), 141.3, 122.9 (d, J_{CF} = 6.6 Hz), 115.8 (d, J_{CF} = 21.5 Hz), 115.2 (d, J_{CF} = 7.6 Hz), 113.6 (d, J_{CF} = 22.3 Hz),

47.7, 30.2, 27.1, 22.9; HRMS for $C_{10}H_{13}FN$ $[M+H]^+$: m/z calcd. 166.1027, found 166.1023.



13n

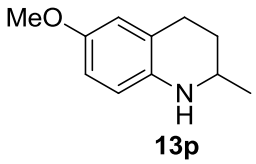
6-Chloro-2-methyl-1,2,3,4-tetrahydroquinoline (13n):[14f] 92% isolated yield and 98% conversion in 24 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.92-6.88 (m, 2H), 6.38 (d, *J* = 8.4 Hz, 1H), 3.69 (brs, 1H), 3.41-3.33 (m, 1H), 2.83-2.75 (m, 1H), 2.72-2.65 (m, 1H), 1.94-1.87 (m, 1H), 1.59-1.49 (m, 1H), 1.20 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 143.7, 129.2, 126.9, 123.0, 121.7, 115.3, 47.5, 30.1, 26.9, 22.9; MS (CI, *m/z*, %) 182:184 = 3:1 (100) $[M+H]^+$; Anal. calcd. for $C_{10}H_{12}ClN$: C, 66.12; H, 6.66; N, 7.71; Found: C, 66.25; H, 6.72; N, 7.61.



13o

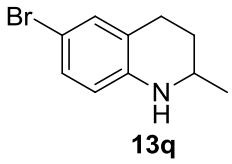
7-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (13o):[14f] 83% isolated yield and 93% conversion in 12 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.85 (t, *J* = 7.4 Hz, 1H), 6.27 (td, *J* = 8.5, 2.5 Hz, 1H), 6.14 (dd, *J* = 10.9, 2.5 Hz, 1H), 3.76 (brs, 1H), 3.38 (ddq, *J* = 9.7, 6.4, 3.1 Hz, 1H), 2.79-2.64 (m, 2H), 1.94-1.88 (m, 1H), 1.59-1.49 (m, 1H), 1.19 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 162.5 (d, J_{CF} = 238.9 Hz), 146.3 (d, J_{CF} = 10.4 Hz), 130.5 (d, J_{CF} = 9.8 Hz), 116.9 (d, J_{CF} = 2.4 Hz), 103.7 (d, J_{CF} =

21.3 Hz), 100.5 (d, J_{CF} = 24.3 Hz), 47.4, 30.4, 26.4, 22.9; HRMS for $C_{10}H_{13}FN$ $[M+H]^+$: m/z calcd. 166.1027, found 166.1024.



13p

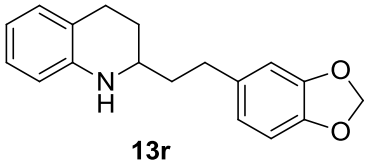
6-Methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (13p):[14f] 73% isolated yield and 97% conversion in 24 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.60-6.56 (m, 2H), 6.44 (d, *J* = 8.3 Hz, 1H), 3.72 (s, 3H), 3.36-3.28 (m, 1H), 2.88-2.80 (m, 1H), 2.73-2.67 (m, 1H), 1.91 (ddt, *J* = 12.9, 5.9, 2.9 Hz, 1H), 1.61-1.51 (m, 1H), 1.19 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 152.3, 139.3, 123.0, 115.8, 115.1, 113.3, 56.2, 47.9, 30.7, 27.3, 23.0; MS (CI, *m/z*, %) 178 (100) $[M+H]^+$; Anal. calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90; Found: C, 74.45; H, 8.59; N, 7.77.



13q

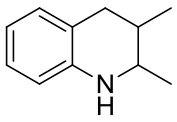
6-Bromo-2-methyl-1,2,3,4-tetrahydroquinoline (13q):[14f] 83% isolated yield and 88% conversion in 48 h, 50 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.06-7.01 (m, 2H), 6.34 (d, *J* = 8.4 Hz, 1H), 3.71 (brs, 1H), 3.37 (ddq, *J* = 9.8, 6.4, 3.1 Hz, 1H), 2.83-2.66 (m, 2H), 1.94-1.88 (m, 1H), 1.59-1.43 (m, 1H), 1.20 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 144.2, 132.1, 129.7, 123.5, 115.8, 108.7, 47.5, 30.0, 26.8, 22.9; MS (CI, *m/z*, %) 226:228 =

1:1 (100) $[M+H]^+$; Anal. calcd. for $C_{11}H_{12}BrN$: C, 53.12; H, 5.35; N, 6.190; Found: C, 53.67; H, 5.46; N, 6.13.



13r

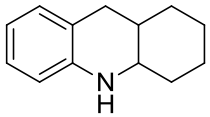
2-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-1,2,3,4-tetrahydroquinoline (13r):[14f] 89% isolated yield and 95% conversion in 15 h, 20 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.97-6.93 (m, 2H), 6.74-6.69 (m, 2H), 6.66-6.58 (m, 2H), 6.45 (d, *J* = 7.7 Hz, 1H), 5.91 (s, 2H), 3.75 (brs, 1H), 3.27 (ddt, *J* = 9.3, 6.3, 3.3 Hz, 1H), 2.84-2.69 (m, 2H), 2.65 (t, *J* = 7.9 Hz, 2H), 2.01-1.94 (m, 1H), 1.80-1.75 (m, 2H), 1.70-1.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 148.1, 146.1, 144.9, 136.1, 129.7, 127.2, 121.7, 121.5, 117.5, 114.6, 109.2, 108.7, 101.2, 51.4, 38.9, 32.3, 28.4, 26.6; MS (CI, *m/z*, %) 282 (100) $[M+H]^+$; Anal. calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98; Found: C, 76.37; H, 6.66; N, 4.96.



13s

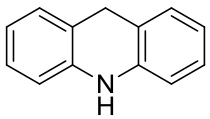
2,3-Dimethyl-1,2,3,4-tetrahydroquinoline (13s):[14f] 69% isolated yield and 92% conversion in 20 h, 50 mol % KI, S/C = 10000, *syn* : *anti* = 6:1; For *syn* isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.97-6.94 (m, 2H), 6.62-6.57 (m, 1H), 6.46 (d, *J* = 7.8, Hz, 1H), 3.44 (dq, *J* = 6.5, 3.0 Hz, 1H), 2.89 (dd, *J* = 16.2, 5.3 Hz, 1H), 2.47 (dd, *J* = 16.2, 6.0 Hz, 1H), 2.07-1.98 (m, 1H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.9

Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 144.3, 130.2, 127.0, 120.4, 117.3, 114.3, 50.4, 34.2, 30.9, 18.5, 14.8; MS (CI, *m/z*, %) 162 (100) $[M+H]^+$; Anal. calcd. for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69; Found: C, 81.92; H, 9.35; N, 8.73.



13t

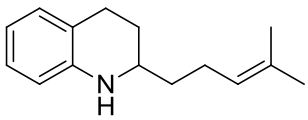
1,2,3,4,4a,9,9a,10-Octahydroacridine (13t):[14f] 95% isolated yield and full conversion in 12 h, 50 mol % KI, S/C = 10000, *syn* : *anti* = 5:2; For *syn* isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.95-6.92 (m, 2H), 6.56 (td, *J* = 7.3, 1.0 Hz, 1H), 6.44 (d, *J* = 7.9 Hz, 1H), 3.59 (br, 1H), 3.50 (q, *J* = 3.5 Hz, 1H), 2.89 (dd, *J* = 16.3, 5.6 Hz, 1H), 2.51 (dd, *J* = 16.3, 4.1 Hz, 1H), 1.99-1.92 (m, 1H), 1.70-1.58 (m, 4H), 1.46-1.28 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 144.3, 130.1, 127.1, 119.7, 116.8, 113.7, 50.4, 33.4, 32.9, 32.2, 27.7, 25.2, 21.1; MS (CI, *m/z*, %) 188 (100) $[M+H]^+$; Anal. calcd. for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48; Found: C, 83.22; H, 9.17; N, 7.13.



13u

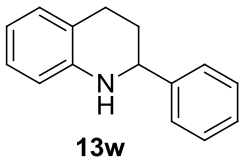
9,10-Dihydroacridine (13u):[21e] 98% isolated yield and full conversion in 12 h, 50 mol % KI, S/C = 5000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.11-7.06 (m, 4H), 6.85 (td, *J* = 7.4, 1.0 Hz, 2H), 6.66 (d, *J* = 7.9 Hz, 2H), 5.94 (br, 1H), 4.05 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 140.5, 129.0, 127.4, 121.0, 120.4, 113.8, 31.8; MS (CI, *m/z*, %)

182 (100) $[M+H]^+$; Anal. calcd. for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73; Found: C, 85.99; H, 6.16; N, 7.69.



13v

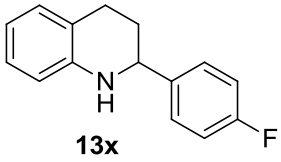
2-(4-Methylpent-3-enyl)-1,2,3,4-tetrahydroquinoline (13v):[14f] 71% isolated yield and 85% conversion in 24 h, 50 mol % KI, S/C = 10000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.97-6.93 (m, 2H), 6.59 (td, *J* = 7.4 Hz, 1.0 Hz, 1H), 6.46 (d, *J* = 8.3 Hz, 1H), 5.17-5.13 (m, 1H), 3.81 (brs, 1H), 3.25 (ddt, *J* = 9.4, 6.4, 3.4 Hz, 1H), 2.85-2.69 (m, 2H), 2.10 (q, *J* = 7.5 Hz, 2H), 1.99-1.93 (m, 1H), 1.70 (s, 3H), 1.64-1.51 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.1, 132.5, 129.7, 127.1, 124.4, 121.8, 117.3, 114.5, 51.7, 36.9, 28.5, 26.8, 26.1, 24.8, 18.1; MS (CI, *m/z*, %) 216 (100) $[M+H]^+$; Anal. calcd. for $C_{15}H_{21}N$: C, 83.67; H, 9.83; N, 6.50; Found: C, 83.82; H, 9.95; N, 6.50.



13w

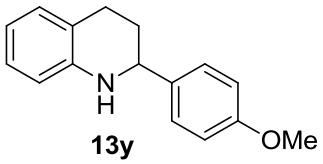
2-Phenyl-1,2,3,4-tetrahydroquinoline (13w):[14f] 98% isolated yield and full conversion in 48 h, 160 mol % KI, S/C = 1000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.40-7.33 (m, 4H), 7.30-7.26 (m, 1H), 7.01-6.99 (m, 2H), 6.67-6.63 (m, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 4.45-4.41 (m, 1H), 4.03 (brs, 1H), 2.96-2.88 (m, 1H), 2.76-2.70 (m, 1H), 2.16-2.08 (m, 1H), 2.05-1.94 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.2, 145.1, 129.7, 129.0, 127.9, 127.3, 127.0, 121.3, 117.6, 114.4, 56.7, 31.4,

26.8; MS (CI, *m/z*, %) 210 (100) $[M+H]^+$; Anal. calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69; Found: C, 86.14; H, 7.27; N, 6.72.



13x

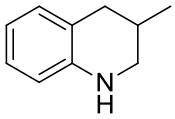
2-(4-Fluorophenyl)-1,2,3,4-tetrahydroquinoline (13x):[14f] 98% isolated yield and full conversion in 48 h, 160 mol % KI, S/C = 1000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.36-7.33 (m, 2H), 7.04-6.99 (m, 4H), 6.67-6.63 (m, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 4.41 (dd, *J* = 9.4, 3.2 Hz, 1H), 3.99 (brs, 1H), 2.95-2.87 (m, 1H), 2.75-2.69 (m, 1H), 2.11-2.05 (m, 1H), 1.99-1.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 162.5 (d, J_{CF} = 243.8 Hz), 145.0, 140.9 (d, J_{CF} = 3.0 Hz), 129.7, 128.5 (d, J_{CF} = 8.0 Hz), 127.4, 121.2, 117.8, 115.8 (d, J_{CF} = 21.2 Hz), 114.5, 56.0, 31.6, 26.7; HRMS for $C_{15}H_{15}FN$ $[M+H]^+$: m/z calcd. 228.1183, found 228.1178.



13y

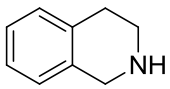
2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline (13y):[14f] 94% isolated yield and full conversion in 26 h, 160 mol % KI, S/C = 1000; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.32-7.30 (m, 2H), 7.02-6.99 (m, 2H), 6.90-6.87 (m, 2H), 6.64 (td, *J* =7.3, 1.1 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 4.38 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.98 (brs, 1H), 3.81 (s, 3H), 2.97-2.88 (m, 1H), 2.77-2.71 (m, 1H), 2.11-2.05 (m, 1H), 2.01-1.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 159.4,

145.2, 137.3, 129.7, 128.0, 127.3, 121.3, 117.5, 114.4, 114.3, 56.1, 55.7, 31.5, 27.0; MS (CI, *m/z*, %) 240 (100) $[M+H]^+$; Anal. calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85; Found: C, 80.46; H, 7.12; N, 5.82.



13z

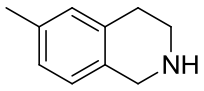
3-Methyl-1,2,3,4-tetrahydroquinoline (13z):[8b] 88% isolated yield and 96% conversion in 12 h, 50 mol % KI, S/C = 5000; Hydrolysis: 100 ^oC and 15 h; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.98-6.92 (m, 2H), 6.60 (td, *J* = 7.4, 1.1 Hz, 1H), 6.47 (d, *J* = 7.9 Hz, 1H), 3.82 (brs, 1H), 3.25 (ddd, *J* = 11.0, 3.7, 2.0 Hz, 1H), 2.91-2.85 (m, 1H), 2.79-2.74 (m, 1H), 2.45-2.39 (m, 1H), 2.11-1.99 (m, 1H), 1.04-1.03 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 144.7, 130.0, 128.1, 127.1, 121.6, 117.4, 114.3, 49.3, 35.9, 27.6, 19.5; MS (CI, *m/z*, %) 148 (100) $[M+H]^+$; Anal. calcd. for $C_{10}H_{13}N$: C, 81.59; H, 8.90; N, 9.51; Found: C, 81.63; H, 9.05; N, 9.47.



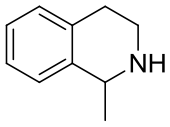
17a

1,2,3,4-Tetrahydroisoquinoline (17a):[8b] 83% isolated yield and full conversion in 24 h, 50 mol % KI, S/C = 500; Hydrolysis: 25 ^oC and 20 h; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.13-7.05 (m, 3H), 6.99-6.96 (m, 1H), 3.99 (s, 2H), 3.11 (t, *J* = 6.0 Hz, 2H), 2.77 (t, *J* = 6.0 Hz, 2H), 1.87 (brs, 1H); ^{13}C NMR (CDCl3, 100 MHz) δ (ppm): 136.4, 135.2, 129.7, 126.6, 126.4, 126.1, 48.8, 44.4, 29.7; MS (CI, *m/z*, %) 134

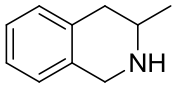
(100) $[M+H]^+$; Anal. calcd. for $C_9H_{11}N$: C, 81.2; H, 8.32; N, 10.5; Found: C, 79.7; H, 8.57; N, 10.4.



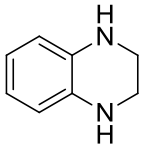
17b **6-Methyl-1,2,3,4-tetrahydroisoquinoline (17b):**[21f] 95% isolated yield and full conversion in 24 h, 50 mol % KI, S/C = 500; Hydrolysis: 40 ^oC and 17 h; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.95-6.88 (m, 3H), 3.97 (s, 2H), 3.11 (t, *J* = 6.0 Hz, 2H), 2.75 (t, *J* = 5.9 Hz, 2H), 2.29 (s, 3H), 1.93 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 135.9, 134.9, 133.2, 130.2, 127.0, 126.5, 48.4, 44.3, 29.5, 21.5; MS (CI, *m/z*, %) 148 (100) $[M+H]^+$; Anal. calcd. for $C_{10}H_{13}N$: C, 81.6; H, 8.90; N, 9.51; Found: C, 79.3; H, 8.68; N, 9.03.



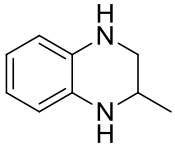
17c **1-Methyl-1,2,3,4-tetrahydroisoquinoline (17c):**[8b] 92% isolated yield and 98% conversion in 24 h, 50 mol % KI, S/C = 500, HCOOH:Et_3N = 3.5:1; Hydrolysis: 80 ^oC and 5 h; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.16-7.07 (m, 4H), 4.11 (q, *J* = 6.7 Hz, 1H), 3.27 (dt, *J* = 12.4, 5.1 Hz, 1H), 3.06-2.99 (m, 1H), 2.91-2.84 (m, 1H), 2.77-2.70 (m, 1H), 1.71 (br, 1H), 1.46 (d, *J* = 6.8 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 131.0, 135.2, 129.6, 126.33, 126.30, 126.26, 52.0, 42.2, 30.5, 23.1; MS (CI, *m/z*, %) 148 (100) $[M+H]^+$; Anal. calcd. for $C_{10}H_{13}N$: C, 81.6; H, 8.90; N, 9.51; Found: C, 80.2; H, 9.03; N, 9.51.



17d **3-Methyl-1,2,3,4-tetrahydroisoquinoline (17d):**[8b] 91% isolated yield and full conversion in 24 h, 50 mol % KI, S/C = 500; Hydrolysis: 60 ^{o}C and 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.13-7.01 (m, 4H), 4.07 (q, *J* = 16.0 Hz, 1H), 3.06-2.97 (m, 1H), 2.78 (dd, *J* = 16.4, 6.0 Hz, 1H), 2.54-2.47 (m, 1H), 1.81 (br, 1H), 1.24 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 135.8, 135.3, 129.5, 126.4, 126.1, 49.7, 49.0, 37.6, 22.9; MS (CI, *m/z*, %) 148 (100) $[M+H]^+$; Anal. calcd. for $C_{10}H_{13}N$: C, 81.6; H, 8.90; N, 9.51; Found: C, 80.3; H, 9.00; N, 9.45.

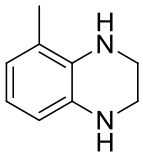


17e **1,2,3,4-Tetrahydroquinoxaline (17e):**[14h] 99% isolated yield and full conversion in 12 h, 50 mol % KI, S/C = 5000; Hydrolysis: 120 ^{o}C and 8 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.60-6.47 (m, 4H), 3.58 (br, 2H), 3.41 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 134.0, 119.2, 115.2, 41.8; MS (CI, *m/z*, %) 135 (100) $[M+H]^+$; Anal. calcd. for $C_8H_{10}N_2$: C, 71.6; H, 7.51; N, 20.9; Found: C, 71.4; H, 7.56; N, 21.1.



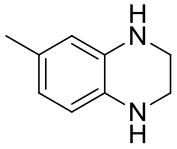
17f

2-Methyl-1,2,3,4-tetrahydroquinoxaline (17f):[14h] 86% isolated yield and full conversion in 12 h, 50 mol % KI, S/C = 5000; Hydrolysis: 100 ^{o}C and 4 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.60-6.56 (m, 2H), 6.50-6.48 (m, 2H), 3.55-3.47 (m, 1H), 3.31 (dd, *J* = 10.7, 2.9 Hz, 1H), 3.03 (dd, *J* = 10.6, 8.2 Hz, 1H), 1.18 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 134.0, 133.6, 119.12, 119.11, 114.90, 114.85, 48.7, 46.1, 20.3; MS (CI, *m/z*, %) 149 (100) $[M+H]^+$; Anal. calcd. for $C_9H_{12}N_2$: C, 72.9; H, 8.16; N, 18.9; Found: C, 72.7; H, 8.28; N, 18.4.

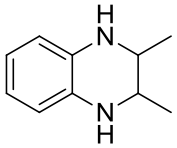


17g

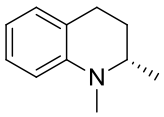
5-Methyl-1,2,3,4-tetrahydroquinoxaline (17g):[21g] 92% isolated yield and 93% conversion in 12 h, 50 mol % KI, S/C = 5000; Hydrolysis: 100 ^{o}C and 4 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.54-6.49 (m, 2H), 6.43-6.39 (m, 1H), 3.50-3.39 (m, 4H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 133.6, 132.1, 122.6, 120.9, 118.4, 113.3, 42.2, 41.6, 17.4; MS (CI, *m/z*, %) 149 (100) $[M+H]^+$; Anal. calcd. for $C_9H_{12}N_2$: C, 72.9; H, 8.16; N, 18.9; Found: C, 73.1; H, 8.33; N, 19.0.



17h **6-Methyl-1,2,3,4-tetrahydroquinoxaline (17h):**[21h] 90% isolated yield and 96% conversion in 12 h, 50 mol % KI, S/C = 5000; Hydrolysis: 100 ^{o}C and 4 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.43-6.38 (m, 2H), 6.33 (s, 1H), 3.39 (s, 4H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 134.2, 131.6, 128.8, 119.5, 115.9, 115.4, 42.00, 41.98, 21.1; MS (CI, *m/z*, %) 149 (100) $[M+H]^+$; Anal. calcd. for $C_9H_{12}N_2$: C, 72.9; H, 8.16; N, 18.9; Found: C, 72.6; H, 8.31; N, 18.5.

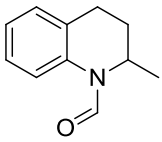


17i **2,3-Dimethyl-1,2,3,4-tetrahydroquinoxaline (17i):**[14h] 91% isolated yield and 93% conversion in 12 h, 50 mol % KI, S/C = 500; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.60-6.55 (m, 2H), 6.51-6.47 (m, 2H), 3.51-3.45 (m, 2H), 1.12 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 133.0, 119.0, 114.8, 49.5, 17.6; MS (CI, *m/z*, %) 163 (100) $[M+H]^+$; Anal. calcd. for $C_{10}H_{14}N_2$: C, 74.0; H, 8.70; N, 17.3; Found: C, 74.0; H, 8.72; N, 17.2.



15 **(S)-1,2-dimethyl-1,2,3,4-tetrahydroquinoline (15):**[21i]

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.12 (t, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.63 (t, *J* = 7.2 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 3.49-3.43 (m, 1H), 2.93-2.84 (m, 5H, *N*-CH_3 overlapped with a CH_2), 2.72 (d, *J* = 16.1 Hz, 1H), 2.06-1.97 (m, 1H), 1.82-1.76 (m, 1H), 1.17 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.6, 128.7, 127.2, 122.2, 115.5, 110.7, 54.0, 37.1, 28.2, 23.9, 17.7; HRMS for C10H14N [M+H]+: m/z calcd 148.1126, found 148.1131; HPLC (Chiralcel OJ, hexane:isopropanol = 99:1, flow rate 0.5 mL/min, 254 nm): t_R = 15.3 min (minor), t_S = 19.4 min (major), 73% ee. The *S* configuration was determined by comparison with **15** obtained from reductive amination of *(S)*-2-methyltetrahydroquinolines.



18

1-Formyl-2-methyl-1,2,3,4-tetrahydroquinoline (18):[21j] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.68 (s, 1H), 7.24-7.10 (m, 4H), 4.81 (sextet, *J* = 6.3, 1H), 2.87-2.80 (m, 1H), 2.76-2.67 (m, 1H), 2.17-2.09 (m, 1H), 1.74-1.66 (m, 1H), 1.22 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 161.6, 136.7, 130.3, 129.6, 127.6, 125.2, 118.9, 45.6, 29.6, 24.7, 18.6; MS (CI, *m/z*, %) 176 (100) $[M+H]^+$, 193 (46) $[M+NH_3+H]^+$; Anal. calcd. for $C_{11}H_{13}NO$: C, 75.4; H, 7.48; N, 7.99; Found: C, 74.8; H, 7.57; N, 8.12.

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CHAPTER 3 CHEMOSELECTIVE TRANSFER HYDROGENATION OF PYRIDINES

3.1 Introduction

Chapter 2 presented an iodide-promoted TH system for reduction of benzo-fused *N*-heteroaromatics including quinolines, isoquinolines and quinoxalines, which demonstrates a simple but efficient protocol for preparation of a variety of *N*-heterocyclic compounds. In comparison, reduction of monocyclic *N*-heteroaromatics such as pyridines, pyrazines and pyrroles is significantly more challenging. The corresponding saturated compounds are of broad utility; thus efficient, general and mild reduction methods are desirable. In this chapter, the efforts to apply the above-mentioned TH system for the reduction of pyridines to piperidine derivatives will be described.

As also stated in Chapter 1, piperidines, which structurally exist in abundant natural products and synthetic bioactive compounds, have attracted a great deal of attention in the chemical and pharmaceutical industries.[1] For instance, among top-selling prescription drugs, Risperdal used for treatment of schizophrenia and bipolar mania,[2] Concerta for attention deficit hyperactivity disorder (ADHD),[3] Aricept for Alzheimer's disease,[4] Paroxetine as an antidepressant[5] and Fentanyl as a pain reliever[6] are piperidine derivatives (Figure 10).

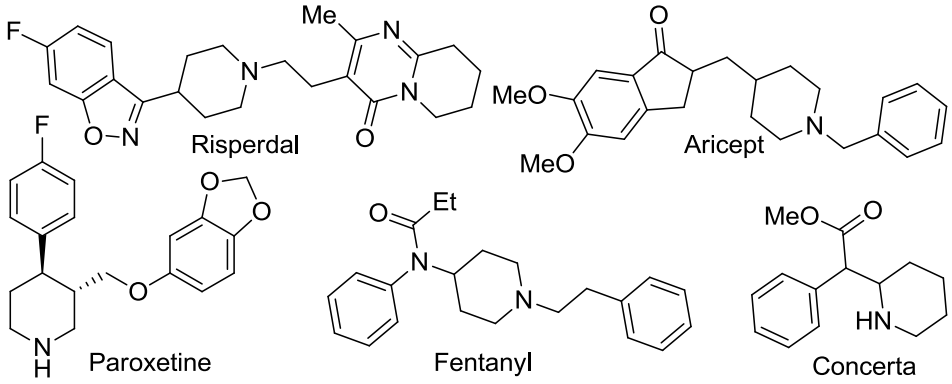
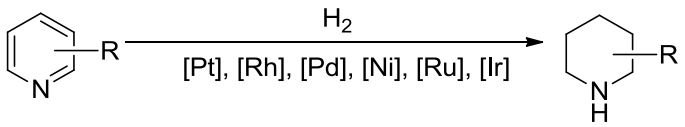


Figure 10: Piperidine derivatives as top-selling prescription drugs

Given their broad pharmaceutical utilities, the synthesis of piperidines has been extensively investigated in both industry and academia.[1a, e-i] Most of the attention has been paid to constructing the piperidine ring by cyclisation, being highlighted by the synthesis of a variety of piperidine based natural products and drugs successfully.[1e-g, i] The disadvantages, however, including the lack of general methods and often tedious preparation of the substrates, limit their prospective applications. From this viewpoint, catalytic hydrogenation of the parent pyridines provides arguably the most convenient and atom-economic route for directly accessing piperidines.[7] Over the past several decades, a variety of classical heterogeneous catalysts, such as Pd/C, Pt_2O_3, Rh/Al_2O_3, and Raney Ni, have been used to fully reduce pyridines with hydrogen gas;[7-9] but most of these catalysts are of low activity and selectivity and often require harsh reaction conditions. Recently, several well-defined homogeneous Rh, Ir and Ru complexes[10] have been reported to catalyse

the hydrogenation including asymmetric versions (Scheme 42).[11] An organocatalyst[12] in combination with Hantzsch esters can also realise the asymmetric reduction. During the preparation of this thesis, diastereomeric hydrogenation of 2,6-disubstituted pyridines was reported using a borane-based, metal-free catalyst.[13]

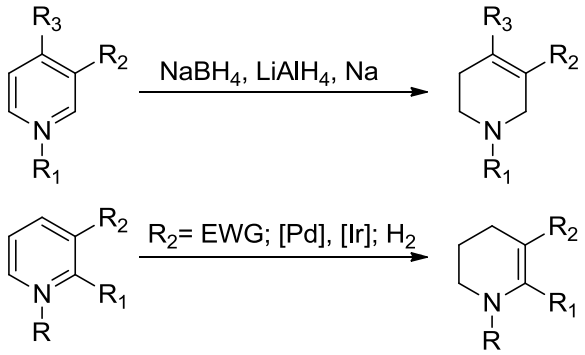


Scheme 42: Full hydrogenation of pyridines by transition metal catalysis

For most of the homogeneous work, the substrates are either limited to electron withdrawing groups (EWG), or lack functional group compatibility. Furthermore, specific activating groups are often needed to be installed on the pyridines and relatively high catalyst loading and hydrogen pressure is necessary.

Partial reduction of pyridines to give tetrahydropyridines is even more interesting, since the resulting unsaturated piperidines with a C=C bond can be further transformed to other value-added products *via* many well-established reactions of alkenes, such as asymmetric hydrogenation, epoxidation, dihydroxylation, and allyic substitution and isomerisation.[14] Consequently, a huge number of reactions have been found for the partial reduction of pyridines.[8, 15] In almost all cases, stoichiometric metal or metal hydride reagents, such as Na, $NaBH_4$ and $LiAlH_4$, are employed for

these reductions. Apart from being hazardous and generating copious amount of toxic waste, using these reagents is often plagued with poor selectivity and fails to tolerate functional groups, which limit their application in modern synthesis. Partial hydrogenation of pyridines with heterogeneous catalysts has also been reported, affording generally only 2,3-unsaturated piperidines with EWG such as carbonyl and cyano (Scheme 43).[16] Therefore, it remains a great challenge to reduce pyridines in an efficient, selective and operationally benign manner.



Scheme 43: Partial hydrogenation of pyridines

In Chapter 2, we described that promoted by iodide, the simple $[Cp^*RhCl_2]_2$ allows for highly efficient transfer hydrogenation of quinolines, isoquinolines and quinoxalines using the azeotropic HCOOH-NEt_3 as reductant under mild conditions. It is a natural extension to explore the possibility to reduce the more inert pyridines with this catalytic system.

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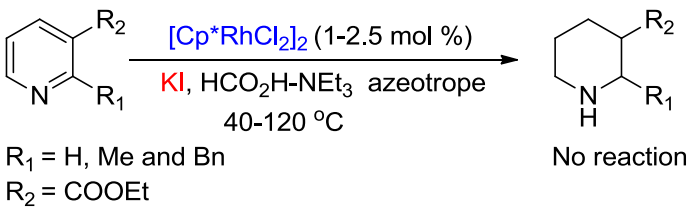
3.2 Results and Discussion

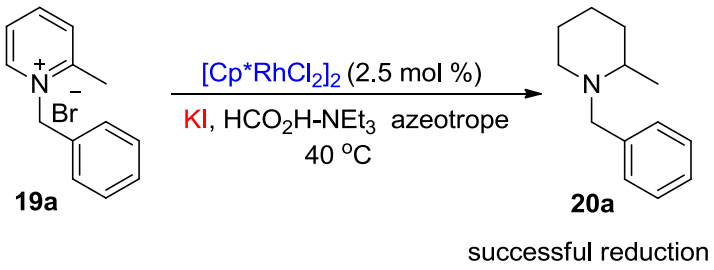
3.2.1 Discovery of TH of pyridines and further optimisation

Bearing in mind that in Chapter 2, 2-methylquinoline (pK_a 5.4) was reduced smoothly with the $[Cp^*RhCl_2]_2$-I^- catalyst, we chose 2-picoline (pK_a 6.0) as model substrate, which has similar basicity to 2-methylquinoline and is expected to be protonated by formic acid (pK_a 3.6). Surprisingly, no reduction was observed by crude ^{1}H NMR even with 2.5 mol % catalyst and the starting material was partially recovered. Given the fact that the supposed product 2-pipercoline is volatile (118-119 °C/753 mmHg) and has a good solubility in aqueous solution, we were wondering if we missed some reduced product because of the insufficient work-up. Therefore, we selected several more hydrophobic pyridines such as ethyl nicotinate and 2-benzylpyridine and tested them under the identical conditions. However, there was no reduction observed as well even at higher temperature (Scheme 44). These results hinted that the supposed protonated pyridines were not activated enough for the TH and we may need to search other methods to afford more activated pyridines.



Scheme 44: TH of neutral pyridines

There are many methods to activate the neutral pyridines by forming pyridinium salts, pyridine *N*-oxides, or *N*-iminopyridinium ylides for example. These lower the LUMO of pyridines, increasing its susceptibility to nucleophilic attack by a metal hydride species and reduction, while coordinatively saturating the nitrogen atom decreasing the tendency to bind to any available metal catalyst. Among these activating methods, the most convenient is the alkylation of the pyridines to form pyridinium salts. Thus, we prepared *N*-benzyl-2-picoline bromide salt **19a** as model substrate, which can be conveniently prepared by alkylation of 2-picoline with benzyl bromide. Given the simplicity of quaternisation with benzyl halides and the importance of benzyl-protected piperidines, we set out to examine the TH of **19a**. Delightfully, the quaternised pyridine salt underwent the reduction readily with 2.5 mol % catalyst in the presence of 0.5 equivalents KI (Scheme 45).



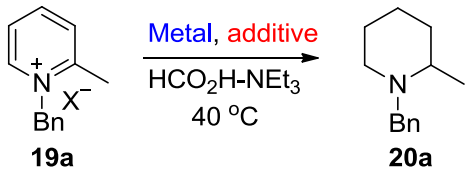
Scheme 45: TH of pyridinium salts

Encouraged by this initial result and with further optimisation, the reduction could be achieved with much lower metal loading. As can be seen from Table 4, catalysed by only 0.005 mol % $[Cp^*RhCl_2]_2$ with 0.1

equivalent KI as additive, the picoline bromide salt **19a** was reduced in HCOOH-NEt_3 at 40 °C, affording *N*-benzyl piperidine in 85% isolated yield (Table 4, entry 1). In order to clarify if iodide ion still plays a key role in this TH, we set several control experiments. The results again show that the iodide salt KI displays a remarkable accelerating effect on the reduction (Table 4, entries 1 *vs* 2). The reaction proceeds well without the iodide, when it was carried out with a much higher catalyst loading (Table 4, entry 3). A lower yield was obtained and some unknown impurities were noticed by using picoline chloride salt under the same conditions (Table 4, entry 4). The halide effect echoed the previous results obtained with 2-methylquinoline in Chapter 2. The concentration of the iodide salt affects the reduction rates as well, with a slightly higher yield obtained using one equivalent KI (Table 4, entry 5 *vs* entries 1 and 6), under which a turnover number (TON) of 9000 is generated. To the best of our knowledge, this is the highest TON value ever reported in catalytic reduction of pyridines. However, higher concentration of I^- deactivates the catalyst (Table 4, entry 6), resembling the results in Chapter 2. The yield was slightly improved when increasing the catalyst loading to 0.05 mol % (Table 4, entry 7). Control experiments show that no reduction occurs without the rhodium catalyst, and other broadly-used metal analogues proved to be ineffective once more (Table 4, entries 8-11). We noticed that excellent yield can be obtained when picolinium iodide salt, conveniently prepared by halides exchange of picolinium bromide salt with NaI, was subjected to the TH. It reinforces that I^- is

crucial for the high activity (Table 4, entries 12 *vs* 2). However, no reaction was observed when the anion of the picolinium salt was replaced with a non-coordinating anion, SbF_6^- (Table 4, entry 13), showing again the importance of coordinating anion to the catalytic activity (also see Chapter 2).

Table 4. Effect of metal compounds and iodide on the TH of **19a**.[a]



Entry	X	Metal, mol %[b]	Additive, equiv.	Yield[c]
1	Br	[Rh], 0.005	KI, 0.1	85
2	Br	[Rh], 0.005	None	9
3	Br	[Rh], 0.5	None	84
4	Cl	[Rh], 0.5	None	62
5	Br	[Rh], 0.005	KI, 1.0	90
6	Br	[Rh], 0.005	KI, 3.0	10
7	**Br**	**[Rh], 0.05**	**KI, 1.0**	**94**
8	Br	None	KI, 1.0	NR
9	Br	[Ir], 0.5	None	4
10	Br	[Ru], 0.5	None	NR
11	Br	$RhCl_3$, 1.0	None	NR
12	I	[Rh], 0.005	None	92

13	SbF_6	[Rh], 0.5	None	NR

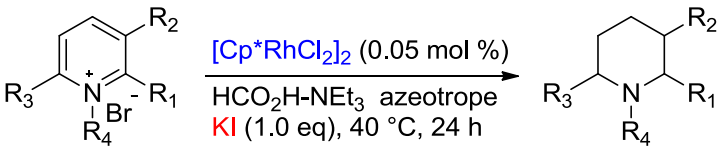
[a] Reaction conditions: pyridinium salt **19a** (0.5 mmol), HCO_{2H}-NEt_3 azeotrope solution (5 mL), 40 °C, 24 h under N_2, Bn = Benzyl. [b] [Rh] = $[Cp^*RhCl_2]_2$, [Ir] = $[Cp^*IrCl_2]_2$ and [Ru] = $[RuCl_2(p\text{-cymene})]_2$. [c] Isolated yields. NR = No reaction or no desired product observed.

3.2.2 Substrate scope

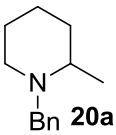
Having the optimised reaction conditions in hand, a variety of pyridinium salts were subjected to TH with 0.05 mol % $[Cp^*RhCl_2]_2$ in the presence of 1 equivalent KI. As shown in Table 5, a range of 2-, 2,3-, and 2,6-disubstituted pyridiniums were reduced, affording the corresponding *N*-benzyl piperidines in good to excellent yields. Thus, 2-alky substituted pyridiniums underwent smooth hydrogenation to give 2-alky piperidines in high yields (Table 5, entries 1-3). A lower yield was obtained with the 2-phenyl piperidine **20d** (Table 5, entry 4), probably due to steric demand of the phenyl ring and/or its stabilisation of the intermediate iminium C=N bond (*vide infra*). Surprisingly somehow, the unsubstituted pyridinium gave a mixture of 3,4-unsaturated piperidine and piperidine, with the latter **20e** accounting for 60% of the mixture as determined by the crude ^1H NMR (Table 5, entry 5). The formation of the unsaturated piperidine is likely a result of competing 1,2-hydride addition (*vide infra*). Most interestingly, substrates bearing hydroxyl and protected amino groups at either 2 or 3 positions were tolerated, generating synthetically valuable amino alcohol and diamine (Table 5, entries 6-8,

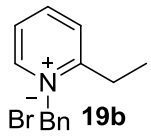
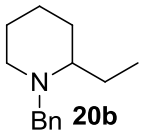
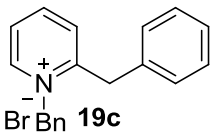
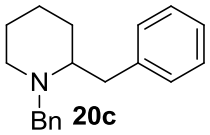
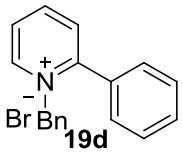
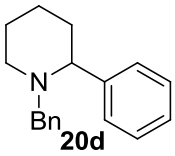
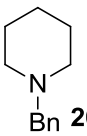
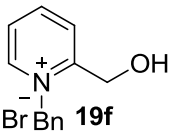
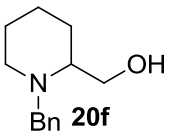
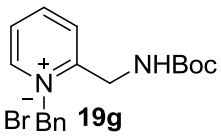
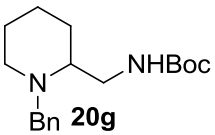
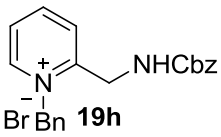
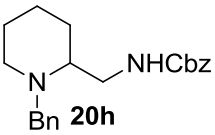
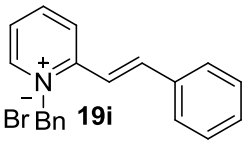
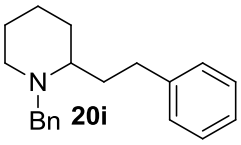
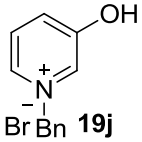
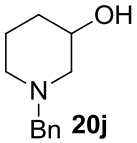
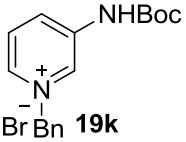
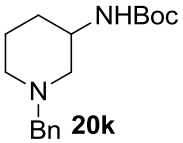
10 and 11). For instance, **20j** and **20k** have found applications in the pharmaceutical industry as cyclic *β*-amino alcohol and diamine.[17] However, conjugated C=C double bond at the 2-postion was reduced to a significant degree, leading to **20i** probably *via* 1,4-hydride addition beginning at the carbon α to the Ph group (Table 5, entry 9). Notably, 2,3-disubstuted pyridinium can be hydrogenated to piperidine exclusively as the *trans* isomer, whilst the 2,6-disubstuted pyridinium affords *cis* piperidine as the major product (Table 5, entries 12 and 13). Non-benzyl quaternised pyridine is also viable. Thus, the *N*-phenylethyl piperidine **20n**, an analogue of a well-known σ receptor antagonist for treating methamphetamine abuse,[18] is obtained from the corresponding pyridinium salt in excellent yield (Table 5, entry 14). However, 3-substituted pyridiniums with electron-deficient groups such as fluoro, chloro, carbonyl and amide failed to generate any isolated products with few exceptions (*vide infra*).

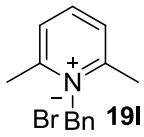
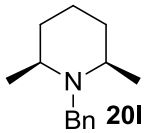
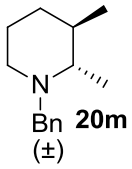
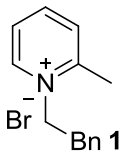
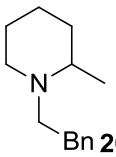
Table 5. TH of pyridiniums to piperidines.[a]



19a-n **20a-n**

Entry	Substrate	Product	Yield [%][b]
1	 **19a**	 **20a**	94 (90)

2	 **19b**	 **20b**	95
3	 **19c**	 **20c**	85
4	 **19d**	 **20d**	66
5	 **19e**	 **20e**	60[c]
6	 **19f**	 **20f**	94
7	 **19g**	 **20g**	79
8	 **19h**	 **20h**	96
9	 **19i**	 **20i**	69
10	 **19j**	 **20j**	99 (63)
11	 **19k**	 **20k**	77

12[d]	 **19l**	 **20l**	94
13[d]	 **19m**	 **20m** (±)	98
14	 **19n**	 **20n**	93

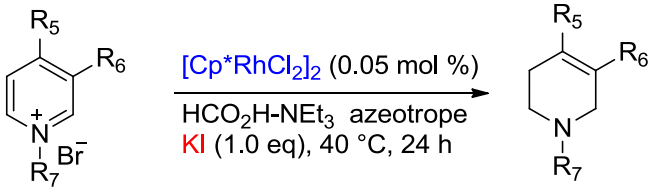
[a] All reactions were carried out under the standard conditions: **19** (0.5 mmol), $[Cp^*RhCl_2]_2$ (0.25 μmol), KI (0.5 mmol), HCO_2H-NEt_3 azeotrope solution (5 mL), 40 °C, N_2, 24 h. [b] Isolated yields; data in bracket was obtained with 0.005 mol% catalyst. [c] 99% total isolated yield; the product was a mixture of **20e** and 3,4-unsaturated piperidine in a ratio of 3:2. [d] **20i**, *cis*/*trans* = 3.2:1, determined by ^{1}H NMR; **20m**, *trans*/*cis* > 99:1, determined by NOE analysis.

Inspired by the observation of 3,4-unsaturated piperidine in the case of **20e**, we wanted to test catalysis on 4-substituted pyridiniums. The *N*-benzyl-4-picoline bromide salt **21a** was prepared by routinely used alkylation procedure with 4-picoline. Thus, under the same conditions as above, surprisingly, the reduction of **21a** afforded primarily the 3,4-unsaturated piperidine **22a** with 89% yield along with 6% fully reduced product (Table 6, entry 1). Prompted by this finding while considering the importance of such products, we subsequently examined the hydrogenation of a series of 4-substituted pyridiniums. It is noteworthy that these 4-substituted pyridiniums can be quantitatively formed under

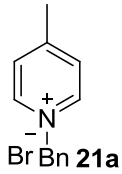
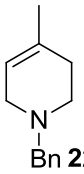
mild conditions. The TH results are summaried in Table 6. To our delight, most of the 4-substituted pyridiniums were reduced with high or exclusive chemoselectivities toward the 3,4-unsaturated piperidine products. Thus, pyridiniums bearing different 4-alkyl substituents were hydrogenated with excellent yields (Table 6, entries 1-4), with bulkier substituent affording higher chemoselectivity favoring **22**. For instance, in the case of 4-*tert*-butyl-substituted **21c**, no fully reduced product was observed. The same is also true with 4-phenyl substituted pyridinium **21e**, which led to **22e** in almost quantitative yield. Of particular note is that the 4-arylsubstituted piperidine derivatives have found tremendous medicinal uses (*vide infra*). The pyridiniums bearing electron-withdrawing and donating groups (**21f**, **g**) and other functionalities, such as hydroxyl (**21h**), ester (**21j**, **k**) and protected amine (**21g**, **i**), were viable as well, being reduced with excellent chemoselectivities and high yields. Conjugated or non-conjugated substitutents (Table 6, entries 10 *vs* 11) have no impact on the chemoselectivity. In sharp contrast to the reduction of **19i** (Table 5, entry 9), the conjugated C=C double bond in **21l** was mainly retained. The 4-styryl substituted **22l** was isolated in 66% yield, exclusively in the s-*cis* conformation (Table 6, entry 12). Moreover, 3,4-disubstituted pyridinium **21m** was also reduced to its tetrahydro analogue, although a higher catalyst loading (0.25 mol %) was required (Table 6, entry 13). The benzyl group is again not a necessity, and replacing it with phenylethyl did not significantly affect the yield (Table 6, entry 14). More interestingly, the benzyl could also be replaced with an allyl group, which

is a challenging functionality in heterogeneous hydrogenation (Table 6, entry 15). Surprisingly, as opposed to the full reduction of other 3-electron-rich substitued pyridiniums (Table 6, entries 10 and 11), **21p** was reduced to 3,4-unsaturated piperidine product (Table 6, entry 16). Although a low yield was observed for *N*-benzyl ethyl nicotinate iodide salt **21q**, which echoed the unreactive nature of 3-EWG substituted pyridinium, the formation of enamine product **22q** supports the proposed mechanism (*vide infra*). From these preliminary results, we believe that the presence of such a variety of functionalities including alkene, diene, hydroxyl, amino, ester and allyl units in these tetrahydropyrindines opens a vast space for further well-established reactions, as indicated before. We also note that 3,4-unsaturated piperidines can be accessed generally only through reduction with boron hydrides.[8]

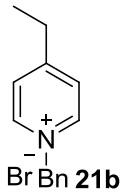
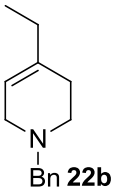
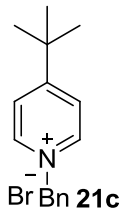
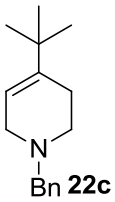
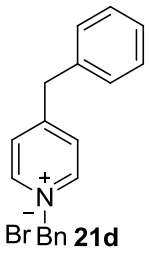
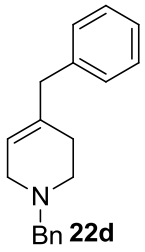
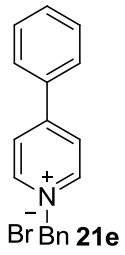
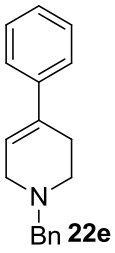
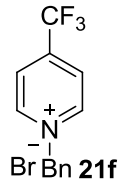
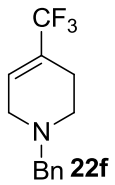
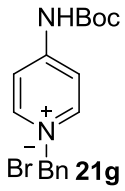
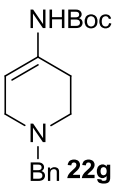
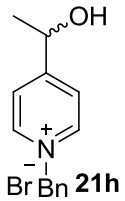
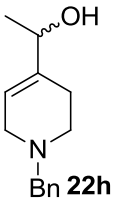
Table 6. Partial TH of 4-substituted pyridiniums.[a]

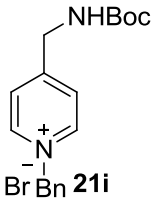
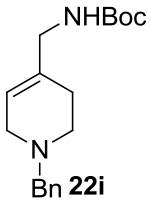
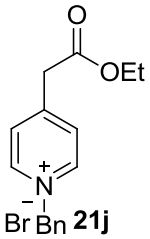
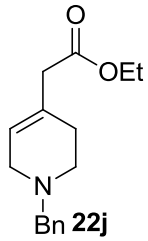
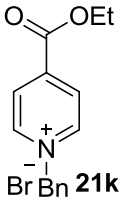
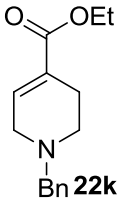
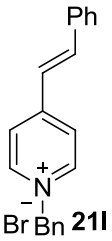
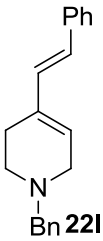
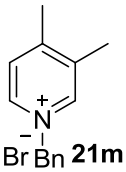
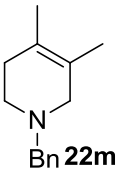
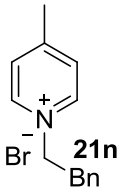
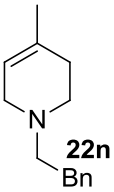
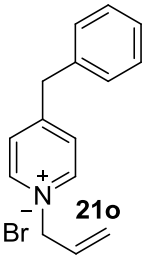
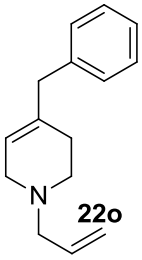


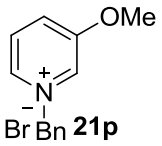
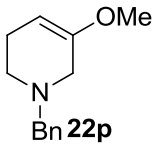
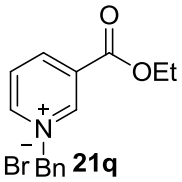
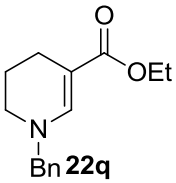
21a-q **22a-q**

Entry	Substrate	Product	Yield [%][b]
1			89 (6)

21a **22a**

2	 **21b**	 **22b**	88 (3)
3	 **21c**	 **22c**	92 (0)
4	 **21d**	 **22d**	95 (4)
5	 **21e**	 **22e**	98
6	 **21f**	 **22f**	86
7	 **21g**	 **22g**	77
8	 **21h**	 **22h**	81

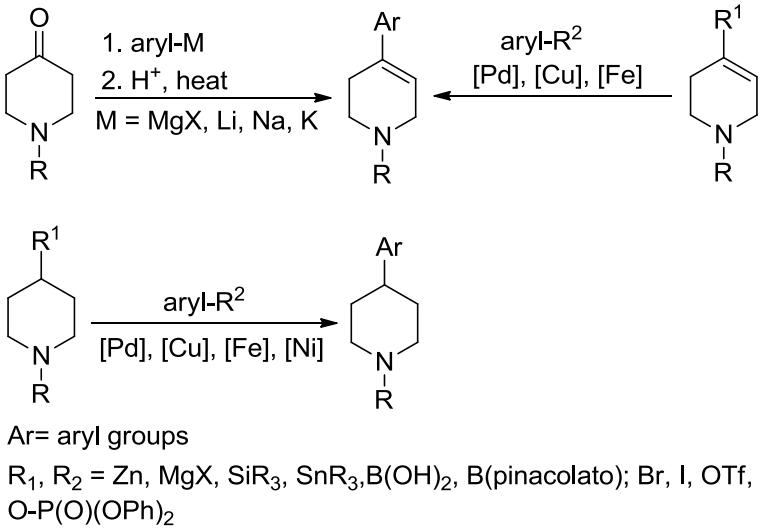
9	 **21i**	 **22i**	95
10	 **21j**	 **22j**	90
11	 **21k**	 **22k**	81
12[d]	 **21l**	 **22l**	66
13[d]	 **21m**	 **22m**	85
14	 **21n**	 **22n**	87 (8)
15	 **21o**	 **22o**	81

16	 **21p**	 **22p**	64
17	 **21q**	 **22q**	21

[a] Reactions were carried out under the standard conditions given in Table 2. [b] Yield of fully reduced product is given in the bracket (determined by ^{1}H NMR). [c] 0.5 mol % catalyst was used. [d] 0.25 mol % catalyst was used. [e] The conformation was determined by NOE analysis.

To further showcase the synthetic utility of this new protocol, we carried out the preparation of compound **22e** on a gram scale. As can be seen in Figure 10, 4-arylpiperidines are a highly valuable structural unit found in drug discovery programs for potential treatment of a variety of symptoms such as asthma, hypertension, depression, cocaine abuse, migraines, benign prostatic hyperplasia, bacterial infection, estrogen-related disorders, Alzheimer's and Parkinson's disease, and allergic rhinitis.[19] However, the common synthetic methods for their synthesis are far from ideal, as presented in Scheme 46. These methods require using aryl organometallic species to react with 4-piperidone derivatives, 3,4-unsaturated or fully saturated piperidines.[19] Apart from environmental concerns, and often harsh and sensitive conditions arising from using Grignard reagents, triflate, zinc, stannane, boron and silane reagents,

these methods need to employ costly or not commercially available piperidines as starting materials.

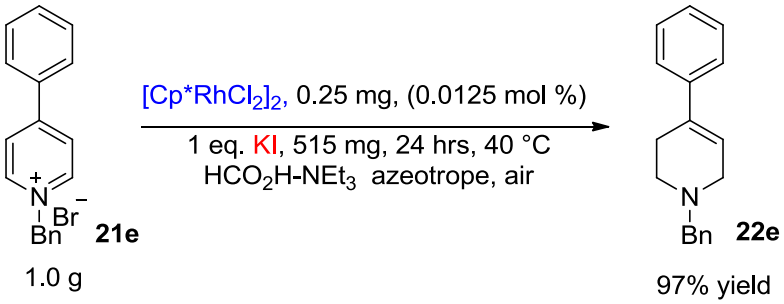


Scheme 46: Common methods for preparation of 4-arylpiperidines

Our synthesis began with commercial and inexpensive 4-phenyl pyridine, which was quaternised readily with benzyl bromide affording **21e** in quantitative yield. Transfer hydrogenation of **21e** (1.0 g) in the HCO_{2H}-NEt_3 azeotrope with an even lower catalyst loading of 0.0125 mol % (0.25 mg) in air provided the 3,4-unsaturated piperidine product **22e** with 97% isolated yield in two steps (Scheme 47). This appears to us to be the most efficient way for accessing this type of compound, regarding cost, effectiveness, practicality and scalability.[19]

It is also worth noting that for most reactions in Tables 5 and 6, the work-up simply involves direct extraction after basifying the reaction

mixture without further purification, due to the high solubility of pyridinium salts in aqueous solution.

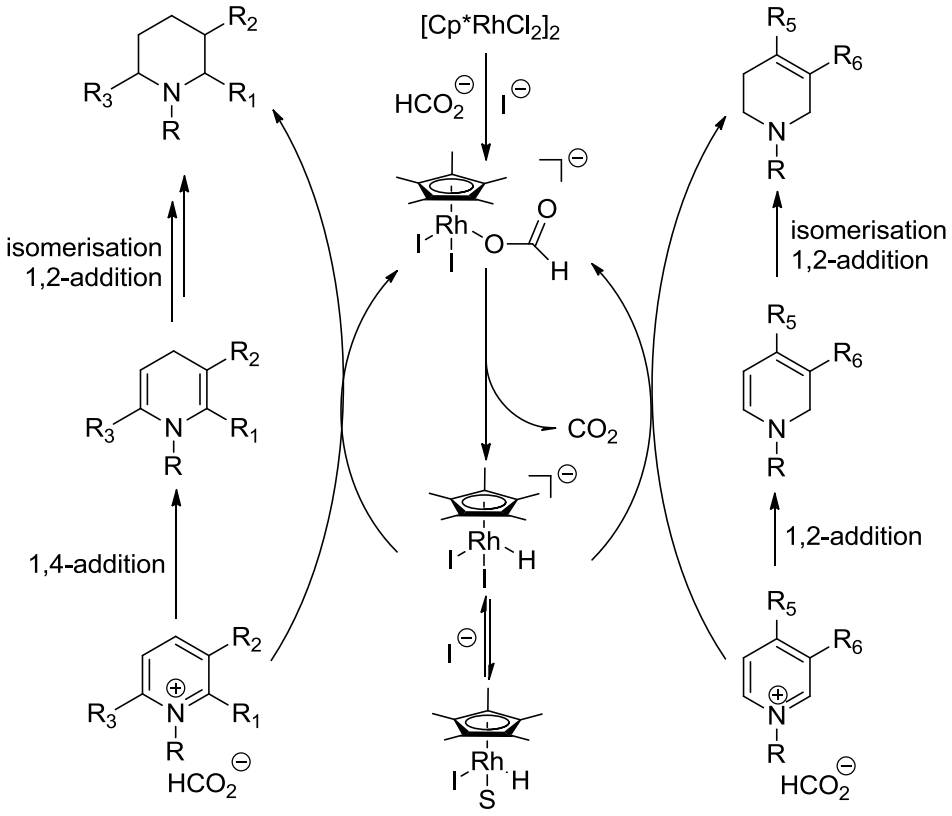


Scheme 47: TH of 4-substitued pyridinium in gram scale

3.2.3 Mechanistic investigations

A plausible mechanism explaining the role of iodide and the observed chemoselectivity is shown in Scheme 48. As suggested before,[16,20] the substrate is likely to be reduced with an anionic diiodo Rh-H hydride species. Both the iodide and anionic charge would render the hydride more hydridic, facilitating its transfer to the pyridinium. However, excess iodide salt is needed in order to suppress the dissociation of iodide anion from the active hydride species. As also observed in Chapter 2, too much iodide salt is not good, as it would facilitate the displacement of the coordinated formate by iodide, leading to catalytically inactive species. In the absence of a 4-substituent, the hydride adds preferentially at the 4 position initially (i.e. 1,4-addition); the resulting enamine isomerises to an iminium species and is then reduced *via* a 1,2-hydride addition. When the 4 position is substituted, 1,4-addition becomes almost impossible. Instead, 1,2-addtion takes place to give 1,2-dihydropyridine;

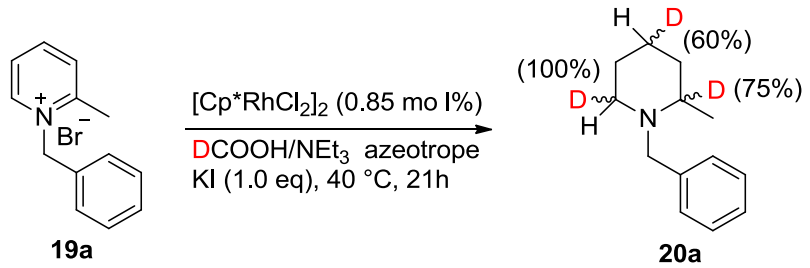
isomerisation of the resulting enamine followed by another 1,2-adddition affords the *N*-substituted 1,2,3,6-tetrahydropyrindines.



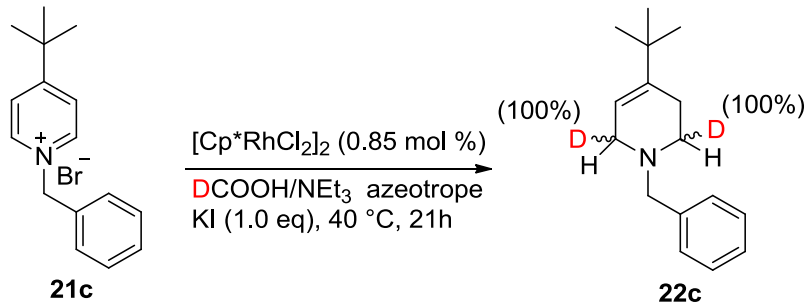
Scheme 48: Plausible mechanism for the TH of pyridinium salts

Consistent with this picture, the 2,4,6-positions of **20a** and the 2,6-postions of **22c** were deuterated when DCOOH-NEt_3 was used to reduce **19a** and **21c**, respectively, as shown in Scheme 49. The analysis of ^1H NMR spectra as indicates that full deuteration was occurred at the C6 and major deuteration at C2 and C4 of **19a**, while full deuteration was detected at the C2 and C6 of **21c** (see Section 3.4.4 for experimental

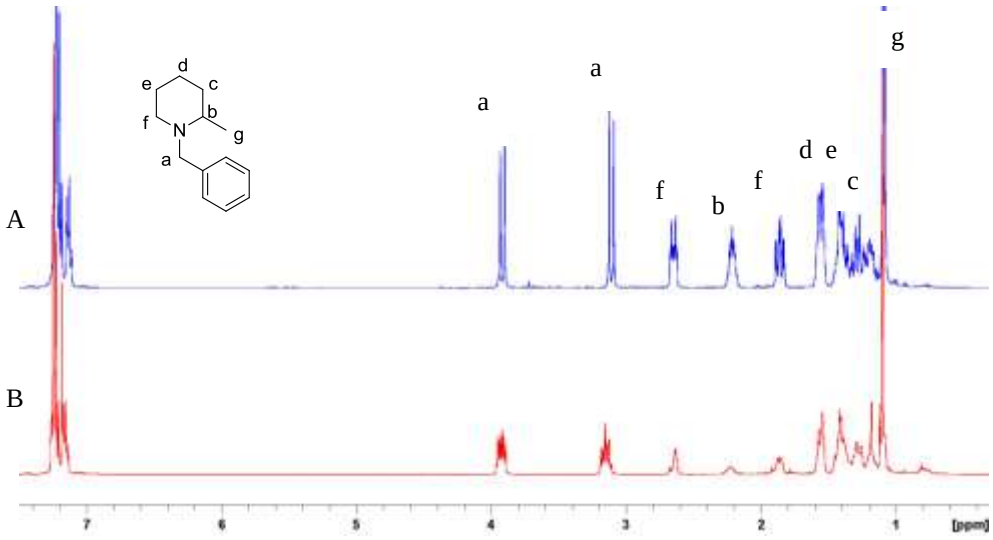
details). These deuteration results, can be readily explained with the mechanism suggested above, as shown in Scheme 50.

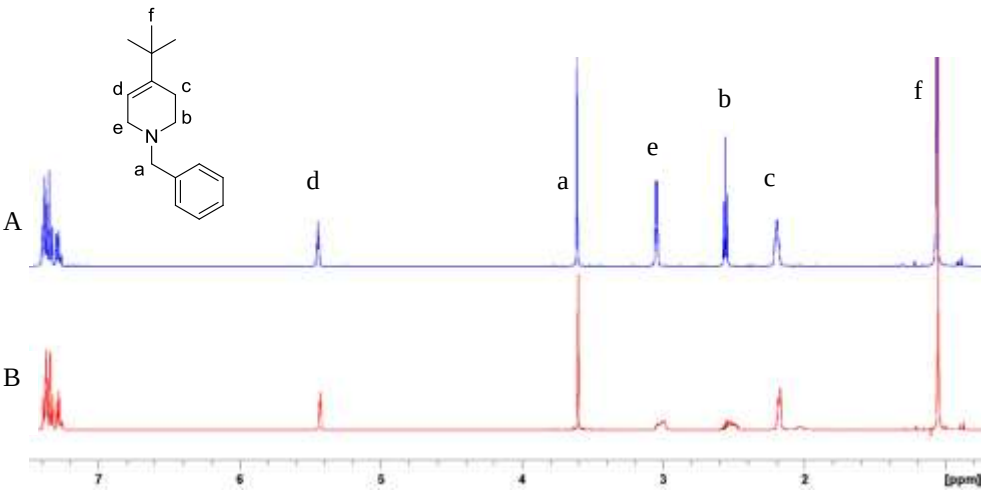


(1)

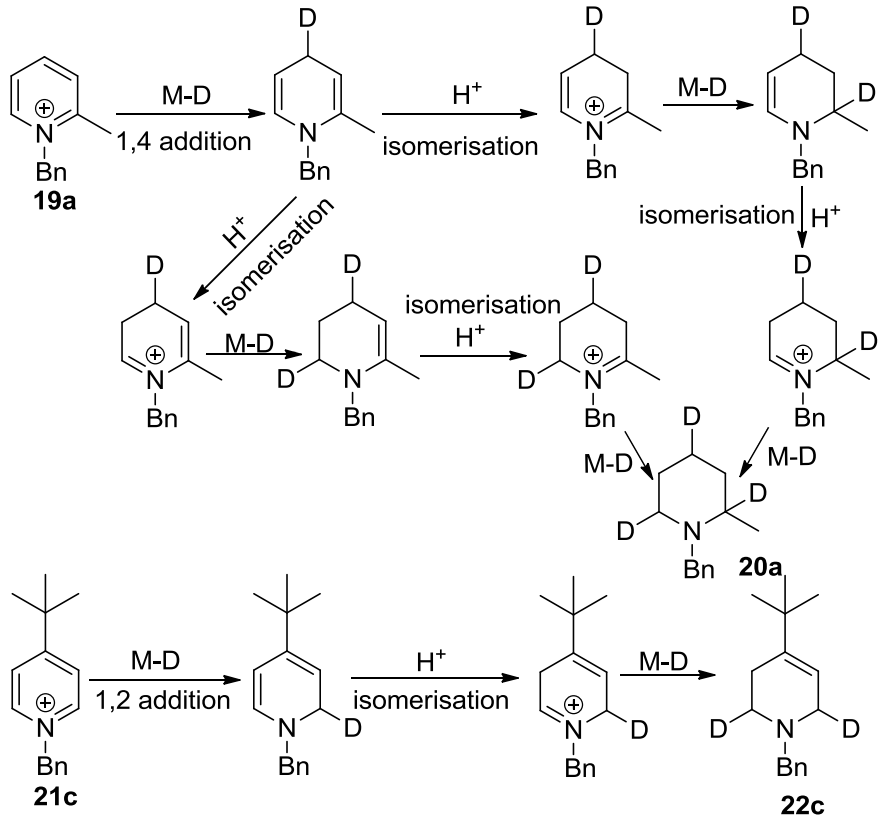


(2)





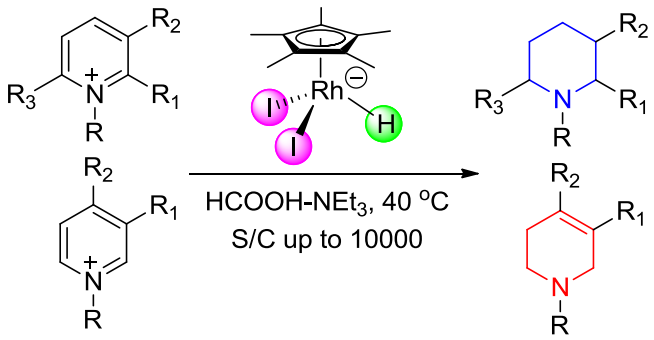
Scheme 49: TH of **19a** and **21c** catalysed by $[Cp^*RhCl_2]_2$. (A) with HCOOH-NEt_3 azeotrope; (B) with DCOOH-NEt_3 azeotrope.



Scheme 50: Proposed reaction pathways for TH of **19a** and **21c** with DCOOH catalysed by $[Cp^*RhCl_2]_2$

3.3 Conclusions and future work

In conclusion, we have developed a simple, efficient catalytic system for the TH of pyridines under mild conditions (Scheme 51). In particular, this protocol affords not only piperidines but also the 3,4-unsaturated variants with high chemoselectivities. A variety of piperidines and 1,2,3,6-tetrahydropyridines were obtained in good to excellent yields, providing valuable intermediates and feedstock for chemical, pharmaceutical and agrochemical synthesis.



Scheme 51: Summary of the chemoselective TH of pyridinium salts

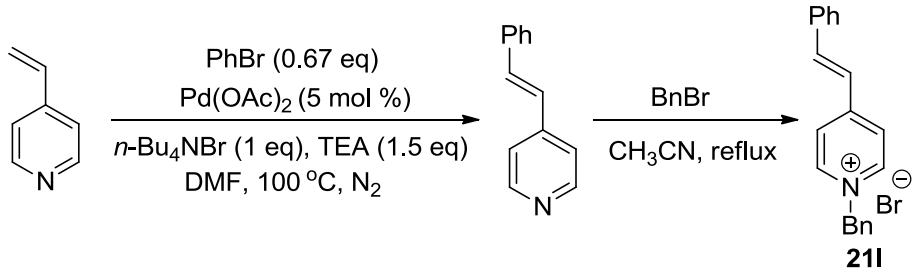
The ATH of 2-substituted pyridinium salts would be a natural extension of the full TH of pyridines. To seek structurally rigid ligands that are compatible with the stoichimetric iodide would probably dominate the efforts. Additionally, a remote idea would be to explore, in combination with the well-established reactions of olefin, to realise further functionalisation of the retainied C=C bonds in 3,4-unsaturated piepridines in a one-pot fashion.

3.4 Experimental

3.4.1 General information

Unless otherwise specified, the chemicals were obtained commercially from Aldrich, Alfa Aesar Apollo Scientific or TCI and used without further purification. Silica gel plates (GF_{254}) were used for TLC monitoring and silica gel (230-400 mesh) was used for running column chromatography. Formic acid-triethyl amine azeotrope was distilled prior to use. NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer with TMS as the internal standard. The mass spectra were obtained by chemical ionization (CI) or electrospray ionization (ESI). No significant difference was observed when the reaction was carried out in air and non-distilled formic acid-triethyl amine azeotrope.

3.4.2 Typical procedure for pyridinium salts preparation



21l

The first step of the above reaction represents a new synthetic procedure for the two compounds trans-2-styrylpyridine and trans-4-styrylpyridine according to the similar Heck reaction conditions,[20a] while the second step demonstrates the general procedure to prepare pyridinium salts.

An oven-dried carousel tube containing a stirring bar was charged with $Pd(OAc)_2$ (0.25 mmol) and *n*-Bu_4NBr (5.0 mmol). After degassing three times with nitrogen, Et_3N (7.5 mmol), PhBr (5 mmol), 4-vinylpyridine (7.5 mmol) and DMF (10 mL) were injected, after which the resulting mixture was stirred at 100 °C for 16 h. After cooling down to room temperature, the reaction mixture was transferred to pass a short silica-gel column to remove all the undissolved materials and washed with EtOAc (100 mL). The organic washes were combined and washed with 30 mL of brine, then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The solid residue was washed with hexane to remove the excessive 4-vinylpyridine which was hard to separate in TLC. After further dryness under vacuum, yellow solid was obtained (550 mg, 60%) as the desired product- *trans*-4-styrylpyridine. For the compound *trans*-2-styrylpyridine (540 mg, 59%), the same procedure was performed and the analytical data of the two compounds are in agreement with literature.[20b,c]

The obtained *trans*-4-styrylpyridine (500 mg, 2.75 mmol) was mixed with benzyl bromide (3.6 mmol, 0.4 mL) and 5 mL CH_3CN (For some substrates, a different solvent, like acetone or methanol, was chose for the quaternisation.) in a carousel tube. The mixture was refluxed at 85 °C for 15 min, light-yellow precipitates appeared and the reaction was stirred for overnight. After cooling down, the slurry was filtered, washed with acetone and dried under vacuum to give light-yellow powder **21l** (900 mg, 93%, unknown compound). ^1H NMR (d^6-DMSO, 400 MHz) δ (ppm):

9.13 (d, *J* = 6.4 Hz, 2H), 8.31 (d, *J* = 6.8 Hz, 2H), 8.06 (d, *J* = 16.4 Hz, 1H), 7.78-7.76 (m, 2H), 7.59-7.55 (m, 3H), 7.52-7.41 (m, 6H), 5.80 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 153.7, 144.8, 141.6, 135.5, 135.0, 130.9, 129.63, 129.60, 129.5, 129.0, 128.6, 124.7, 123.7, 62.6; HRMS (ESI+) for $C_{2H18}N$ $[M\text{-}Br]^+$ m/z Calcd: 272.1439; Found: 272.1440. Anal. calcd. for $C_{2H18}BrN$: C, 68.19; H, 5.15; N, 3.98; Found: C, 67.97; H, 5.06; N, 3.90. Substrate **19i** was obtained through the same procedure as yellow powder (unknown compound). ^{1}H NMR (d^6-DMSO, 400 MHz) δ (ppm): 9.22 (d, *J* = 6.4 Hz, 1H), 8.61 (d, *J* = 4.4 Hz, 2H), 8.09-8.03 (m, 1H), 7.89 (d, *J* = 16.0 Hz, 1H), 7.78-7.75 (m, 2H), 7.72 (d, *J* = 16.0 Hz, 1H), 7.50-7.43 (m, 3H), 7.40-7.30 (m, 5H), 6.19 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 152.6, 146.5, 145.6, 143.4, 135.1, 134.6, 131.2, 129.5, 129.4, 129.1, 129.0, 128.8, 127.8, 126.5, 126.2, 118.0, 60.6; HRMS (ESI+) for $C_{2H18}N$ $[M\text{-}Br]^+$ m/z Calcd: 272.1439; Found: 272.1438. Anal. calcd. for $C_{2H18}BrN$: C, 68.19; H, 5.15; N, 3.98; Found: C, 67.79; H, 5.04; N, 3.84.

3.4.3 General procedure for TH of pyridines

A carousel reaction tube containing a magnetic stirring bar and $[Cp^*RhCl_2]_2$ (0.155 mg, 0.25 μmol, measured using a stock DCM solution), *N*-benyl-2-methylpyridinium bromide salt (**19a**, 132 mg, 0.5 mmol) and potassium iodide (83 mg, 0.5 mmol) in 5 mL HCOOH-NEt_3 azeotrope was sealed after degassing and placed in a carousel reactor. The reaction mixture was stirred at 40 °C for 24 h, cooled to room

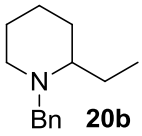
temperature and then basified with an aqueous solution of KOH. The resulting mixture was extracted with ethyl acetate (3×20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and after further dryness under vacuum, the product was sent for analysis without further purification. In the case of **20c-d**, **20f-i**, and **20k**, **22f-i**, **22k-m** and **22o**, the crude product was purified by column chromatography (EtOAc/hexane).

3.4.4 Deuteration experiments

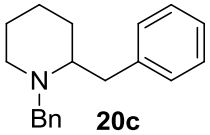
In a carousel reaction tube containing a magnetic stirring bar was charged $[Cp^*RhCl_2]_2$ (1.8 mg, 0.0028 mmol), **19a** (80 mg, 0.3 mmol) and potassium iodide (50 mg, 0.3 mmol). The pre-prepared DCOOH-NEt_3 mixture (DCOOH, 10 mmol, 0.40 mL; NEt_3, 4 mmol, 0.56 mL) was then introduced into the reaction tube, which was placed in a carousel reactor. The reaction mixture was stirred at 40 °C for 21 h. After cooling to room temperature and basifying with an aqueous solution of KOH, the resulting mixture was extracted with ethyl acetate (3×15 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to afford the pure product **20a** (39 mg, 68%), which was then analysed with ^{1}H NMR (Scheme 49, eq. 1). For TH of **21c**, after the same procedure was performed, pure product **22c** (64 mg, 93%) was obtained, which was also analysed with ^{1}H NMR (Scheme 49, eq. 2).

3.5 Analytic data of isolated products

20a **1-Benzyl-2-methylpiperidine (20a):**[20d] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.40-7.34 (m, 4H), 7.30-7.26 (m, 1H), 4.07 (d, *J* = 13.6 Hz, 1H), 3.26 (d, *J* = 13.6 Hz, 1H), 2.80 (dt, *J* = 11.6, 3.7 Hz, 1H), 2.40-2.32 (m, 1H), 2.01 (td, *J* = 10.8, 3.6 Hz, 1H), 1.74-1.69 (m, 2H), 1.61-1.29 (m, 4H), 1.24 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 139.6, 129.7, 128.5, 127.1, 58.8, 56.8, 52.5, 35.1, 26.4, 24.4, 20.0; MS (CI, *m/z*, %) 190 (100) $[M+H]^+$; Anal. calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40; Found: C, 81.87; H, 10.25; N, 7.35.

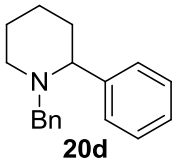


20b **1-Benzyl-2-ethylpiperidine (20b):**[20e] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.39-7.32 (m, 4H), 7.29-7.24 (m, 1H), 4.04 (d, *J* = 13.6 Hz, 1H), 3.24 (d, *J* = 13.6 Hz, 1H), 2.79 (dt, *J* = 11.6, 3.8 Hz, 1H), 2.28-2.22 (m, 1H), 2.07-2.01 (m, 1H), 1.75-1.63 (m, 4H), 1.53-1.44 (m, 3H), 1.38-1.31 (m, 1H), 0.97 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 140.3, 129.4, 128.5, 127.0, 62.3, 58.0, 52.4, 30.2, 25.8, 24.9, 24.3, 10.2; MS (CI, *m/z*, %) 204 (100) $[M+H]^+$; Anal. calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89; Found: C, 82.58; H, 10.63; N, 7.18.



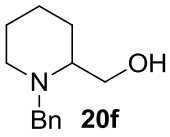
20c **1,2-Dibenzypiperidine (20c):**[20e] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.37-7.28 (m, 5H), 7.24-7.13 (m, 5H), 4.06 (d, *J* = 13.6

Hz, 1H), 3.49 (d, *J* = 13.6 Hz, 1H), 3.17 (d, *J* = 9.6 Hz, 1H), 2.80-2.74 (m, 1H), 2.68-2.58 (m, 2H), 2.25-2.19 (m, 1H), 1.67-1.60 (m, 1H), 1.54-1.50 (m, 3H), 1.36-1.23 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 140.9, 140.1, 129.8, 129.3, 128.64, 128.59, 127.2, 126.2, 62.2, 58.9, 51.3, 36.9, 29.7, 25.8, 22.9; HRMS for $C_{19}H_{24}N$ $[M+H]^+$: m/z calcd 266.1909, found 266.1908.



20d

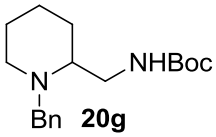
1-Benzyl-2-phenylpiperidine (20d):[20f] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.45 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 4.4 Hz, 4H), 7.24-7.17 (m, 2H), 3.76 (d, *J* = 13.6 Hz, 1H), 3.10 (dd, *J* = 11.0, 2.6 Hz, 1H), 2.96 (d, *J* = 11.6 Hz, 1H), 2.80 (d, *J* = 13.2 Hz, 1H), 1.96-1.89 (m, 1H), 1.80-1.74 (m, 2H), 1.67-1.51 (m, 3H), 1.42-1.30 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 146.2, 140.3, 129.1, 128.9, 128.4, 127.9, 127.3, 126.9, 69.6, 60.2, 53.8, 37.5, 26.4, 25.7; HRMS for $C_{18}H_{22}N$ $[M+H]^+$: m/z calcd 252.1752, found 252.1750.



20f

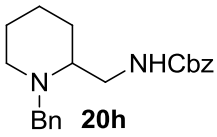
(1-Benzylpiperidin-2-yl)methanol (20f):[20g] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.34-7.28 (m, 4H), 7.26-7.22 (m, 1H), 4.06 (d, *J* = 13.6 Hz, 1H), 3.87 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.52 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.31 (d, *J* = 13.2 Hz, 1H), 2.89-2.84 (m, 3H), 2.70 (br, 1H), 2.45 (dq, *J* = 8.8, 4.2 Hz, 1H), 2.17-2.11 (m, 1H), 1.73-1.52 (m, 4H), 1.42-1.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 139.4, 129.3,

128.8, 127.4, 62.7, 61.3, 58.1, 51.2, 27.7, 24.5, 23.9; MS (CI, *m/z*, %) 206 (100) $[M+H]^+$; Anal. calcd. for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82; Found: C, 76.11; H, 9.70; N, 7.17.



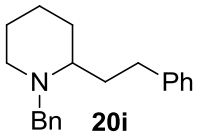
20g

***tert*-Butyl ((1-benzylpiperidin-2-yl)methyl)carbamate (20g):**[20h] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.34-7.29 (m, 4H), 7.26-7.23 (m, 1H), 5.05 (br, 1H), 4.00 (d, *J* = 13.2 Hz, 1H), 3.43 (dt, *J* = 13.6, 4.4 Hz, 1H), 3.29-3.23 (m, 1H), 3.20 (d, *J* = 13.6 Hz, 1H), 2.83-2.79 (m, 1H), 2.43-2.33 (m, 1H), 2.03 (td, *J* = 11.1, 2.5 Hz, 1H), 1.73-1.60 (m, 2H), 1.57-1.49 (m, 2H), 1.45 (s, 9H), 1.40-1.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 156.8, 139.5, 129.3, 128.7, 127.3, 59.9, 58.0, 52.2, 42.6, 29.3, 28.9, 25.2, 24.1; HRMS for $C_{18}H_{29}N_2O_2$ $[M+H]^+$: m/z calcd 305.2229, found 305.2233.



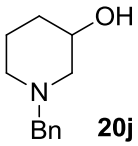
20h

Benzyl ((1-benzylpiperidin-2-yl)methyl)carbamate (20h, unknown compound**):** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.35-7.19 (m, 10H), 5.36 (br, 1H), 5.09 (s, 2H), 3.98 (d, *J* = 13.6 Hz, 1H), 3.48 (dt, *J* = 13.6, 4.4 Hz, 1H), 3.34-3.29 (m, 1H), 3.19 (d, *J* = 13.2 Hz, 1H), 2.81-2.75 (m, 1H), 2.43-2.39 (m, 1H), 2.01 (td, *J* = 11.2, 2.8 Hz, 1H), 1.70-1.25 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 157.2, 139.4, 137.2, 129.2, 128.9, 128.7, 128.50, 128.48, 127.3, 67.0 59.7, 58.1, 52.2, 43.1, 29.3, 25.2, 24.1; HRMS for $C_{21}H_{27}N_2O_2$ $[M+H]^+$: m/z calcd 339.2073, found 339.2059.



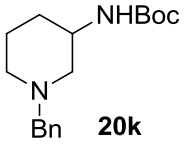
20i

1-Benzyl-2-phenethylpiperidine (20i, unknown compound**):** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.39-7.21 (m, 10H), 4.04 (d, *J* = 13.6 Hz, 1H), 3.32 (d, *J* = 13.6 Hz, 1H), 2.83-2.76 (m, 2H), 2.70-2.62 (m, 1H), 2.48-2.44 (m, 1H), 2.16-2.08 (m, 1H), 2.04-1.88 (m, 2H), 1.79-1.71 (m, 2H), 1.64-1.49 (m, 3H), 1.44-1.33 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 142.9, 129.0, 128.4, 128.2, 126.8, 125.7, 60.2, 57.4, 51.4, 33.5, 31.7, 29.9, 24.9, 23.5; MS (CI, *m/z*, %) 280 (100) $[M+H]^+$; Anal. calcd. for $C_{12H17}NO$: C, 85.97; H, 9.02; N, 5.01; Found: C, 84.74; H, 9.17; N, 4.82.



20j

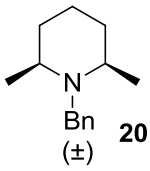
1-Benzylpiperidin-3-ol (20j):[20i] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.33-7.22 (m, 5H), 3.81-3.76 (m, 1H), 3.49 (s, 1H), 2.67 (br, 1H), 2.52-2.43 (m, 3H), 2.35-2.28 (m, 1H), 1.81-1.73 (m, 1H), 1.63-1.48 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 138.6, 129.5, 128.7, 127.5, 66.7, 63.5, 60.7, 53.9, 32.2, 22.1; MS (CI, *m/z*, %) 192 (100) $[M+H]^+$; Anal. calcd. for $C_{12H17}NO$: C, 75.35; H, 8.96; N, 7.32; Found: C, 73.71; H, 9.01; N, 7.28.



20k

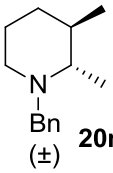
***tert*-Butyl (1-benzylpiperidin-3-yl)carbamate (20k):**[20j] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.28-7.15 (m, 5H), 4.94 (br, 1H), 3.68 (br, 1H), 3.39 (s, 2H), 2.43-2.12 (m, 4H), 1.61-1.40 (m, 4H), 1.37 (s,

9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 155.6, 138.7, 129.4, 128.6, 127.4, 79.4, 63.5, 59.1, 53.8, 46.8, 30.1, 28.9, 22.7; MS (CI, *m/z*, %) 291 (100) $[M+H]^+$; Anal. calcd. for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65; Found: C, 69.72; H, 9.03; N, 9.57.



20l

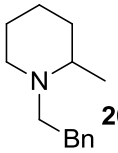
(±)-***cis*-1-Benzyl-2,6-dimethylpiperidine (20l):**[20k] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.38 (d, *J* = 6.8 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 3H), 3.81 (s, 2H), 2.54-2.45 (m, 2H), 1.67-1.51 (m, 4H), 1.37-1.33 (m, 2H), 1.07 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 142.5, 128.5, 128.3, 126.5, 57.7, 54.1, 35.1, 24.7, 22.6; MS (CI, *m/z*, %) 204 (100) $[M+H]^+$; Anal. calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89; Found: C, 82.38; H, 10.49; N, 7.14. The ratio of *cis*-conformation is determined by ^{1}HNMR integration, according to the literature.[20k]



20m

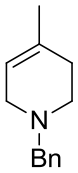
(±)-***trans*-1-Benzyl-2,3-dimethylpiperidine (20m**, unknown compound**):** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.29 (d, *J* = 7.2 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.15 (t, *J* = 7.2 Hz, 1H), 3.58 (d, *J* = 13.6 Hz, 1H), 3.45 (d, *J* = 13.6 Hz, 1H), 2.72-2.67 (m, 1H), 2.41-2.35 (m, 1H), 2.27-2.25 (m, 1H), 1.87-1.80 (m, 1H), 1.52-1.44 (m, 2H), 1.39-1.33 (m, 1H), 1.24-1.14 (m, 1H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 140.8, 129.0, 128.5, 126.9, 59.5, 58.1, 47.0, 35.4, 28.3, 25.4, 18.4; MS (CI, *m/z*, %) 204 (100) $[M+H]^+$;

Anal. calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89; Found: C, 82.37; H, 10.76; N, 7.26. The *trans*-conformation is determined by NOE analysis.



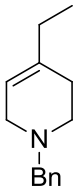
20n

2-Methyl-1-phenethylpiperidine (20n):[20l] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.30-7.26 (m, 2H), 7.20-7.17 (m, 3H), 2.97-2.67 (m, 5H), 2.40-2.30 (m, 2H), 1.71-1.53 (m, 4H), 1.37-1.26 (m, 2H), 1.15 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 141.4, 129.1, 128.8, 126.3, 56.7, 55.8, 52.7, 35.2, 31.9, 26.7, 24.6, 19.7; MS (CI, *m/z*, %) 204 (100) $[M+H]^+$; Anal. calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89; Found: C, 83.05; H, 10.49; N, 6.97.



22a

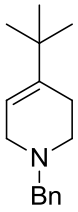
1-Benzyl-4-methyl-1,2,3,6-tetrahydropyridine (22a):[20m] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.41-7.26 (m, 5H), 5.41-5.39 (m, 1H), 3.60 (s, 2H), 2.98-2.96 (m, 2H), 2.59 (t, *J* = 5.8 Hz, 2H), 2.11 (br s, 2H), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 138.9, 133.2, 129.7, 128.6, 127.4, 119.8, 63.3, 53.4, 50.4, 31.3, 23.4; HRMS for $C_{13}H_{18}N$ $[M+H]^+$: m/z calcd 188.1434, found 188.1435.



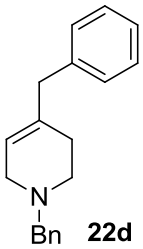
22b

1-Benzyl-4-ethyl-1,2,3,6-tetrahydropyridine (22b):[20n] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.29-7.15 (m, 5H), 5.29-5.27 (m, 1H),

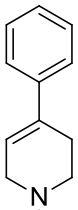
3.50 (s, 2H), 2.91-2.88 (m, 2H), 2.48 (t, *J* = 5.8 Hz, 2H), 2.02 (br s, 2H), 1.91 (q, *J* = 7.1 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 138.8, 138.4, 129.7, 128.6, 127.4, 117.8, 63.3, 53.4, 50.4, 29.9, 29.7, 12.2; HRMS for $C_{14}H_{20}N$ $[M+H]^+$: m/z calcd 202.1590, found 202.1589.



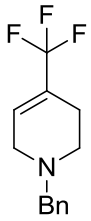
22c **1-Benzyl-4-(tert-butyl)-1,2,3,6-tetrahydropyridine (22c**, unknown compound**):** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.36-7.22 (m, 5H), 5.41-5.39 (m, 1H), 3.57 (s, 2H), 3.02-3.00 (m, 2H), 2.52 (t, *J* = 5.8 Hz, 2H), 2.15 (br s, 2H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 144.6, 138.8, 129.6, 128.6, 127.4, 116.3, 63.3, 53.9, 50.6, 35.3, 29.2, 25.9; HRMS for $C_{16}H_{24}N$ $[M+H]^+$: m/z calcd 230.1903, found 230.1906.



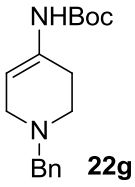
22d **1,4-Dibenzyl-1,2,3,6-tetrahydropyridine (22d):**[20o] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.33-7.15 (m, 10H), 5.36-5.35 (m, 1H), 3.55 (s, 2H), 3.27 (s, 2H), 2.97-2.96 (m, 2H), 2.51 (t, *J* = 5.8 Hz, 2H), 2.03 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 140.0, 138.8, 136.3, 129.7, 129.6, 128.69, 128.65, 127.5, 126.5, 121.3, 63.2, 53.4, 50.3, 43.9, 29.4; HRMS for $C_{19}H_{22}N$ $[M+H]^+$: m/z calcd 264.1747, found 264.1748.



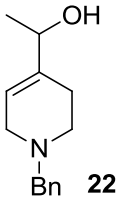
22e **1-Benzyl-4-phenyl-1,2,3,6-tetrahydropyridine (22e):**[20n] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.39-7.19 (m, 10H), 6.07-6.05 (m, 1H), 3.64 (s, 2H), 3.18 (q, *J* = 3.0 Hz, 2H), 2.72 (t, *J* = 5.6 Hz, 2H), 2.57(br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 141.3, 138.6, 135.4, 129.7, 128.70, 128.68, 127.5, 127.4, 125.3, 122.3, 63.2, 53.8, 50.4, 28.4; HRMS for $C_{18}H_{20}N$ $[M+H]^+$: m/z calcd 250.1590, found 250.1593. The reaction condition for gram-scale TH of **21e** is as follows: **21e** (1.01 g), $[Cp^*RhCl_2]_2$ (0.25 mg), KI (515 mg), non-distilled HCOOH-Et_3N azeotrope (10 mL), 24 hrs in air.



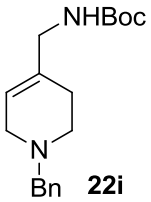
22f **1-Benzyl-4-(trifluoromethyl)-1,2,3,6-tetrahydropyridine (22f):**[20p] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.33 (d, *J* = 4.4 Hz, 4H), 7.31-7.25 (m, 1H), 6.28-6.25 (m, 1H), 3.62 (s, 2H), 3.10-3.06 (m, 2H), 2.63 (t, *J* = 5.6 Hz, 2H), 2.29 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 138.2, 129.4, 128.82, 128.75 (q, J_{CF} = 57.0 Hz), 127.7, 127.2 (q, J_{CF} = 31.3 Hz), 124.0 (q, J_{CF} = 268.5 Hz), 62.7, 51.9, 48.9, 23.6; HRMS for $C_{13}H_{15}NF_3$ $[M+H]^+$: m/z calcd 242.1151, found 242.1153.



22g ***tert*-Butyl (1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)carbamate (22g):**[20q] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.37-7.22 (m, 5H), 5.79 (br, 1H), 5.68 (s, 1H), 3.57 (s, 2H), 3.06-3.04 (m, 2H), 2.60 (t, *J* = 5.8 Hz, 2H), 2.24 (br s, 2H), 1.45 (s, 9H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 153.2, 138.8, 131.3, 129.5, 128.7, 127.5, 106.4, 80.4, 62.8, 52.1, 49.7, 29.0, 28.7; HRMS for $C_{17}H_{25}N_2O_2$ $[M+H]^+$: m/z calcd 289.1911, found 289.1906.

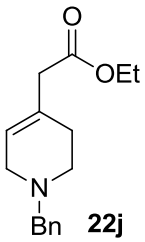


22h **1-(1-Benzyl-1,2,3,6-tetrahydropyridin-4-yl)ethanol (22h):**[20r] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.35-7.22 (m, 5H), 5.57 (s, 1H), 4.15 (q, *J* = 6.4 Hz, 1H), 3.57 (s, 2H), 3.33 (br, 1H), 2.96 (d, *J* = 2.4 Hz, 2H), 2.61-2.51 (m, 2H), 2.15 (d, *J* = 1.2 Hz, 2H), 1.24 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 140.5, 138.1, 129.8, 128.7, 127.6, 119.2, 71.0, 63.1, 52.8, 50.1, 25.1, 21.9; HRMS for $C_{14}H_{20}NO$ $[M+H]^+$: m/z calcd 218.1539, found 218.1541.



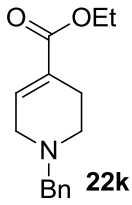
22i ***tert*-Butyl ((1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methyl)carbamate (22i**, unknown compound**):** ^{1}H NMR ($CDCl_3$, 400

MHz) δ (ppm): 7.35-7.29 (m, 4H), 7.27-7.23 (m, 1H), 5.53-5.51 (m, 1H), 4.60 (br, 1H), 3.66 (d, *J* = 4.8 Hz, 2H), 3.57 (s, 2H), 2.97 (br s, 2H), 2.57 (t, *J* = 5.8 Hz, 2H), 2.10 (br s, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 156.4, 138.6, 134.3, 129.6, 128.64, 128.55, 127.5, 120.9, 71.0, 63.1, 53.0, 50.0, 46.1, 28.8, 27.6; HRMS for $C_{18}H_{27}N_2O_2$ $[M+H]^+$: m/z calcd 303.2073, found 303.2069.



22j

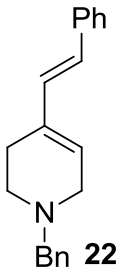
Ethyl 2-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)acetate (22j):[20s] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.38-7.22 (m, 5H), 5.55 (br s, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.58 (s, 2H), 2.99 (s, 4H), 2.59 (t, *J* = 5.8 Hz, 2H), 2.18 (br s, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 171.9, 138.7, 130.2, 129.6, 128.6, 127.5, 124.0, 63.0, 61.0, 53.1, 50.1, 42.9, 29.6, 14.7; HRMS for $C_{16}H_{22}NO_2$ $[M+H]^+$: m/z calcd 260.1651, found 260.1658.



22k

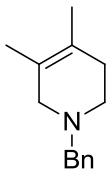
Ethyl 1-benzyl-1,2,3,6-tetrahydropyridine-4-carboxylate (22k):[20t] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.28-7.17 (m, 5H), 6.80 (br s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.54 (s, 2H), 3.06 (q, *J* = 3.2 Hz, 2H), 2.53 (t, *J* = 5.6 Hz, 2H), 2.34 (br s, 2H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 167.1, 138.4, 137.0, 129.4, 129.3,

128.7, 127.6, 62.8, 60.8, 53.1, 49.7, 25.7, 14.7; HRMS for $C_{15}H_{20}NO_2$ $[M+H]^+$: m/z calcd 246.1489, found 246.1491.



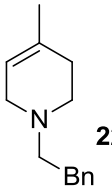
22l

s-*cis*-1-Benzyl-(*trans*-4-styryl)-1,2,3,6-tetrahydropyridine (22l):[20n] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.42-7.23 (m, 10H), 6.83 (d, *J* = 16.0 Hz, 1H, CH=CHPh), 6.48 (d, *J* = 16.0 Hz, 1H, CH=CHPh), 5.85 (s, 1H), 3.67 (s, 2H), 3.18 (s, 2H), 2.67 (t, *J* = 5.2 Hz, 2H), 2.46 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 138.2, 137.7, 134.3, 130.9, 129.2, 128.6, 128.3, 127.2, 126.3, 126.0, 62.7, 53.3, 49.7, 25.5; MS (CI, *m/z*, %) 276 (100) $[M+H]^+$; Anal. calcd. for $C_{2H21}N$: C, 87.23; H, 7.69; N, 5.09; Found: C, 86.91; H, 7.74; N, 5.04. The *s-cis* conformation is determined by NOE analysis.



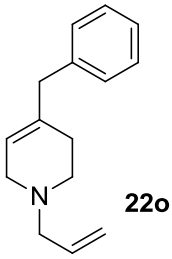
22m

1-Benzyl-4,5-dimethyl-1,2,3,6-tetrahydropyridine (22m):[20u] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.37-7.29 (m, 4H), 7.27-7.23 (m, 1H), 3.55 (s, 2H), 2.83 (s, 2H), 2.50 (t, *J* = 5.8 Hz, 2H), 2.06 (br s, 2H), 1.62 (d, *J* = 0.8 Hz, 3H), 1.56 (d, *J* = 0.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 138.8, 129.7, 128.6, 127.4, 124.9, 124.4, 63.3, 58.6, 50.7, 32.5, 18.7, 17.0; HRMS for $C_{14}H_{20}N$ $[M+H]^+$: m/z calcd 202.1590, found 202.1589.



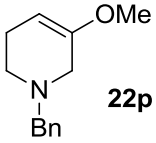
22n

4-Methyl-1-phenethyl-1,2,3,6-tetrahydropyridine (22n):[20v] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.31-7.29 (m, 2H), 7.22-7.18 (m, 3H), 5.39 (br s, 1H), 3.01 (s, 2H), 2.87-2.83 (m, 2H), 2.68-2.62 (m, 4H), 2.12 (br s, 2H), 1.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 140.9, 133.2, 129.1, 128.8, 126.4, 119.5, 60.8, 53.2, 50.8, 34.5, 31.3, 23.3; HRMS for $C_{14}H_{20}N$ $[M+H]^+$: m/z calcd 202.1590, found 202.1590.



22o

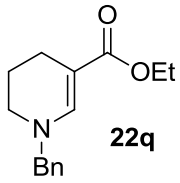
1-Allyl-4-benzyl-1,2,3,6-tetrahydropyridine (22o, unknown compound**):** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.29-7.25 (m, 2H), 7.20-7.16 (m, 3H), 5.95-5.85 (m, 1H), 5.39-5.36 (m, 1H), 5.20-5.11 (m, 2H), 3.28 (s, 2H), 3.05 (dt, *J* = 6.8, 1.2 Hz, 2H), 2.97-2.94 (m, 2H), 2.52 (t, *J* = 5.8 Hz, 2H), 2.07-2.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 139.9, 136.4, 135.9, 129.5, 128.7, 126.4, 121.3, 118.1, 61.8, 53.2, 50.3, 43.9, 29.4; HRMS for $C_{15}H_{20}N$ $[M+H]^+$: m/z calcd 214.1590, found 214.1594. HRMS for $C_{14}H_{20}N$ $[M+H]^+$: m/z calcd 202.1590, found 202.1590.



22p

1-benzyl-5-methoxy-1,2,3,6-tetrahydropyridine (22p, unknown compound**):** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.36-7.23

(m, 5H, overlapped with $CHCl_3$ peak), 4.66 (t, *J* = 4.0 Hz, 1H), 3.60 (s, 2H), 3.51 (s, 3H), 2.92 (q, *J* = 1.2 Hz, 2H), 2.52 (t, *J* = 6.0 Hz, 2H), 2.20-2.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 153.3, 138.2, 129.3, 128.4, 127.2, 91.2, 62.6, 54.2, 54.1, 50.2, 23.8; HRMS for $C_{13}H_{18}NO$ $[M+H]^+$: m/z calcd 204.1383, found 204.1388.



22q

Ethyl 1-benzyl-1,4,5,6-tetrahydropyridine-3-carboxylate (22q):[20w] ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.55 (s, 1H), 7.37-7.33 (m, 2H), 7.31-7.27 (m, 1H), 7.23-7.21 (m, 2H), 4.29 (s, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 2.99 (t, *J* = 5.6 Hz, 2H), 2.29 (t, *J* = 6.0 Hz, 2H), 1.79 (quintet, *J* = 5.6 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H),; ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 168.9, 146.3, 137.2, 128.9, 127.8, 127.5, 94.9, 59.9, 59.1, 45.5, 21.4, 20.1, 14.9; MS (CI, *m/z*, %) 268 (100) $[M+Na]^+$; Anal. calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71; Found: C, 73.07; H, 8.01; N, 6.01.

3.6 References

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CHAPTER 4 IRIDIUM CATALYSED HYDROGENATION OF *N*-HETEROAROMATIC COMPOUNDS

4.1 Introduction

In Chapters 2 and 3, we described that a rhodium-catalysed TH system, promoted by iodide ion, can reduce a range of *N*-heteroaromatics including quinolines, isoquinolines, quinoxalines and pyridinium salts, affording a series of valuable heterocycles under mild conditions. In this Chapter, we will present a complementary approach by using a cyclometalated iridium catalyst to hydrogenate *N*-heteroaromatics with dihydrogen, which was accidentally discovered during attempts to search for new TH catalysts.

The hydrogenation of organic compounds with H_2 is one of the great success stories of homogeneous catalysis. Building on the pioneering work of Wilkinson, Crabtree, Knowles and Noyori, highly effective hydrogenations of C=C and C=O bonds including the asymmetric versions have been developed and widely adopted by the synthetic community.[1] However the field of C=N bond hydrogenation is much less well developed and utilised, particularly for the case of *N*-heterocycles. As stated in Chapters 1 and 2, reduced heterocyclic compounds are present in many pharmaceuticals, natural products, organic dyes, fragrances and as hydrogen storage materials, and as a result, efficient methods for the synthesis of these compounds are desirable.[2] Of these, the catalytic hydrogenation of the parent unsaturated *N*-heterocycles with hydrogen gas is the most atom-economical route to these products. Additionally, hydrogenation offers an environmentally sound alternative

to the traditional reductions, due to the lack of stoichiometric waste products associated with the use of reactive metals and metal hydrides or other hydrogen sources.[3]

In comparison to the hydrogenation of olefins, carbonyls and imines, the hydrogenation of *N*-heterocycles is more challenging due to the aromaticity of the *N*-heterocyles. Transition metal catalysts based on Rh, Ir, Ru, Os, Mo and Fe have been applied to the homogeneous hydrogenation of *N*-heterocycles, including the asymmetric versions.[4, 5] Unfortunately, these reactions are often characterised with the use of high temperatures or hydrogen pressures, while many systems require the use of additives such as Brønsted acids[5g], chloroformates[5h] or I_2[5f] to activate the substrates or catalysts. Furthermore, to the best of our knowledge, there is no single reported catalyst capable of hydrogenating quinolines, 3,4-dihydroisoquinolines, quinoxalines and indoles, let alone under mild conditions. Recently, Crabtree and co-workers reported that a $[Ir(NHC)(PPh_3)(COD)]PF_6$ complex is active for the reduction of *N*-heteroaromatics at room temperature and low H_2 pressures (1-5 atm).[5d] However, additional PPh_3 was required for catalytic activity and the substrates were limited mainly to quinolines.

4.2 Results and Discussion

4.2.1 Initial results and further optimisation

Recently, Xiao and co-workers reported that cyclometallated Cp*Ir(N^C)Cl complexes derived from substituted acetophenone imines are highly active catalysts for a range of hydrogen transfer reactions such as TH of imines, reductive amination and dehydrogenation of formic acid.[6] Among these catalysts, which are now commercially available, we found that a catalyst bearing an electron-donating group can catalyse dehydrogenation of various benzo-fused *N*-heterocycles, releasing H_2 as the only byproduct.[6e] As can be seen in Figure 11, using as low as 0.1 mol% catalyst and in the absence of acceptors and additives, the reaction realises the oxidation without oxidants, affording quinolines, indoles, quinoxalines, isoquinolines and β-carbolines in high yields.

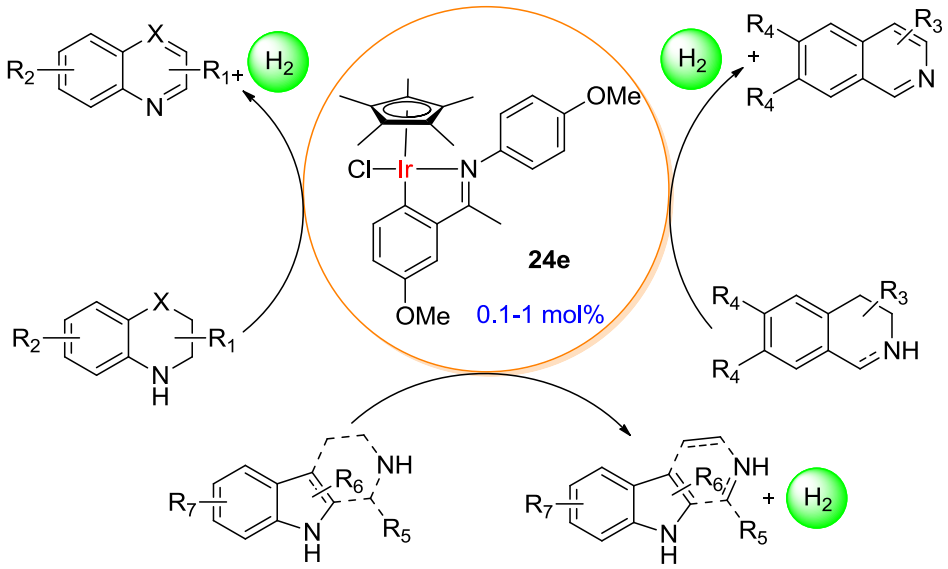
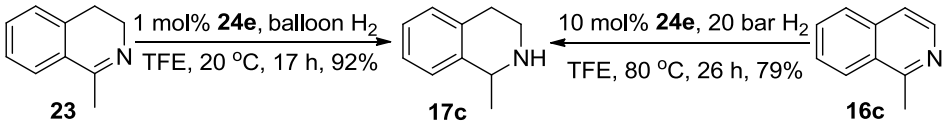


Figure 11: Acceptorless dehydrogenation of *N*-heterocycles

During this work, we observed that under the same conditions, the catalyst for dehydrogenation also can catalyse the hydrogenation of 3,4-dihydroisoquinoline **23** at 20 °C and 1 atm H_2 pressure in excellent yield. The stable isoquinoline **16c** can be hydrogenated as well in good yield although more forcing conditions are needed (Scheme 52). Encouraged by these initial results, we wondered if we could find an appropriately functionalised complex to catalyse the selective reduction of *N*-heterocycles under mild conditions, allowing for the operationally simple synthesis of reduced *N*-heterocyclic compounds.



Scheme 52: Hydrogenation of isoquinoline derivatives

In comparison to cyclic imines, quinolines are more challenging to reduce and their mild hydrogenation by homogeneous catalysis is scarce.[5d] Thus, we chose 2-methylquinoline **12a** as a model substrate to test a range of $Cp^*Ir(N\text{^}C)Cl$ complexes for their hydrogenation ability (Figure 12) in as-received 2,2,2-trifluoroethanol (TFE) at ambient temperature with 1 mol% catalyst (Table 1). A hydrogen balloon (1 atm H_2 pressure) was used as the hydrogen source. It was delightful, yet surprising, that of the complexes **24a-f**, only the electron rich 3,4-methylenedioxy-substituted complex **24f** showed any activity (Table

7, entries 1-6). To assess the effect of the *N*-donor substituent, complexes **24g-i, 24l-n** were prepared and tested,[6] all of them were found to catalyse the hydrogenation although with diminished activity in comparison to **24f** (Table 7, entries 7-9, 12-14).

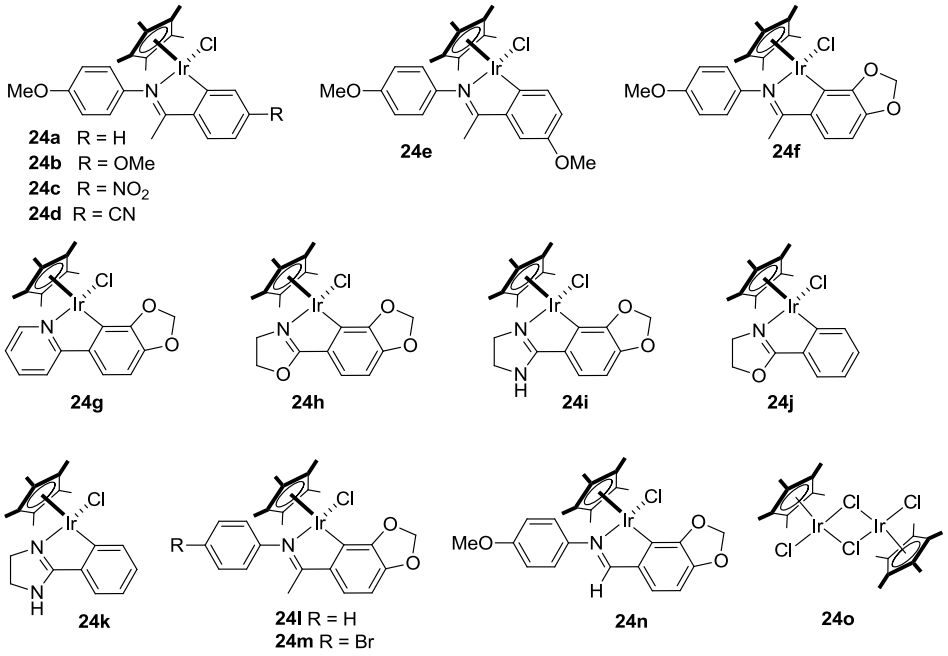
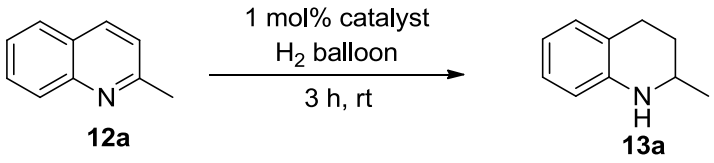


Figure 12: Catalysts examined for hydrogenation of *N*-heteroaromatics

As with **24a-e**, complexes **24j** and **24k** did not show any activity, which indicates that the 3,4-methylenedioxybenzene motif in the catalyst is essential to the activity. Furthermore, the more electron-rich *N*-donors are required for higher activity (Table 7, entries 9 *vs* 7 and 8). In keeping with the need for a highly electron rich ligand set, the *N*-phenyl (**24j**) and *N*-*p*-bromophenyl (**24k**) analogues showed slightly lower activities than **24f** (Table 7, entries 12 and 13). Interestingly, the aldimine derived complex **24n** was considerably less active than its ketimine analogue **24f**

possibly due to its less rigid character (Table 7, entry 14). No reaction was observed when $[Cp^*IrCl_2]_2$ (**24m**) or no catalyst was used (Table 7, entries 15 and 24). It is worth to note that the use of distilled TFE did not show any significant difference. Screening a variety of different reaction solvents suggested that the use of TFE was essential for good catalytic activity at 1 atm H_2 pressure (Table 7, entries 16-23).

Table 7. Optimisation of the hydrogenation of **12a**.[a]



Entry	Complex	Solvent	Conversion [%][b]
1	**24a**	TFE	NR
2	**24b**	TFE	NR
3	**24c**	TFE	NR
4	**24d**	TFE	NR
5	**24e**	TFE	NR
6	**24f**	**TFE**	**100**
7	**24g**	TFE	9
8	**24h**	TFE	21
9	**24i**	TFE	77
10	**24j**	TFE	NR
11	**24k**	TFE	NR
12	**24l**	TFE	87

13	**24m**	TFE	88
14	**24n**	TFE	6
15	**24o**	TFE	NR
16	**24f**	MeOH	NR
17	**24f**	EtOH	NR
18	**24f**	^{i}PrOH	NR
19	**24f**	DCM	NR
20	**24f**	THF	NR
21	**24f**	toluene	NR
22	**24f**	H_2O	NR
23	**24f**	EtOAc	NR
24	None	TFE	NR

[a] Conditions: 2-methylquinoline **12a** (0.5 mmol), complex (5 μmol), solvent (3 mL), rt, 3h, H_2 (1 atm). [b] Conversion determined by ^{1}H NMR of the crude reaction mixture and normalising the sum of the product and starting material integrals to 100%. NR = no reaction.

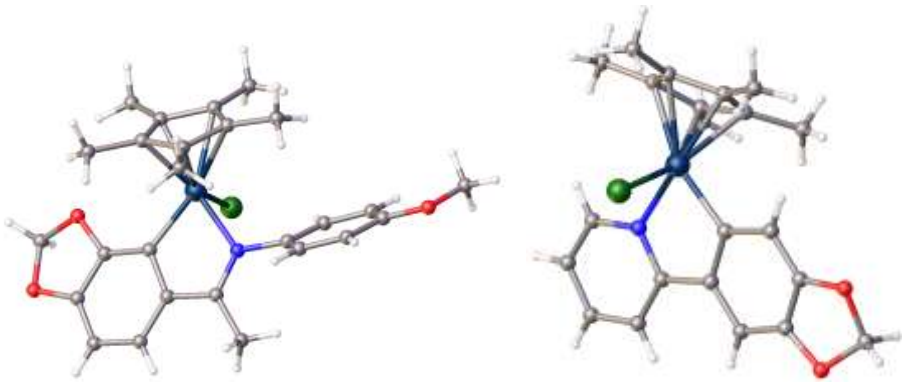


Figure 13: Molecular structures of **24f** (major isomer, left) and **24g** (minor isomer, right) determined by X-ray diffraction. Thermal ellipsoids are shown at 50%.

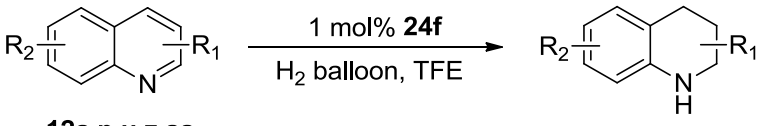
Ligands bearing the 3,4-methylenedioxy group underwent selective cyclometallation with $[Cp^*IrCl_2]_2$[7] to give the more hindered products with 85:15-95:5 isomeric ratios (Figure 13), due to the *ortho*-directing effect of the oxygen atoms.[8] In contrast, the 3-OMe group of **24e** resulted in selective cyclometallation *para* to the OMe, and **24e** proved to be an inactive catalyst (Table 7, entry 5).

4.2.2 Substrate scope

Using the optimised conditions, a variety of quinolines (including substituents at 2-, 3-, 4-, 6- and 8-positions), were hydrogenated to give the 1,2,3,4-tetrahydroquinoline products in good to excellent yields (Table 8). The reaction was found to be highly tolerant of other functionalities such as halides, esters, and free hydroxyl groups (Table 8, entries 10, 12-14 and 16). It is worthy to note that 3- and 4-methylquinolines, which are often challenging substrates,[5b,e] were reduced with full conversion, although a slightly elevated temperature and prolonged time was necessary. Reduction of phenanthrolines gave the partially hydrogenated 1,2,3,4-tetrahydrophenanthrolines as the exclusive products (Table 8, entries 8 and 9). Notably, entry 6 represents the first homogeneous hydrogenation of 2,2'-biquinoline. Acridine was reduced to the 9,10-dihydro product (Table 8, entry 7). The presence (or lack of) 2-substituents did not unduly affect the reaction, showing that coordination of the substrate and/or product to the single active site does

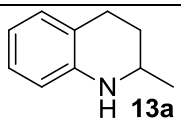
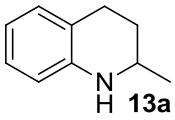
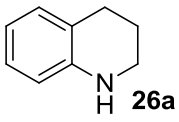
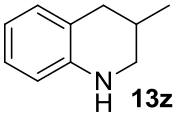
not hamper the reaction. The catalyst loading can be lowered. For instance, in the reduction of **12a**, a TON of 9,200 (85% isolated yield) was achieved at 85 ^{o}C in 16 h and 1 atm H_2 pressure, showing the robust nature of the hydrogenation reaction (Table 8, entry 2). Mild conversion was observed for the 2-functional substrate (Table 8, entry 16) which was sluggish by the TH in Chapter 2. Attempting to demonstrate the chemoselective reduction of C=N bonds over terminal C=C bonds failed (Table 8, entry 17), which may be due to the alkene coordinating to the single metal site preventing the formation of Ir hydride.

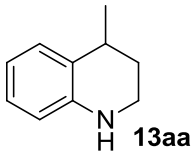
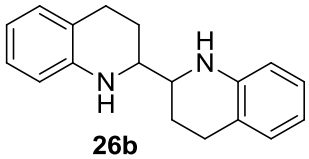
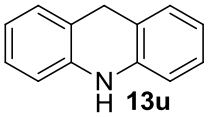
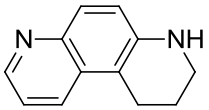
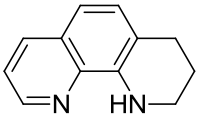
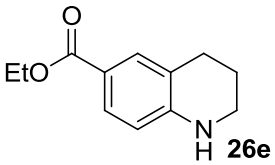
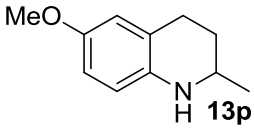
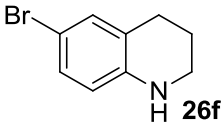
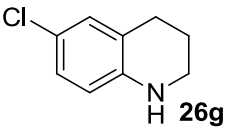
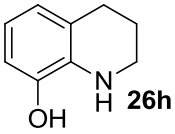
Table 8 Hydrogenation of quinolines with **24f**.[a]

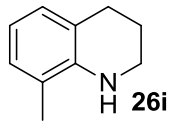
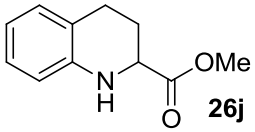
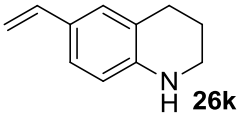


12a,p,u,z,aa
25a-k

13a,p,u,z,aa
26a-k

Entry	Product	Temp (°C)	Time [h]	Yield [%][b]
1	 **13a**	rt	3	96 (100)
2[c]	 **13a**	85	16	85 (92)
3	 **26a**	rt	3	95 (100)
4	 **13z**	40	20	97 (100)

5	 **13aa**	40	20	98 (100)
6	 **26b**	rt	3	97 (100) 4:1 dr
7	 **13u**	rt	3	99 (100)
8	 **26c**	40	20	93 (100)
9	 **26d**	40	20	80 (100)
10	 **26e**	rt	3	97 (100)
11	 **13p**	40	3	92 (95)
12	 **26f**	rt	3	97 (100)
13	 **26g**	rt	3	96 (100)
14	 **26h**	rt	3	98 (100)

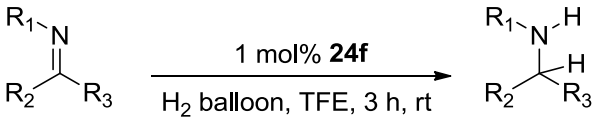
15	 **26i**	40	3	97 (100)
16	 **26j**	rt	18	(56)
17	 **26k**	40	96	NR

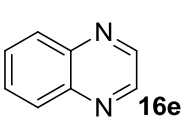
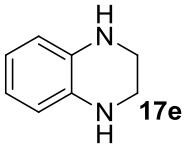
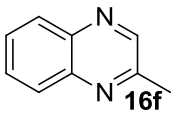
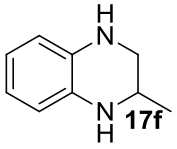
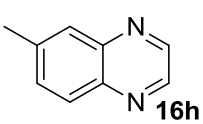
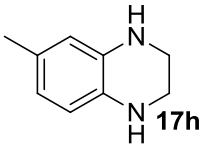
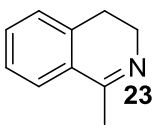
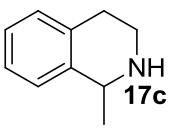
[a] Reaction conditions: **12** or **25** (0.5 mmol), **24f** (5 μmol), TFE (3 mL), H_2 (1 atm). [b] Yields of isolated products. Conversion in parentheses determined by ^{1}H NMR of the crude reaction mixture and normalising the sum of the product and starting material integrals to 100%. NR = no reaction. [c] 0.01 mol% **24f** was used.

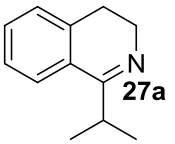
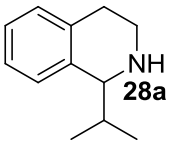
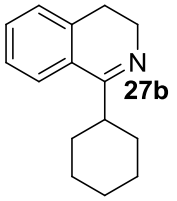
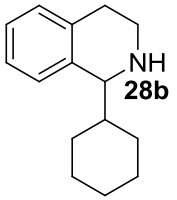
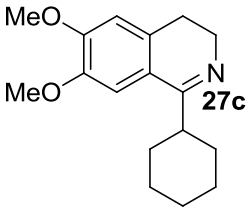
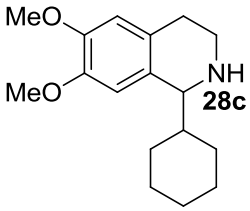
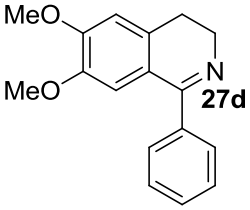
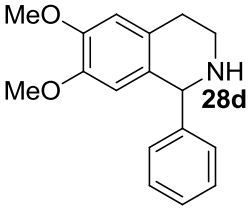
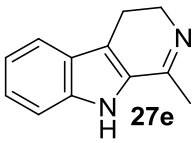
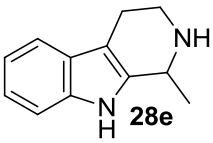
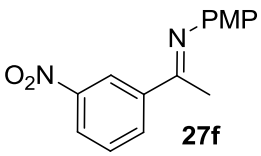
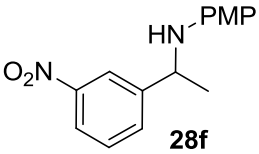
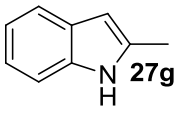
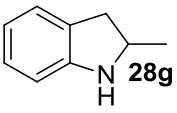
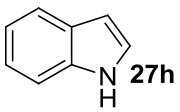
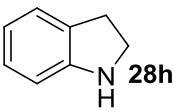
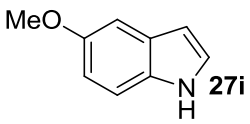
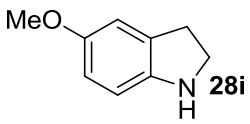
We also investigated the reductions of a variety of other *N*-heterocycles and imines (Table 9). Quinoxalines were fully reduced, which to our knowledge is the first example of homogeneous hydrogenation of these substrates under ambient conditions (Table 9, entries 1-3). Cyclic imino C=N bonds were also efficiently hydrogenated, with 1,2,3,4-tetrahydroisoquinolines and a β-carboline (Table 9, entries 4-9) obtained in high yields from the corresponding dihydro substrates, whilst an acyclic ketimine was smoothly reduced within 3 h at ambient temperature. The presence of a nitro group was well tolerated (Table 9, entry 10). Unprotected indoles (Table 9, entries 11-13), which are often challenging substrates for homogeneous hydrogenation,[9] could be reduced to the corresponding indolines. However, indoles with electron-

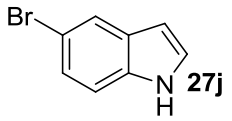
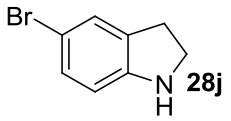
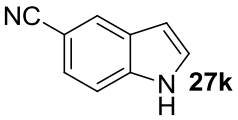
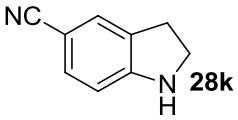
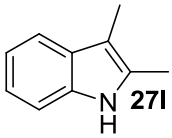
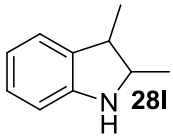
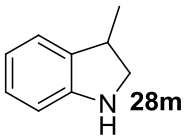
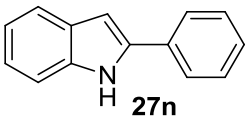
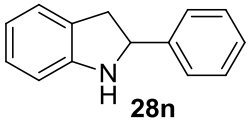
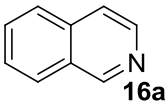
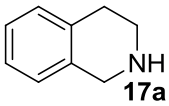
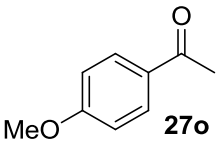
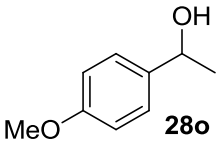
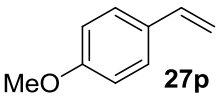
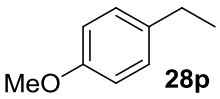
deficient groups were proved to be less active or inactive (Table 9, entries 14 and 15), maybe a result of the difficulty of enamine-imine tautomerisation. Similarly low reactivity was also observed for 2-phenyl and 3-substitued indoles (Table 9, entries 16-18). No reaction was observed for either ketone or styrene substrates (Table 9, entries 20 and 21) showing the chemoselectivity of **24f** for reduction of C=N bonds over C=O and C=C bonds. The isoquinoline which can be fully reduced by the $[Cp^*RhCl_2]_2$-I⁻ catalyst, was inactive in this system (Table 9, entry 19).

Table 9 Hydrogenation of other C=N bonds with **24f**.[a]



Entry	Substrate	Product	Yield [%][b]
1[c]			96 (100)
2			85 (92)
3			95 (100)
4			97 (100)

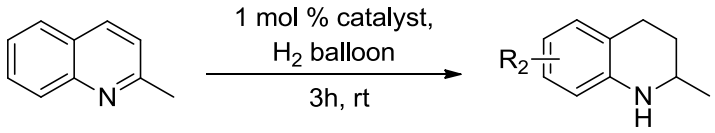
5	 **27a**	 **28a**	98 (100)
6	 **27b**	 **28b**	97 (100) 4:1 dr
7	 **27c**	 **28c**	99 (100)
8	 **27d**	 **28d**	93 (100)
9	 **27e**	 **28e**	80 (100)
10	 **27f**	 **28f**	97 (100)
11	 **27g**	 **28g**	92 (95)
12	 **27h**	 **28h**	97 (100)
13[d]	 **27i**	 **28i**	96 (100)

14[d]	 **27j**	 **28j**	(9)
15[d]	 **27k**	 **28k**	NR
16	 **27l**	 **28l**	(40) *trans*:*cis* = 4:1
17	 **27m**	 **28m**	NR
18[d]	 **27n**	 **28n**	NR
19[d]	 **16a**	 **17a**	NR
20	 **27o**	 **28o**	NR
21	 **27p**	 **28p**	NR

[a] Reaction conditions: **16, 23** or **27** (0.5 mmol), **24f** (5 µmol), TFE (3 mL), rt, 3 h, H_2 (1 atm). [b] Yields of isolated products. Conversion in parentheses determined by ^{1}H NMR of the crude reaction mixture and normalising the sum of the product and starting material integrals to 100%. NR = no reaction. [c] 0.5 mol% **24f** was used. [d] 40 °C, 20 h.

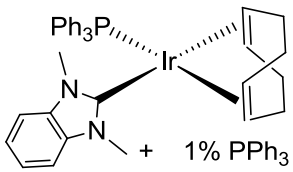
To further demonstrate the utility of complex **24f** for the reduction of *N*-heterocycles, three widely used heterogeneous hydrogenation catalysts[10] and five homogeneous catalysts, including systems that have been shown to be extremely effective for quinoline hydrogenations,[5c,d,i] were compared to **24f** for the reduction of **12a** (Table 10). Complex **24f** was found to be over 14 times more active than Rh/C which was the most active of the heterogeneous catalysts (Table 10, entry 3) and 6 times as active as $[IrCl(COD)]_2$/P-Phos/I_2, which was the most active of the other homogeneous catalysts previously reported (Table 10, entry 9).[5i] To eliminate the possibility that the use of TFE solvent, rather than the choice of catalyst, was responsible for the high activity of **24f**, all reactions were repeated in TFE. However, the use of TFE did not increase the effectiveness of any of the other catalysts (Table 10, entries 2-6).

Table 10 Comparison of **24f** with other commonly used catalysts.[a]



12a **13a**

Entry	Catalyst	Solvent[b]	T(h)	Conv. (%)[c]
1	**24f**	TFE	1	91
2	Pd/C (10%)	MeOH	3	5 (0)

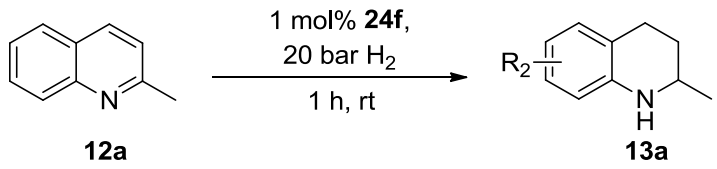
3	Rh/C (5%)	MeOH	3	7 (4)
4	PtO_2	MeOH	3	4 (0)
5	$Rh(PPh_3)_3Cl$	MeOH	3	0 (0)
6	$[Ir(Py)(PCy_3)COD][PF_6]$	DCM	3	0 (0)
7[d]		toluene	1	7
8	$[Ru(p\text{-cymene})Cl_2]_2$ / 5% I_2	THF	1	0
9	$[Ir(Cl)COD]_2$ /P-Phos / 5% I_2	THF	1	15

[a] Conditions: **12a** (0.5 mmol), catalyst (1 mol%), solvent (3 mL), rt, H_2 balloon. [b] Dry, degassed solvent was used, apart from TFE. [c] Conversion determined by ^{1}H NMR of the crude reaction mixture and normalising the sum of the product and starting material integrals to 100%. Data in parentheses were obtained by using TFE as solvent. [d] Reaction was prepared in an N_2 filled glovebox.

4.2.3 Mechanistic investigations

As was stated before, the use of TFE was essential for good catalytic activity at 1 atm H_2 pressure (Table 7). However, the reaction was found to occur slowly in MeOH and EtOH at 20 bar (Table 11, entries 2 and 3), although TFE remained the most effective solvent. The hydrogenation did not take place in other commonly used solvents (Table 11, entries 4-9).

Table 11 Hydrogenation of **12a** in various solvents at 20 bar H_2 pressure[a]



12a **13a**

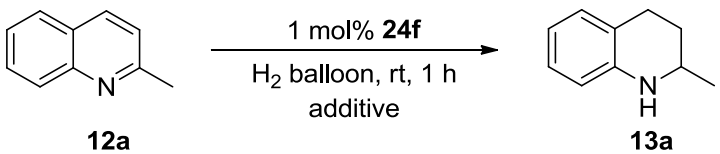
Entry	Solvent	Solvent pKa[b]	Conversion(%)[c]
1	TFE	12.5	83
2	MeOH	15.5	5
3	EtOH	15.8	1
4	^{i}PrOH	16.5	0
5	THF	-	0
6	DCM	-	0
7	EtOAc	-	0
8	H_2O	15.7	0
9	toluene	41	0

[a] Conditions: **12a** (0.5 mmol), catalyst **24f** (5 µmol), solvent (3 mL), 20 bar H_2, rt, 1 h. [b] pKa data from http://evans.harvard.edu/pdf/evans_pka_table.pdf. [c] Conversion determined by ^{1}H NMR of the crude reaction mixture and normalising the sum of the product and starting material integrals to 100%.

TFE is known to solvate chloride ions more strongly than MeOH,[11] and so may enhance the dissociation of chloride from the coordinatively saturated 18 electron complexes **24**, creating a vacant, active site on

Ir(III). In line with this, hydrogenations in TFE were found to be inhibited by the addition of chloride ions (6 fold decrease in conversion with 10% NBu_4Cl) or PPh_3 (no reaction with 1% PPh_3) (Table 12, entries 2 and 4). It is important to note that NaCl is poorly soluble in TFE so the amount of dissolved chloride ions is considerably less than the amount of NaCl used in entry 3. In addition, as TFE (p*K*a 12.4) is more acidic than MeOH (p*K*a 15.5) or EtOH (p*K*a 15.8),[12] it can hydrogen bond to substrate or product more effectively, and thereby may help prevent them from competing with H_2 for the single vacant site on Ir(III). Indeed, ^1H NMR showed that upon mixing **12a** with TFE in $CDCl_3$, the chemical shift of the TFE hydroxyl proton changed from 2.5 to 3.5 ppm, suggesting that TFE hydrogen bonds to **12a** (Figure 14). Not entirely surprisingly, the use of chloride abstracting agents ($AgSbF_6$ and $NaBAr^F{}_4$) did not allow the reaction to proceed in MeOH at 1 atm H_2 pressure (Table 12, entries 5 and 6), given the weaker hydrogen bonding ability of MeOH.

Table 12 Effect of additives on the hydrogenation of **12a**.[a]



12a **13a**

Entry	Solvent	Additive	Conversion (%)[b]
1	TFE	none	91

2	TFE	10% TBACl	15
3	TFE	100% NaCl	48
4	TFE	1% PPh_3	0
5	MeOH[c]	1% $AgSbF_6$	0
6	MeOH[c]	2% $NaBAr^F_4$	0

[a] Conditions: **12a** (0.5 mmol), catalyst **24f** (5 µmol), TFE (3 mL), rt, 1 h, H_2 balloon. [b] Conversion determined by ^{1}H NMR of the crude reaction mixture and normalising the sum of the product and starting material integrals to 100%. [c] Dry, degassed solvent was used.

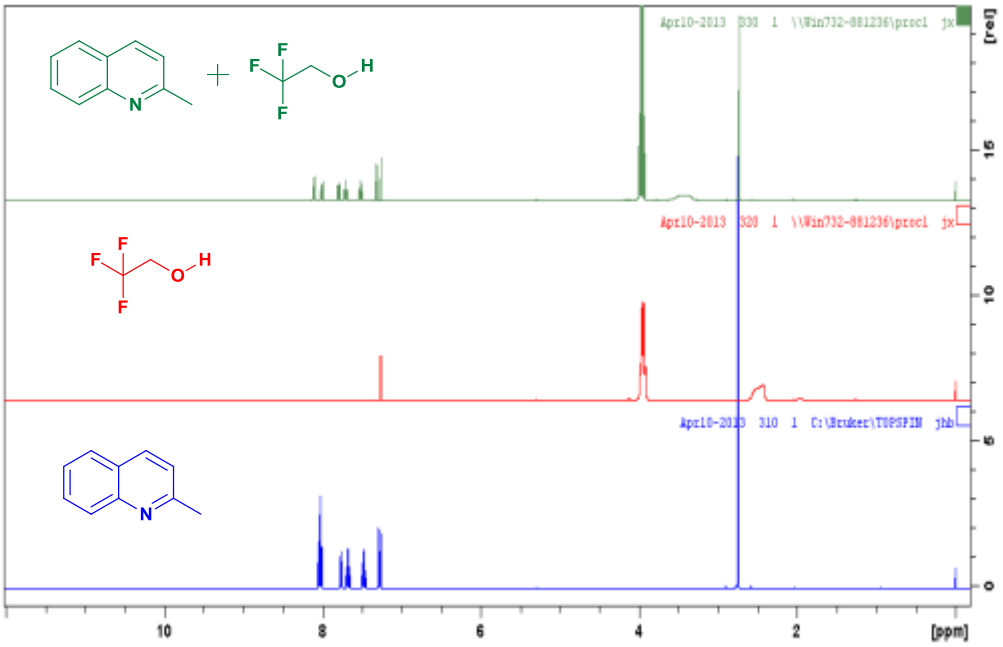
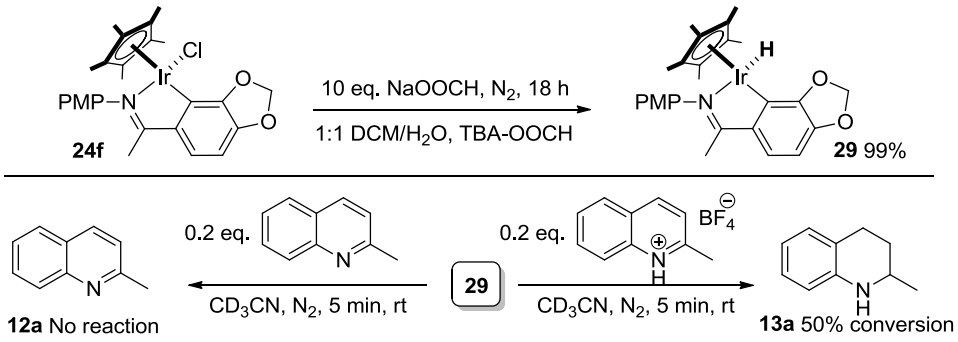


Figure 14 Hydrogen bonding between TFE and 2-methylquinoline **12a**. Superimposed ^{1}H NMR spectra (400 MHz, $CDCl_3$) of **12a** (bottom, 1 drop, blue), TFE (middle, 1 drop, red), and **12a** and TFE (top, 1 drop

each, green). As shown above, the OH proton of TFE hydrogen bonds to **12a**, resulting in a change of its ^{1}H NMR shift from 2.5 ppm to 3.5 ppm.

In order to gain further information about the reaction mechanism, we prepared the iridium hydride[13] species **29** by treating **24f** with an excess of sodium formate in DCM/H_2O. Treatment of **29** with 0.2 equivalents of 2-methylquinoline **12a** did not lead to the formation of **13a**. However, the reaction of **29** with 0.2 equivalents of 2-methyl quinolinium tetrafluoroborate led to the rapid formation of the fully reduced product **13a** (Scheme 53). Repeating the reactions in the presence of TFE did not alter the results. These results suggest that the protonated, instead of the neutral quinoline, is the species that is reduced in the reaction.



Scheme 53: Synthesis and reactions of hydride **29**

4.3 Conclusions and future work

In conclusion, this chapter reports the reduction of a diverse range of *N*-heterocyclic compounds under mild conditions (ambient temperature, 1 atm H_2) without the use of any additives (Figure 15). Key to the success of the reaction is the choice of ligand and the use of TFE as solvent. The reaction was found to be tolerant of a wide range of other, potentially reducible, functional groups and could be carried out using standard laboratory glassware and non-purified solvent. Thus, our results demonstrate a simple, yet highly selective reduction of *N*-heterocycles and imines with hydrogen gas as a highly effective alternative to the heterogeneous metal catalysts and borohydrides commonly used for these reactions, whilst offering greatly increased reactivity and selectivity. Considering the activity enhancement of the electron-rich donor in the ligand, future work will focus on installing electron-richer units, which may deliver a better catalyst for the mild hydrogenation of *N*-heteroaromatics.

Figure 15 Mild hydrogenation of *N*-heterocycles with Ir(III) complexes

4.4 Experimental

4.4.1 General information

All reactions were performed in air unless otherwise specified. CH_2Cl_2 and hexane were dried over CaH and distilled under nitrogen. Tetrahydrofuran was dried over sodium in the presence of benzophenone and distilled under nitrogen. Toluene was dried over sodium and distilled under nitrogen. Methanol and ethanol were dried over magnesium turnings and distilled under nitrogen. Acetonitrile was dried over 4Å MS and distilled under nitrogen. All other solvents were used as received. $[Cp^*IrCl_2]_2$, was purchased from Strem Chemicals Inc. Complexes **24a**, **24b** and **24d** were prepared as following Wang *et al.*[6a] Complex **24c** was prepared as following Lei *et al.*[6d] Complex **24i** was prepared as following Barnard *et al.*[6b] Data was found to be consistent with that reported in all cases. Compound **29** was prepared according to the literature.[14] Ketimine ligands were prepared by literature procedures.[6a, 15] 2-Methylquinolinium tetrafluoroborate was prepared by a literature procedure.[16a] All other commercial compounds were purchased from Aldrich, Apollo Scientific or Alfa Aesar and used without further purification. NMR spectra were recorded on a Bruker DPX-400 spectrometer with TMS as the internal standard and referenced to the residual solvent peak or TMS if the solvent peak was obscured by other resonances (ppm). The mass spectra were obtained by electrospray ionisation (ESI) or chemical ionisation (CI) at the Department of Chemistry, Liverpool University or by (FAB) at the EPSRC National Mass Spectrometry Service Centre, Swansea. Elemental

analyses were performed by the Department of Chemistry, Liverpool University elemental analysis service.

4.4.2 Information for hydrogenation of 12a in various solvents at 20 bar H_2 pressure

Although complex **24f** is not soluble in toluene on its own, it was found that the mixture of **24f** (3.3 mg) and 2-methylquinoline (71 mg) dissolved completely in all the organic solvent examined to give bright yellow, clear solutions. In H_2O the catalyst dissolved in the substrate 2-methylquinoline which subsequently formed a suspension in water. Thus, the reaction with H_2O as solvent (Table 5, entry 8) is best described as 'on water.' To ensure accurate comparison the reactions were performed simultaneously in glass vials within a larger autoclave. This allowed slight differences in temperature, time and H_2 pressure to be eliminated. The vessel was pressurized with H_2 and then depressurized 3 times before being subsequent pressurized to 20 bar and stirred. After 1 h the H_2 pressure was released and the reactions concentrated *in vacuo* before being analyzed by ^{1}H NMR spectroscopy to determine the percentage conversion.

4.4.3 Information for effect of additives on hydrogenation of 12a by 24f

Reductions of 2-methylquinoline **12a** (0.5 mmol scale) were performed with 1 mol% of the catalyst, in the presence or absence (Table 6, control experiments) of 10 mol% tetra-*n*-butylammonium chloride (13.9 mg, 0.05 mmol, 10 equivalents w.r.t. catalyst **24f**), 100% NaCl

(29.2 mg, 0.5 mmol, 10 equivalents w.r.t. catalyst **24f**) or 1% PPh_3 (1.3 mg, 0.005 mmol, 1 equivalent w.r.t. catalyst **24f**). The reactions were analysed by ^1H NMR spectroscopy after 1 h. For entries 5 and 6, **24f** and the additive were stirred in 1 mL dry, degassed MeOH under N_2 for 30 minutes in the reaction vessel before the substrate in 2 mL of dry MeOH was added by syringe *via* the septa. For entry 5, the formation of AgCl was observed as a white precipitate. The reactions were then stirred under H_2 as normally.

4.4.4 Information for reactions of hydride 29

Reaction of iridium hydride 29 with 2-methylquinoline. In a dry, N_2 filled glovebox, a solution of **29** (8 mg, 13 μmol) in MeCN-*d3* (0.7 mL) was prepared and added to a vial containing 2-methylquinoline (0.2 eq.). The solution was transferred to an NMR tube fitted with a J. Young type Teflon® cap, the tube sealed, removed from the glovebox and analysed immediately by NMR spectroscopy.

Reaction of iridium hydride 29 with 2-methylquinolinium tetrafluoroborate. In a dry, N_2 filled glovebox, a solution of **29** (8 mg, 13 μmol) in MeCN-*d3* (0.7 mL) was prepared and added to a vial containing 2-methylquinolinium tetrafluoroborate (0.2 eq.). A slight colour change from orange/yellow to yellow was observed. The solution was transferred to an NMR tube fitted with a J. Young type Teflon® cap, the tube sealed, removed from the glovebox and analysed immediately by NMR spectroscopy.

The above reactions were also repeated the presence of 0.1 mL of TFE.

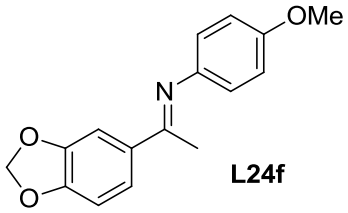
4.4.5 Typical procedure for the hydrogenation reactions

In a fume hood in air, a solution of the substrate was prepared by adding 3 mL of pre-prepared stock solution of **24f** in unpurified 2,2,2-trifluoroethanol (typically 1.66 M, 0.005 mmol in 3 mL) to a vial containing the substrate. Reactions were typically performed on a 0.5 mmol scale in 3 mL of solvent. The mixture was transferred into a N_2-filled carousel tube and the tube sealed. A H_2-filled party balloon attached to a length of rubber tubing and a hypodermic needle was connected to the reaction by inserting the needle through the septum of the carousel tube. The reaction was stirred at the described temperature for the appropriate period of time. The hydrogen was then released in the fume hood and the solution was concentrated *in vacuo* and analysed by ^{1}H NMR spectroscopy to give the percentage conversion. The reaction mixture was then purified by silica gel chromatography to give the analytically pure product.

Figure 16 The reduction of 0.5 mmol quinoxaline **16e** (see Table 3, entry 1) by 1 mol% **24f** at ambient temperature.

4.4.6 Synthesis of the ligands

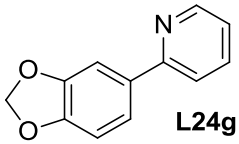
N-Aryl ketimine ligands **L24a-L24f**, **L24j**, **L24k** were prepared by the following procedure. A mixture of ketone and amine (0.95 eq.) in dry toluene were heated to reflux over 4Å molecular sieves for 18 h. The mixture was filtered through celite, eluting with ethyl acetate and the solvent removed *in vacuo*. The crude mixture was recrystallised from hexanes to give the pure imine products. Analytical data were consistent with that reported in the literature. [6a, 15]



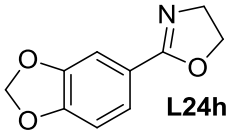
L24f

(*E*)-*N*-(1-(Benzo[d][1,3]dioxol-5-yl)ethylidene)-4-methoxyaniline (L24f). The compound was prepared on a 10 mmol scale using the standard method described above. White solid; yield 2.04 g, 76%; m.p. 85-90 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 2.0 Hz, 1H), 7.44 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 9.0 Hz, 2H), 6.01 (s, 2H) 3.81 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.99, 149.67, 148.12, 122.15, 121.00, 114.33, 107.81, 107.38, 101.56, two resonances were not observed, possibly due to overlapping, 55.61, 17.42; *m/z* (ES^+)

270 (100%, MH^+); HRMS (ES^+) calcd. for $C_{16}H_{15}NO_3$ (MH^+) 270.1130; found 270.1127.

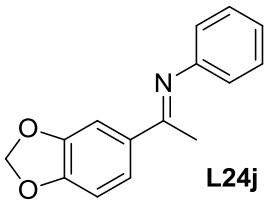


L24g **2-(Benzo[d][1,3]dioxol-5-yl)pyridine (L24g).** To a thick-walled glass tube fitted with a J. Young type Teflon® cap was added benzo[d][1,3]dioxole-5-boronic acid (500 mg, 3.01 mmol), K_2CO_3 (831 mmol, 6.02 mmol) and $Pd(PPh_3)_4$ (34 mg, 0.03 mmol). The vessel was placed under a N_2 atmosphere and the cap replace by a septa. A 1:1 mixture of propan-2-ol and water (non-degassed) was added *via* syringe followed by 2-bromopyridine (476 mg, 3.0 mmol). The septa was replaced by the Teflon® cap, and then the vessel was sealed and heated at 70 ^oC for 18h. The reaction was diluted with EtOAc (20 mL) and sat. NaCl (aq.). The mixture was washed with water (3x20 mL), dried over $MgSO_4$, filtered and evaporated to give a crude product which was purified by silica gel chromatography (4:1 hexane/EtOAc) to give the product. The data was consistent with those reported by Monguchi *et al.*[16b] White solid; yield 477 mg, 80%; m.p. 50-52 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 4.9 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.19 (m, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.02 (s,2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.98, 149.51, 148.61, 148.41, 136.97, 133.82, 121.82, 121.09, 120.17, 108.59, 107.49, 101.44; *m/z* (ES^+) 199.9 (100%, MH^+).



L24h

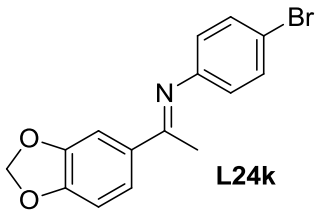
2-(Benzo[d][1,3]dioxol-5-yl)-4,5-dihydrooxazole (L24h). Using a modification of the method of Togo,[15c] ethanolamine (92 mg, 1.5 mmol) and piperonal (150 mg, 1.0 mmol) were added to thick-walled glass tube fitted with a stirrer bar, a Teflon® cap and a rubber septum along with *tert*-butanol (15 mL). The reaction was stirred vigorously at 30 ^{o}C for 0.5 h, after which time I_2 (317 mg, 1.25 mmol) and K_2CO_3 (414 mg, 3.0 mmol) were added and the mixture stirred vigorously at 70 ^{o}C for 3 h. The mixture was diluted with CH_2Cl_2 (100 mL), washed with sat. aqueous $Na_2S_2O_3$ (100 mL), brine (100 mL) and H_2O (5x100 mL). The organic layer was separated, dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give a crude solid, which was washed with hexane to give the pure product. White solid; yield 146 mg, 75%; m.p. 120-125 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.40 (d, *J* = 1.5 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.00 (s, 2H), 4.40 (t, *J* = 9.5 Hz, 2H), 4.02 (t, *J* = 9.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.37, 150.32, 147.73, 123.26, 121.77, 108.46, 108.18, 101.64, 67.79, 54.87; *m/z* (ES^+) 192 (100%, MH^+); HRMS (ES^+) calcd. for $C_{10}H_{10}NO_3$ (MH^+) 192.0655; found 192.0655.



L24j

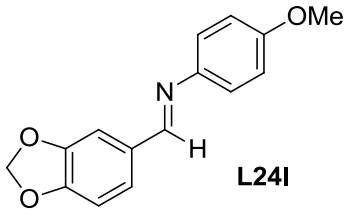
(*E*)-*N*-(1-(Benzo[d][1,3]dioxol-5-yl)ethylidene)aniline (L24j). The compound was prepared on a 10 mmol

scale using the standard method described above. The product could not be obtained in its pure form (~90% purity by ^{1}H NMR). The crude product was used in the cyclometallation step with the mass adjusted to account for the impurity of the imine.



L24k

(*E*)-*N*-(1-(Benzo[d][1,3]dioxol-5-yl)ethylidene)-4-bromoaniline (L24k). The compound was prepared on a 10 mmol scale using the standard method described above. The product could not be obtained in its pure form (~75% purity by ^{1}H NMR). The crude product was used in the cyclometallation step with the mass adjusted to account for the impurity of the imine.



L24l

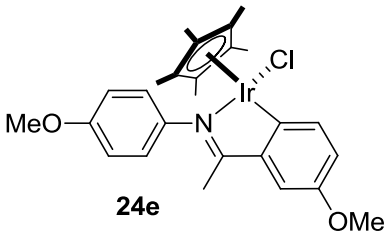
(*E*)-*N*-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-methoxyaniline (L24l). Piperonal (175 mg, 1.67 mmol) and *p*-anisidine (143 mg, 1.67 mmol) were dissolved in absolute ethanol (5 mL) in a screw top vial. Formic acid (1 drop) was added and the mixture stirred at room temperature for 0.5 h. The mixture was filtered and the precipitate washed with cold MeOH (3x5 mL) and dried *in vacuo* to give the product. White solid; yield 222 mg, 75%; m.p. 115-120 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.27-7.20 (m,

2H, overlapped with residual $CHCl_3$), 6.92 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.0 Hz, 1H), 6.04 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.18, 157.69, 150.35, 148.53, 145.03, 131.56, 125.46, 122.24, 114.47, 108.33, 106.84, 101.69, 55.62; *m/z* (ES^+) 256 (100%, MH^+); HRMS (ES^+) calcd. for $C_{15}H_{14}NO_3$ (MH^+) 256.0975; found 256.0972.

4.4.7 Synthesis of cyclometallated iridium complexes

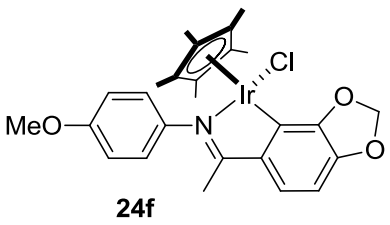
Complexes were synthesised using the method of Davies *et. al*.[7] Unless specified, iridium complexes **24** were synthesised from the corresponding ligands **L24**. Ligand (2.05 eq.), $[Cp^*IrCl_2]_2$ (1.0 eq.) and NaOAc (20.0 eq.) were added to thick-walled glass tube fitted with a stirrer bar, a Teflon® cap and a rubber septum. The vessel was degassed 3 times and placed under a dry N_2 atmosphere. Dry, degassed CH_2Cl_2 (10 mL) was added *via* syringe through the septum. The reaction was stirred vigorously at room temperature for 18 h. The reaction mixture was filtered through celite, eluting with CH_2Cl_2, dried over $MgSO_4$ and filtered. The solvent was evaporated to give a crude solid. Recrystallisation from 10:1 hexanes/DCM and drying *in vacuo* gave the pure products as fine powders often containing a molecule of DCM or H_2O of crystallisation. Please note that for *N*-arylketimine derived complexes such as **24e**, **24f**, **24j** and **24k** the resonances for the *N*-aryl protons are significantly broadened due to interaction with the Cp^* ligand and the inability of the -*N*-aryl ring to rotate due to steric interactions with the Cp^* ligand and the

ketimine methyl group (see crystal structures in Wang *et al.*[S1]). In contrast, in the aldimine derived complex **24l** the steric interactions are lessened due to the smaller size of H compared to CH_3 and such broadening effects are not observed.



24e

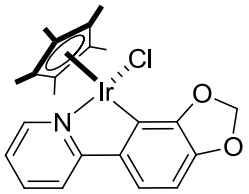
Complex 24e: The complex formed as a single regioisomer as determined by ^{1}H NMR. Red solid; yield 23 mg, 90%; m.p. >250 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (s, br, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.05 (d, *J* = 3.0 Hz, 1H), 6.94 (dd, *J* = 8.5, 3.0 Hz, 1H), 6.80 (s, br, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 2.41 (s, 3H), 1.43 (s, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.44, 158.19, 157.84, 155.29, 151.03 (br), 148.16, 144.44, 135.41, 124.34 (br), 119.63, 113.53, 89.00, 55.67, 55.60, 17.09, 8.73; *m/z* (FAB) 582 (100%, M^+-Cl); HRMS (FAB) for $C_{26}H_{31}ClIrNO_2$ (M^+-Cl), calcd. 582.1984; found 582.1980.



24f

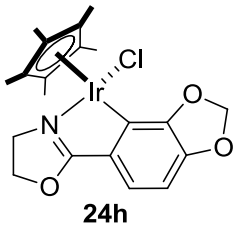
Complex 24f: The compound was formed as a mixture of 2 stereoisomers in a 95:5 ratio (by ^{1}H NMR). Data is reported for the major isomer. Data was recorded at 298 K leading to broadening of the *p*-anisolyl resonances and lower than expected integrals.

Yellow solid; yield 30 mg, 94% combined; m.p. >250 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.0 Hz, 1H) 6.92 (s, br 2.2 H, corresponds to 4 protons), 6.56 (d, *J* = 8.0 Hz, 1H), 6.06 (d, *J* = 1.5 Hz, 1H), 5.99 (d, *J* = 8.0 Hz, 1H), 3.84 (s, 3H), 2.35 (s, 3H), 1.48 (s, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.44, 158.19, 157.84, 155.29, 151.03, 148.16, 144.44, 135.41, 124.34, 119.63, 113.53 (1 resonance was not observed), 89.00, 55.67, 55.60, 17.09, 8.73; *m/z* (ES^+) 596 (100%, M-Cl); HRMS (FAB) for $C_{26}H_{29}IrNO_3$ (M^+-Cl); calcd. 596.1772; found 596.1765.



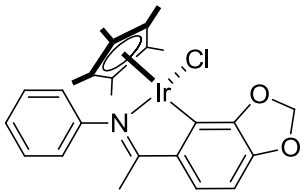
24g

Complex 24g: The reaction was performed at 80 ^{o}C in a sealed vessel. The compound was formed as a mixture of 2 stereoisomers in an 85:15 ratio (by ^{1}H NMR). Data is reported for the major isomer. Yellow solid; yield 24.5 mg, 87% combined; m.p. >250 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (ddd, *J* = 6.0, 1.0, 0.5 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.60 (td, *J* = 8.0, 1.5 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 6.99 (td, *J* = 6.0, 1.5 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.03 (d, *J* = 1.5 Hz, 1H), 5.98 (d, *J* = 1.5 Hz, 1H), 1.72 (s, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.99, 151.39, 151.25, 147.83, 139.73, 138.87, 136.97, 121.59, 119.85, 118.88, 103.55, 99.42, 89.17, 9.41; *m/z* (FAB) 561 (100%, M^+); HRMS (FAB) for $C_{22}H_{23}IrClNO_2$ (M^+) calcd. 561.1033; found 561.1024.



24h

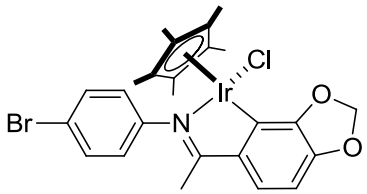
Complex 24h: The compound was formed as a mixture of 2 stereoisomers in a 90:10 ratio (by ^{1}H NMR). Data is reported for the major isomer. Yellow solid; yield 19.7 mg, 71% combined; m.p. >250 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 6.01 (d, *J* = 1.5 Hz, 1H), 5.96 (d, *J* = 1.5 Hz, 1H), 4.78 (td, *J* = 8.5, 1.0 Hz, 2H), 4.06 (m, 1H), 3.94 (m, 1H), 1.82 (s, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.59, 151.39, 149.00, 138.17, 125.88, 122.88, 103.45, 99.44, 88.17, 71.23, 50.19, 9.82; elemental analysis for $C_{20}H_{23}ClIrNO_3 \cdot 0.5H_2O$, calcd. C 42.74, H 4.30, N 2.49; found C 42.95, H 4.18, N 2.37.



24j

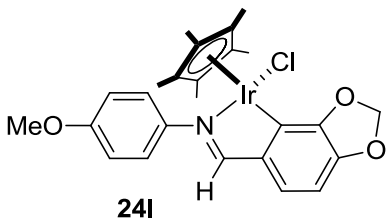
Complex 24j: The compound was formed as a mixture of 2 stereoisomers in a 95:5 ratio (by ^{1}H NMR). Data is reported for the major isomer. Data was recorded at 298 K leading to broadening of the phenyl resonances and lower than expected integrals. Yellow solid; yield 25.6 mg, 85% combined; m.p. >250 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, br, 1H), 7.42 (s, br, 3H), 7.20 (m, 1H overlapped with residual $CHCL_3$), 6.87 (s, br, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.07 (s, 1H), 6.00 (s, 1H), 2.37 (s, 3H), 1.47 (s, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.91,

150.78, 149.99, 149.02, 143.02, 142.94, 125.82, 119.65, 103.17, 99.63 (two resonances were not observed), 89.75, 17.45, 9.02; elemental analysis for $C_{25}H_{27}ClIrNO_2$, calcd. C 49.95, H 4.53, N 2.33; found C 50.01, H 4.60, N 2.10.



24k

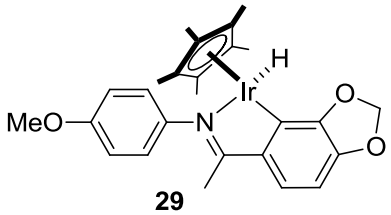
Complex 24k: The compound was formed as a mixture of 2 stereoisomers in a 95:5 ratio (by ^{1}H NMR). Data is reported for the major isomer. Data was recorded at 298 K leading to broadening of the resonances corresponding to one set of 2 protons on the *p*-bromophenyl group. Yellow solid; yield 26 mg, 77% combined; m.p. >250 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, br, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.76 (s, br, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.07 (s, 1H), 6.01 (s, 1H), 2.37 (s, 3H), 1.48 (s, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.44, 151.02, 150.75, 148.79, 143.34, 142.69, 126.28, 125.46, 102.99, 99.56, (two resonances were not observed), 89.70, 17.45, 8.94; elemental analysis for $C_{25}H_{26}BrClIrNO_2 \cdot H_2O$, calcd. C 43.01, H 4.04, N 2.01; found C 42.53, H 4.15, N 2.05.



24l

Complex 24l: The compound was formed as a mixture of 2 stereoisomers in a 95:5 ratio (by ^{1}H NMR). Data is

reported for the major isomer. Orange solid; yield 24 mg, 24% combined; m.p. >250 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.07 (d, *J* = 1.5 Hz, 1H), 6.01 (d, *J* = 1.5 Hz, 1H), 3.84 (s, 3H), 1.53 (s, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.84, 158.57, 151.08, 149.15, 145.50, 143.35, 142.82, 126.54, 123.66, 114.04, 103.65, 99.70, 89.55, 55.67, 9.20; elemental analysis for $C_{25}H_{27}ClIrNO_3 \cdot CH_2Cl_2$, calcd. C 44.48, H 4.16, N 2.00; found C 44.27, H 4.16, N 1.87.

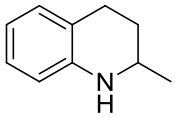


29

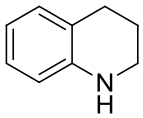
Complex 29: A solution of **24f** (6.6 mg, 1x10^{-2} mmol) in freshly distilled CH_2Cl_2 (2 mL) was added to a thick walled glass tube fitted with a J. Young type Teflon® cap. The solution was degassed by three freeze-pump-thaw cycles and placed under a dry N_2 atmosphere. A solution of NaOOCH (6.8 mg, 10 eq., 0.1 mmol) and a minimum quantity of TBA·OOCH (<0.5 mg) in deionised water (2 mL) was prepared and similarly degassed and placed under a dry N_2 atmosphere. The aqueous solution was added to the solution of **24** by cannulla and the vessel sealed under N_2 and stirred vigorously at room temperature. After 18 h the aqueous layer was removed by syringe and the organic layer washed with degassed water (5x3 mL) under N_2. The organic layer was evaporated *in vacuo* to give a moderately air sensitive bright yellow solid (6.0 mg, 99%). Complex **29** was formed as two

regioisomers in a 95:5 ratio (by ^{1}H NMR), due to the starting compound **24f** existing as a mixture of regioisomers in the same ratio. Data is given for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.0 Hz, 1H), 6.99 (s, br, 4H) 6.53 (d, *J* = 8.0 Hz, 1H), 5.96 (s, 1H), 5.88 (s, 1H), 3.81 (s, 3H), 2.22 (s, 3H), 1.67 (s, 15H), -15.76 (s, 1H). Unfortunately satisfactory elemental analyses could not be obtained for compound **6** and its instability in air for prolonged manipulation prevented further purification in addition to that described above. Thus **29** was used in its semi-crude form for subsequent reactions.

4.5 Analytic data of isolated products

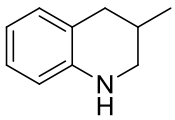


13a **2-Methyl-1,2,3,4-tetrahydroquinoline (13a):**[16d] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99-6.96 (m, 2H), 6.62 (td, *J* = 7.5, 1.0 Hz, 1H), 6.49 (dd, *J* = 8.5, 1.0 Hz, 1H), 3.71 (s, br, 1H), 3.42 (m, 1H), 2.85 (m, 1H), 2.77 (m, 1H), 1.95 (m, 1H), 1.60 (m, 1H), 1.22 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.87, 129.39, 126.81, 121.24, 117.11, 114.13, 47.28, 30.25, 26.72, 22.73; *m/z* (CI^+) 148 (100%, MH^+).



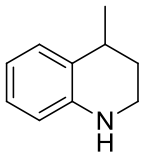
26a **1,2,3,4-Tetrahydroquinoline (26a):**[16e] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (m, 2H), 6.70 (m, 1H), 6.54 (d, *J* = 7.0 Hz, 1H), 3.78 (s, br, 1H), 3.35 (m, 2H), 2.84 (m, 2H), 2.02 (m, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 144.78, 129.53, 126.74, 121.44, 116.94, 114.23, 41.99, 27.00, 22.18; *m/z* (CI^+) 134 (100%, MH^+).



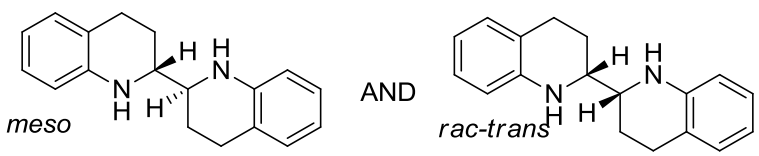
13z

3-Methyl-1,2,3,4-tetrahydroquinoline (13z):[16d] ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (m, 2H), 6.65 (td, *J* = 7.5, 1.0 Hz, 1H), 6.52 (dd, *J* = 8.0, 1.0 Hz, 1H), 3.81 (s, br, 1H), 3.30 (ddd, *J* = 11.0, 4.0, 2.0 Hz, 1H), 2.92 (t, *J* = 10.0 Hz, 1H), 2.81 (ddd, *J* = 16.0, 5.0, 2.0 Hz, 1H), 2.47 (dd, *J* = 16.0, 10.0 Hz, 1H), 2.10 (m, 1H), 1.08 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.34, 129.63, 126.79, 121.23, 117.04, 113.99, 48.93, 35.56, 27.27, 19.15; *m/z* (CI^+) 148 (100%, MH^+).



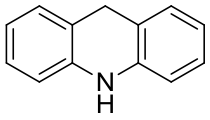
13aa

4-Methyl-1,2,3,4-tetrahydroquinoline (13aa):[16f] ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 7.5 Hz, 1H), 6.97 (td, *J* = 7.5, 1.0 Hz, 1H), 6.64 (td, *J* = 7.5, 1.0 Hz, 1H), 6.49 (dd, *J* = 8.0, 1.0 Hz, 1H), 3.30 (m, 2H), 2.92 (m, 1H), 2.00 (m, 1H), 1.69 (m, 1H) 1.30 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.21, 128.58, 126.85, 126.82, 117.18, 114.37, one resonance was not observed, 39.13, 30.32, 29.95, 22.77; *m/z* (CI^+) 148 (100%, MH^+).



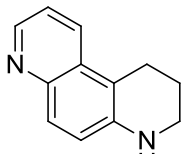
26b

1,1',2,2',3,3',4,4'-Octahydro-2,2'-biquinoline (26b):[16g] meso:racemic = 4.2:1, determined by NMR analysis. Data for the *meso* compound**;** m.p. 139-142 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05-7.02 (m, 4H), 6.69 (td, *J* = 7.5, 1.0 Hz, 2H), 6.57 (d, *J* = 8.0 Hz, 2H), 4.00 (br, 2H), 3.48-3.44 (m, 2H), 2.92-2.80 (m, 4H), 2.02-1.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.79, 129.30, 126.99, 121.52, 117.42, 114.35, 55.37, 26.68, 23.12; *m/z* (CI^+) 265 (100%, MH^+).



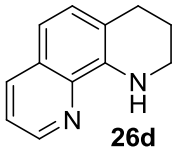
13u

9,10-Dihydroacridine (13u):[16d] m.p. 169-70 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12-7.07 (m, 4H), 6.87 (td, *J* = 7.5, 1.0 Hz, 2H), 6.67 (d, *J* = 7.5 Hz, 2H), 5.96 (s, br, 1H), 4.07 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.24, 128.73, 127.12, 120.76, 120.16, 113.56, 31.50; *m/z* (CI^+) 182 (100%, MH^+).



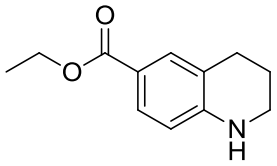
26c

1,2,3,4-Tetrahydro-4,7-phenanthroline (26c):[16h] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, *J* = 4.0, 1.5 Hz, 1H) 8.03 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.28 (q, *J* = 8.5, 4.0 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 1H), 4.13 (s, br, 1H), 3.35 (t, *J* = 5.5 Hz, 2H), 2.97 (t, *J* = 7.0 Hz, 2H), 2.10-2.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.45, 143.39, 142.40, 129.43, 128.70, 128.34, 121.77, 121.08, 110.62, 41.59, 22.27, 21.83; *m/z* (CI^+) 182 (100%, MH^+).



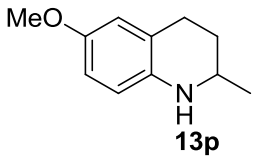
26d

1,2,3,4-Tetrahydro-1,10-phenanthroline (26d):[16i] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.01 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.29 (q, *J* = 8.0, 4.0 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 5.95 (s, br, 1H), 3.53 (m, 2H), 2.93 (t, *J* = 6.5 Hz, 2H), 2.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.03, 140.77, 137.59, 135.93, 129.14, 127.44, 120.62, 116.62, 113.17, 41.35, 27.12, 21.90; *m/z* (CI^+) 182 (100%, MH^+).



26e

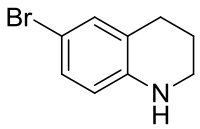
Ethyl 1,2,3,4-tetrahydroquinoline-6-carboxylate (26e):[16j] m.p. 80-82 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 2H), 6.39 (d, *J* = 9.0 Hz, 1H), 4.29 (m, 3H overlapped), 3.35 (t, *J* = 5.5 Hz, 2H), 2.77 (t, *J* = 5.5 Hz, 2H), 1.92 (m, 2H), 1.35 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.20, 148.80, 131.36, 129.20, 119.99, 117.93, 112.72, 60.19, 41.84, 27.02, 21.56, 14.60; *m/z* (CI^+) 206 (100%, MH^+).



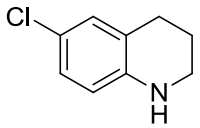
13p

6-Methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (13p):[16d] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61-6.58 (m, overlapped, 2H), 6.46 (d, *J* = 8.5 Hz, 1H), 3.73 (s, 3H), 3.60-3.00, (s, br) overlapped with 3.50-3.30 (m, 1H), 2.90-2.81 (m, 1H), 2.74-2.69 (m, 1H), 1.94-1.89 (m,

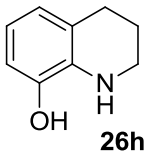
1H), 1.64-1.55 (m, 1H), 1.20 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.05, 138.87, 122.73, 115.54, 114.75, 112.97, 55.92, 47.64, 30.40, 27.02, 22.64; *m/z* (CI^+) 178 (100%, MH^+).



26f **6-Bromo-1,2,3,4-tetrahydroquinoline (26f):**[5d] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (m, 2H), 6.34 (d, *J* = 8.5 Hz, 1H), 3.84 (s, br, 1H), 3.29 (t, *J* = 5.5 Hz, 2H), 2.72 (t, *J* = 5.5 Hz, 2H), 1.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.83, 131.95, 129.44, 123.48, 115.61, 108.26, 41.88, 26.93, 21.77; *m/z* (CI^+) 212 (100%, MH^+) 214 (95%, MH^+).

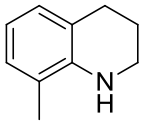


26g **6-Chloro-1,2,3,4-tetrahydroquinoline (26g):**[16f] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (m, 2H), 6.39 (d, *J* = 8.5 Hz, 1H), 3.79 (s, br, 1H), 3.28 (t, *J* = 5.5 Hz, 2H), 2.73 (t, *J* = 5.5 Hz, 2H), 1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.34, 129.07, 126.54, 122.93, 121.15, 115.16, 41.90, 26.93, 21.78; *m/z* (CI^+) 168 (100%, MH^+), 170 (35%, MH^+).

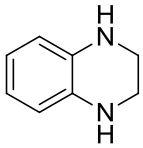


26h **8-Hydroxy-1,2,3,4-tetrahydroquinoline (26h):**[16f] m.p. 117-120 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60-6.53 (m, 3H), 4.78 (s, 2H),

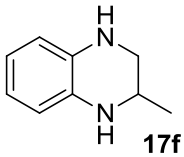
3.31 (s, br 2H), 2.77 (s, br 2H), 1.95 (s, br 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.20, 133.54, 123.65, 122.02, 117.20, 112.53, 41.91, 26.68, 22.34; *m/z* (CI^+) 150 (100%, MH^+).



26i **8-Methyl-1,2,3,4-tetrahydroquinoline (26i):**[16e] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91-6.86 (m, 2H), 6.59 (t, *J* = 7.5 Hz, 1H), 3.76 (s, br, 1H), 3.40 (t, *J* = 5.5 Hz, 1H), 2.81 (t, *J* = 6.5 Hz, 1H), 2.10 (s, 3H), 1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.70, 127.96, 127.49, 121.39, 121.06, 116.60, 42.46, 27.39, 22.24, 17.30; *m/z* (CI^+) 148 (100%, MH^+).

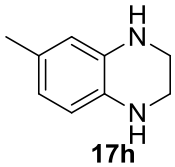


17e **1,2,3,4-Tetrahydroquinoxaline (17e):**[16d] m.p. 95-97 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (m, 2H), 6.50 (m, 2H), 3.52 (s, br, 2H), 3.42 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.67, 118.99, 114.94, 41.46; *m/z* (CI^+) 135 (100%, MH^+).

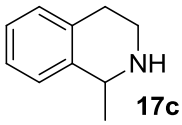


17f **2-Methyl-1,2,3,4-tetrahydroquinoxaline (17f):**[16d] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (m, 2H), 6.53 (m, 2H), 3.63 (s, br, 2H), 3.52 (m, 1H), 3.30 (m, 1H), 3.02 (m, 1H), 1.20 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.58, 133.19, 118.92, 114.72, 114.67, one aromatic

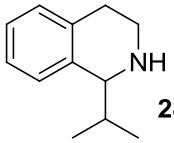
resonance is not observed, 48.29, 45.81, 19.92; *m/z* (CI^+) 149 (100%, MH^+).


17h

6-Methyl-1,2,3,4-tetrahydroquinoxaline (17h):[16d] m.p. 100-102 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 6.42 (m, 2H), 6.34 (s, 1H), 3.40 (s, 6H overlapped), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.82, 131.07, 128.64, 119.28, 115.59, 115.19, 41.65, one resonance was not observed, 20.79; *m/z* (CI^+) 149 (100%, MH^+).

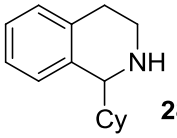

17c

1-Methyl-1,2,3,4-tetrahydroisoquinoline (17c):[16k] ^1H NMR (400 MHz, $CDCl_3$) δ 7.23-7.08 (m, 4H), 4.16 (m, 1H), 3.32-3.27 (m ,1H) 3.08-3.02 (m, 1H), 2.97-2.87 (m, 1H), 2.78 (m, 2H), 1.49 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.53, 134.83, 129.36, 126.12, 126.04, one resonance was not observed, 51.68, 41.86, 30.09, 22.79; *m/z* (CI^+) 148 (100%, MH^+).


28a

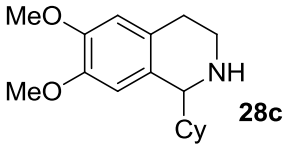
1-*iso*-Propyl-1,2,3,4-tetrahydroisoquinoline (28a):[16k] ^1H NMR (400 MHz, $CDCl_3$) δ 7.16-7.07 (m, 4H), 3.96 (d, *J* = 3.0 Hz, 1H), 3.32-3.28 (m, 1H), 2.97-2.84 (m, 2H), 2.67 (m, 1H), 2.35 (m, 1H), 1.85 (s, br, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.75 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.84, 136.34, 129.22, 126.02, 125.84,

125.71, 61.09, 42.61, 32.36, 30.50, 20.40, 15.83; *m/z* (CI^+) 176 (100%, MH^+).



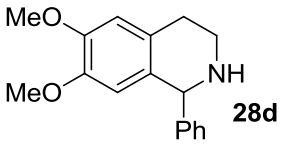
28b

1-Cyclohexyl-1,2,3,4-tetrahydroisoquinoline (28b):[16k] ^1H NMR (400 MHz, $CDCl_3$) δ 7.15-7.06 (m, 4H), 3.92 (d, *J* = 3.5 Hz, 1H), 3.29 (m, 1H), 2.96-2.82 (m, 2H), 2.68 (m, 1H), 2.05-1.68 (m, 6H), 1.40-1.07 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.43, 136.28, 129.25, 126.20, 125.78, 125.74, 60.85, 43.07, 42.42, 31.03, 30.31, 27.17, 26.76, 26.68, 26.51; *m/z* (CI^+) 216 (100%, MH^+).



28c

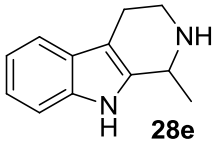
1-Cyclohexyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (28c):[16k] m.p. 78-80 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 1H), 6.55 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.25 (m, 1H), 2.92-2.85 (m, 1H), 2.78-2.71 (m, 1H), 2.60-2.55 (m, 1H), 1.84 (m, 2H), 1.70 (m, 4H), 1.39-1.12 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.16, 147.12, 130.43, 128.51, 111.79, 109.37, 60.47, 56.18, 55.89, 43.34, 42.58, 31.01, 29.95, 27.18, 26.80, 26.70, 26.46; *m/z* (CI^+) 276 (100%, MH^+).



28d

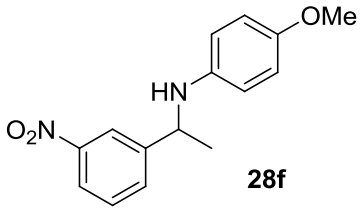
1-Phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (28d):[16k] m.p. 109-111 ^oC; ^1H NMR (400 MHz,

$CDCl_3$) δ 7.31-26 (m, 5H), 6.64 (s, 1H), 6.24 (s, 1H), 5.07 (s, 1H), 3.88 (s, 3H), 3.64 (s, 3H), 3.20 (m, 1H), 3.05 (m, 1H), 2.94 (m, 1H), 2.79 (m, 1H), 2.43 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.79, 147.20, 144.44, 129.48, 129.11, 128.56, 127.61, 127.59, 111.46, 110.99, 61.39, 55.96, 41.77, 29.16; *m/z* (CI^+) 270 (100%, MH^+).



28e

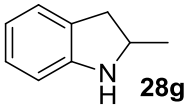
1-Methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (28e):[16k] m.p. 165-170 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, br, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.16 (td, *J* = 8.0, 1.0 Hz, 1H), 7.10 (td, *J* = 8.0, 1.0 Hz, 1H), 4.19 (q, *J* = 6.5 Hz, 1H), 3.40-3.35 (m, 1H), 3.06 (m, 1H), 2.74 (m, 2H), 1.70 (s, br, 1H), 1.17 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.62, 135.80, 127.50, 121.73, 119.54, 118.24, 110.92, 108.32, 48.26, 42.47, 22.44, 20.56; *m/z* (CI^+) 187 (100%, MH^+).



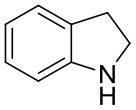
28f

4-Methoxy-*N*-(1-(3-nitrophenyl)ethyl)aniline (28f):[16l] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 2.0 Hz, 1H), 8.08 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 9.0 Hz, 2H), 6.43 (d, *J* = 9.0 Hz, 2H), 4.50 (m, 1H), 3.87 (s, br, 1H), 3.69 (s, 3H), 1.53 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.36, 146.77, 146.21, 138.83,

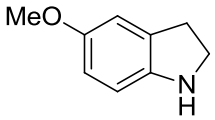
130.30, 127.73, 120.15, 119.08, 112.92, 112.66, 53.78, 51.98, 23.20; *m/z* (CI^+) 273 (100%, MH^+).



28g **2-Methylindoline (28g):**[9b] ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 7.0 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.70 (t, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 7.5 Hz, 1H), 4.00 (m, 1H), 3.59 (s, br, 1H), 3.15 (dd, *J* = 16.0, 8.5 Hz, 1H), 2.64 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.30 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.92, 129.06, 127.34, 124.84, 118.73, 109.38, 55.35, 37.84, 22.35; *m/z* (CI^+) 134 (100%, MH^+).

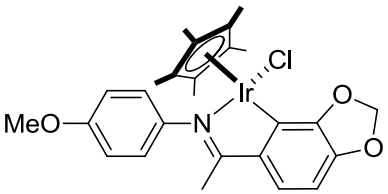


28h **Indoline (28h):**[9b] ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.0 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.73 (td, *J* = 7.5, 1.5 Hz, 1H), 6.67 (d, *J* = 7.5 Hz, 1H), 3.73(s, br, 1H), 3.56 (t, *J* = 8.5 Hz, 2H), 3.05 (t, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.69, 129.40, 127.29, 124.72, 118.73, 109.53, 47.42, 29.93; *m/z* (CI^+) 120 (100%, MH^+).

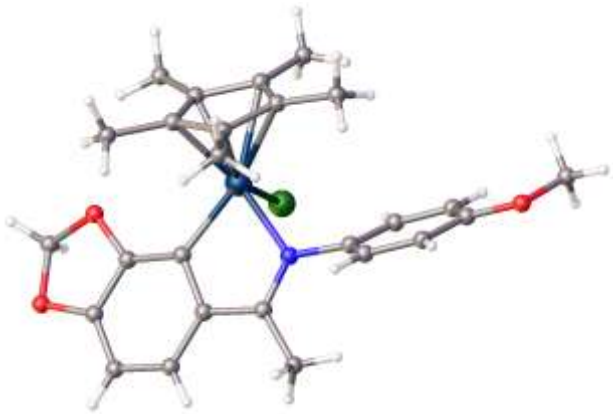


28i **5-Methoxyindoline (28i):**[9b] ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (s, 1H), 6.60 (m, 2H), 3.75 (s, 3H), 3.53 (t, *J* = 8.5 Hz, 2H), 3.45 (s, br, 1H), 3.01 (t, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.62, 145.34, 131.26, 112.18, 111.61, 110.22, 56.03, 47.86, 30.53; *m/z* (CI^+) 150 (100%, MH^+).

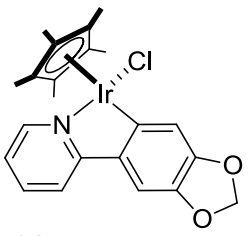
4.6 Crystallographic data of 24f and 24g minor isomer[17]



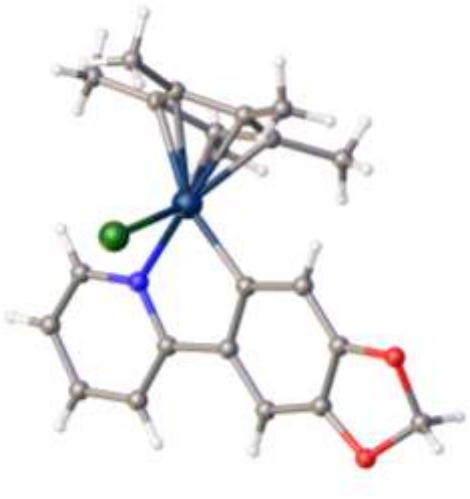
24f



$C_{26}H_{29}ClIrNO_3$, M = 631.15, monoclinic, a = 7.4023(9) Å, b = 15.5707(19) Å, c = 20.203(3) Å, β = 100.426(2)°, V = 2290.2(5) Å^3, T = 569.3, space group $P2_1/c$ (no. 14), Z = 4, μ(MoKα) = 5.975, 19921 reflections measured, 4719 unique (R_{int} = 0.0254) which were used in all calculations. The final wR_2 was 0.1380 (all data) and R_1 was 0.0565 (>2 sigma(I)).



24g minor isomer



$C_{22}H_{23}ClIrNO_2$, M = 561.06, monoclinic, a = 7.4378(8) Å, b = 14.0123(16) Å, c = 18.702(2) Å, β = 97.756(3)°, V = 1931.3(4) Å^3, T = 569.3, space group $P2_1/n$ (no. 14), Z = 4, μ(MoKα) = 7.069, 24448 reflections measured, 4009 unique (R_{int} = 0.0368) which were used in all calculations. The final wR_2 was 0.0394 (all data) and R_1 was 0.0167 (>2sigma(I)).

4.7 References

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CHAPTER 5 SYNTHESIS OF CHIRAL PIPERIDINES FROM PYRIDINES ENABLED BY TRANSAMINATION

5.1 Introduction

Chapter 3 reports an iodide-promoted TH system to effectively reduce pyridinium salts to the corresponding piperidines and 3,4-unsaturated variants with high chemoselectivities. It would be a natural extension for us to attempt the ATH of pyridines, which is broadly recognised as a challenging and topical research direction. In this chapter, an unprecedented reaction discovered by serendipity for the direct preparation of optically pure piperidines from pyridines, will be discussed.

Small chiral, cyclic amines, such as piperidines are privileged chemical scaffolds present in many natural products and pharmaceutical compounds.[1] However, effective methods for their synthesis from simple starting materials are rare. An attractive approach is the catalytic reduction of the precursors of piperidines, i.e. normal pyridines, using hydrogen gas or other hydrogen sources. Although much progress has been made in the asymmetric reduction of the more reactive benzo-fused *N*-heteroaromatics, direct synthesis of chiral piperidines by the reduction of simple pyridine derivatives remains challenging.[2] Previous efforts have concentrated on the use of well-defined chiral transition metal catalysts as well as elaborated substrates activation strategies.

The aromatic nature of pyridine (resonance energy 27 kcal/mol), coupled with the tendency of pyridines to poison metal catalysts by coordination through the basic nitrogen atom makes the reduction of pyridines a challenging task, which typically requires heterogeneous

catalysts and forcing conditions. As a result, the great advances made in homogeneous asymmetric hydrogenation have not been brought to bear, and a simple cost-effective asymmetric reduction of pyridines remains unrealised.[2] One method to overcome these problems is the alkylation or acylation of the pyridine nitrogen atom. This simultaneously lowers the LUMO of pyridine, increasing its susceptibility to nucleophilic attack by a metal hydride species and reduction, while coordinatively saturating the nitrogen atom, decreasing the tendency to bind to any available metal catalyst.

In this context, we have recently described the synthesis of piperidine derivatives by the TH of *N*-benzylpyridinium salts using a 5:2 $HCOOH/NEt_3$ mixture as the hydrogen source and a catalyst generated *in situ* from $[Cp^*RhCl_2]_2$ and potassium iodide, as also can be seen in Chapter 3. Realising the unmet need for a simple and effective asymmetric reduction of pyridine derivatives, we sought to develop a chiral analogue of this reaction. Progress was hindered by the need for an active rhodium catalyst bearing a single Cp* ligand and two iodide ligands, making modification of the coordination sphere of Rh(III) by the addition of chiral ligands impossible. Although highly effective asymmetric reactions based on Rh(III) and chiral Cp ligands have recently been reported,[3] our attempts at using chiral metal complexes as catalysts for this transformation were fruitless.

Due to the requirement of an additional synthetic step in which an auxiliary is attached to the pyridine, with the associated purification steps,

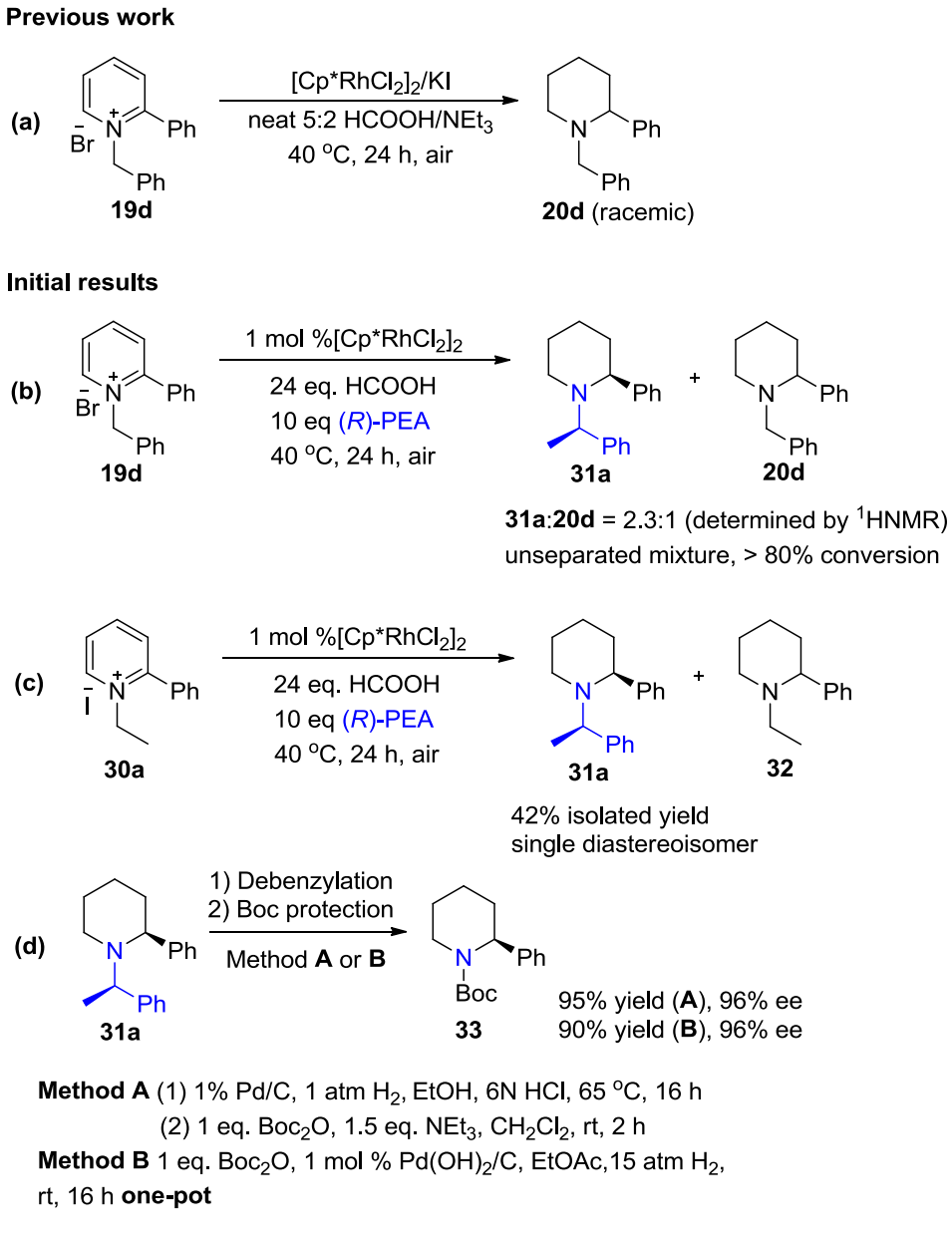
we also discounted the use of chiral auxiliaries, despite their effectiveness in controlling the stereochemical outcome of similar reactions.[4] Other drawbacks include the prohibitive expense of the frequently used *N*-acyl based auxiliaries (e.g. $314/gram for (-)-8-phenylmenthol), mandating their recovery and purification after use, and the limited substrate scope (2-substitutents are not tolerated) for the synthesis of chiral *N*-alkyl pyridinium salts by the Zincke reaction.[5]

5.2 Results and Discussion

5.2.1 Initial discovery of *in situ* transamination

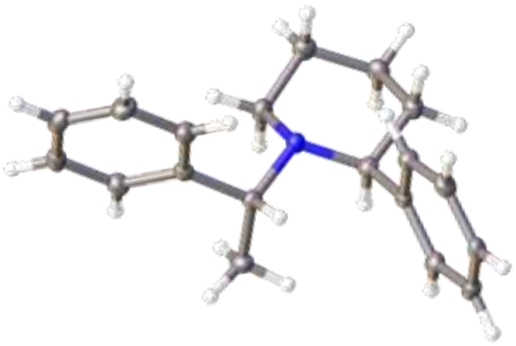
To circumvent the problem mentioned above, we pursued the use of chiral additives in an attempt to induce asymmetry into the reaction by the creation of a chiral local environment through non-covalent interactions.[6] During the course of this work, we surprisingly observed the incorporation of the chiral amine (*R*)-1-phenylethylamine ((*R*)-PEA, >98% ee) into the product, resulting from a formal exchange of the ethylimido fragment with (*R*)-1-phenylethylimido as shown in Scheme 54. Initially using *N*-benzyl pyridinium bromide salt led to an unseparated mixture, in which there were two structurally similar piperidines **31a** and **20d** as determined by ^{1}HNMR. In order to obtain pure **31a** for further analysis, *N*-ethyl pyridinium iodide salt was subjected to the identical reaction conditions, aiming to produce a separable mixture. Delightfully, pure **31a** was isolated readily as single distereoisomer, although the yield was a moderate 42%. Further simple derivatization by debenzylation and

Boc-protection was carried out to generate piperidine **33** in 96% enantiomeric excess. X-ray crystallography finally confirmed the absolute configuration of the transamination product **31a** as (*R*, *S*) (Scheme 54 (e)).



Method A (1) 1% Pd/C, 1 atm H_2, EtOH, 6N HCl, 65 °C, 16 h
(2) 1 eq. Boc_2O, 1.5 eq. NEt_3, CH_2Cl_2, rt, 2 h
Method B 1 eq. Boc_2O, 1 mol % $Pd(OH)_2/C$, EtOAc,15 atm H_2, rt, 16 h **one-pot**

(e)



Scheme 54: Synthesis of chiral piperidines by *in situ* transamination/transfer hydrogenation. **(a)** Previously described achiral transfer hydrogenation of *N*-benzyl pyridinium salts. **(b)** *In situ* transamination of *N*-benzyl pyridinium bromide salts. **(c)** *In situ* transamination of *N*-ethyl pyridinium iodide salts. **(d)** Derivatisation of **31a**. **(e)** X-ray structure of product **31a**.

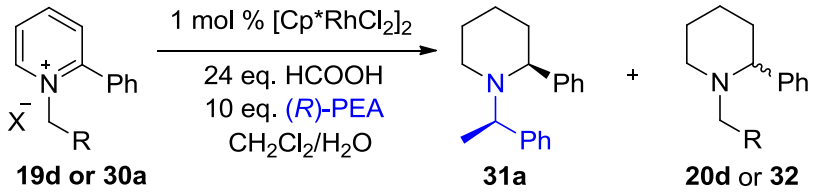
Despite the low yield, the incorporation of the chiral amine (*R*)-PEA into the final product held great promise. Such a process in which a non-activated substrate is chirally modified by the addition of a chiral substrate without modification of the reaction conditions would alleviate the need for prior steps in which to attach the chiral auxiliary to a pre-activated pyridine substrate.[7] The incorporation of the chiral *N*-phenylethyl moiety would render the final reduction of the C=N double bond diastereoselective, alleviating the need for complex or costly chiral transition metal catalysts.

In addition, PEA is a highly economic chiral reagent (<$1.00/gram), of which both enantiomers are readily available, and the chiral *N*-alkyl group can be cleaved using the same conditions required for removal of the widely used *N*-benzyl protecting group, giving chiral piperidine products with no additional synthetic steps.

Screening a variety of transition metals salts and complexes showed that only the group 6 "piano stool" complexes were effective, with $[Cp^*RhCl_2]_2$ being the most active catalyst. Due to the propensity of formic acid / PEA mixtures to solidify, a co-solvent was required, with CH_2Cl_2 being optimal. The exclusion of air was neither required, nor found to be beneficial, as both the reagents and the Rh(III) catalyst are stable to air and moisture in the solid state and in solution. As also can be seen in Scheme 54, exchanging the *N*-benzyl group to an *N*-ethyl group facilitated easier separation of the chiral and achiral products. Despite this, the percentage conversion and isolated yield of the chiral product was highly changeable and difficult to reproduce. Rigorous drying of the solvents and reagents and employing newly received formic acid led to a decrease in yield (35%) and the further adding of 3 Å molecular sieves significantly hampered **31a** formation (Table 13, entries 1 and 2), implicating the presence of adventitious traces of water in the highly hydroscopic PEA and formic acid as the critical factor. Indeed, the addition of water remarkably enhanced the yields of **31a** and decreased the yields of the undesired product **20b** at the same time (Table 13, entries 3-6). Changing the anion Br^- to I^- and *N*-benzyl to ethyl substituent

were found to improve the yield slightly (Table 13, entires 7 and 8). Rescreening the water effect using *N*-ethyl pyridinium iodide salt **30a** as the substrate (Table 13, entries 8-14) afforded the best yield of 86%, demonstrating again the water benefits for the reaction (Table 13, entries 9-12). However, the reaction was inactive when water was used as sole solvent (Table 13, entry 15). The chloride anion considerably inhibited the yield of **31a**, while a non-coordinating anion, SbF_6^-, was found to totally deactivate the reaction (Table 13, entries 16 and 17).

Table 13. Effects of H_2O and anion on *in situ* transamination of pyridinium satls.[a]



Entry	X, R	CH_2Cl_2/H_2O [mL]	**31a**/**20d**[b]	Yield of **31a** [%][c]
1	Br, Ph	4.00/0.00	1/1.83	35
2[d]	Br, Ph	4.00/0.00	1/8.05	8.6
3	Br, Ph	3.75/0.25	1/0.54	60
4	Br, Ph	3.50/0.50	1/0.40	71
5	Br, Ph	3.00/1.00	1/0.36	70
6	Br, Ph	2.00/2.00	1/0.39	68
7	I, Ph	3.50/0.50	1/0.22	76

8	I, Me	3.50/0.50	NA	81
9	I, Me	4.00/0.00	NA	46
10	I, Me	4.00/0.01	NA	57
11	I, Me	3.90/0.10	NA	76
12	**I, Me**	**3.75/0.25**	**NA**	**86 (77)**
13	I, Me	3.00/1.00	NA	79
14	I, Me	2.00/2.00	NA	71
15	I, Me	0.00/4.00	NA	<2
16	Cl, Ph	3.50/0.50	1/5.40	14
17	SbF_6, Ph	3.50/0.50	NA	<2

[a] Reaction conditions: pyridinium salt **19d** or **30a** (0.5 mmol), HCOOH (12 mmol), (*R*)-PEA (5 mmol), $[Cp^*RhCl_2]_2$ (5 μmol), CH_2Cl_2/H_2O mixture (4 mL), 40 °C, 22 h, in air. Ph = Phenyl, Me = Methyl. CH_2Cl_2 and (*R*)-PEA were dried over CaH_2. [b] Mole ratio, determined by ^1H NMR analysis; NA = Not available.[c] Isolated yields; data in bracket were obtained with 5 eq. (*R*)-PEA and 12 eq. HCOOH. [d] 3 g of 3 Å molecular sieves were added.

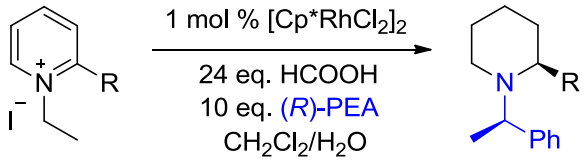
5.2.2 Substrate scope

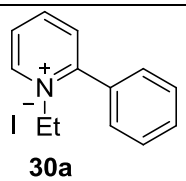
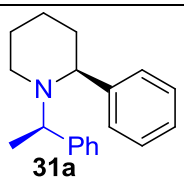
Under the optimised conditions, the reaction proceeds smoothly with *N*-ethylpyridium salts bearing a variety of 2-aryl and alkyl substituents, affording the corresponding *N*-(1-phenylethyl)piperidines in good yields and uniformly high diastereoselectivities (>20:1) (Table 14). In contrast to homogeneous methods, the reduction of the pyridinium ring occurred selectively in the presence of other potentially reducible functional

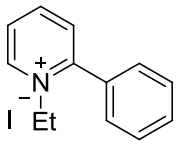
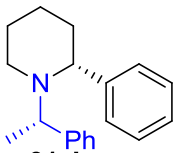
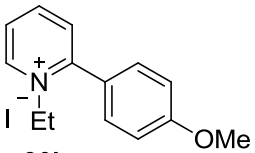
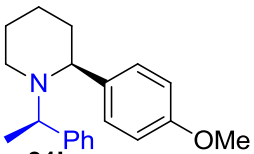
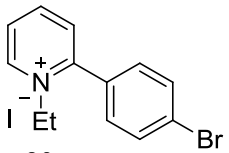
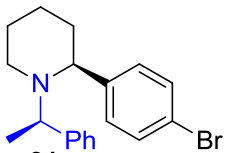
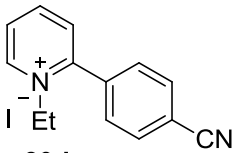
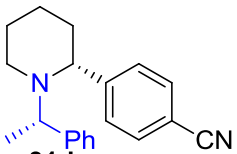
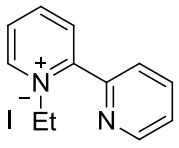
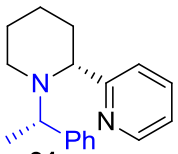
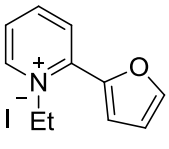
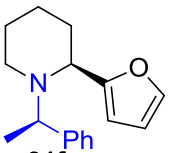
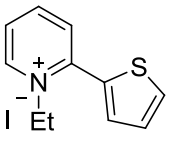
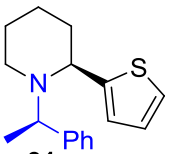
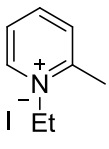
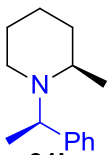
groups, including, aryl bromides, esters and cyano groups (Table 14, entries 4, 5 and 13). Heterocyclic substituents, such as pyridine, thiophene and furan, were also well tolerated albeit in diminished yields (Table 14, entries 6-8). The presence of other groups including protected amines and free alcohols did not inhibit the reaction (Table 14, entries 12 and 14). Thus, this method allows for a broad range of chiral piperidines to be accessed with excellent diastereoselectivities in a single step from simple precursors.

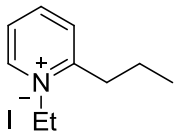
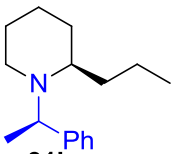
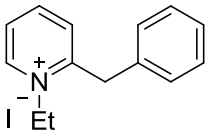
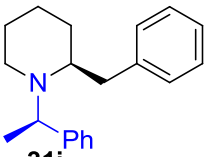
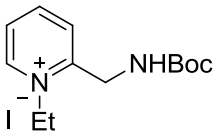
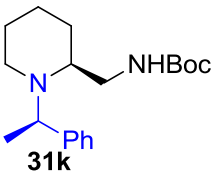
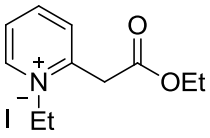
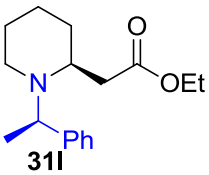
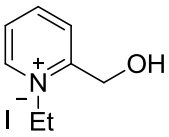
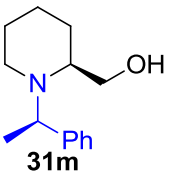
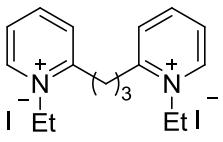
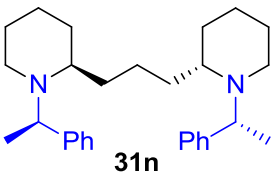
In some cases, naturally occurring alkaloids such as coniine, previously always by multistep synthesis starting from complex materials, could be directly obtained by a simple debenzylation (Table 14, entry 10). Chiral *bis*-piperidines could also be produced by this method (Table 14, entry 15), which may find use in asymmetric catalysis as chiral diamine ligands.

Table 14. *In situ* transamination of 2-substituted pyridiniums to piperidines.[a]



Entry	Substrate	Product	Yield [%][b]
1	 **30a**	 **31a**	86

2	 **30a**	 **31a'**	83[c]
3	 **30b**	 **31b**	82
4	 **30c**	 **31c**	86
5	 **30d**	 **31d**	70[c],[d]
6	 **30e**	 **31e**	54[c]
7	 **30f**	 **31f**	71
8	 **30g**	 **31g**	48
9	 **30h**	 **31h**	88

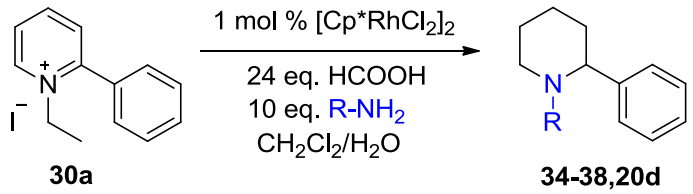
10	 **30i**	 **31i**	82
11	 **30j**	 **31j**	55
12	 **30k**	 **31k**	82
13	 **30l**	 **31l**	68
14	 **30m**	 **31m**	83
15[e]	 **30n**	 **31n**	75

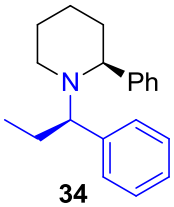
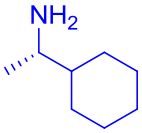
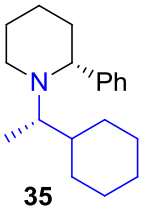
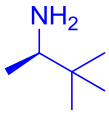
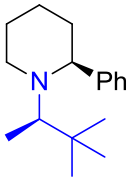
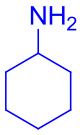
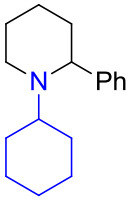
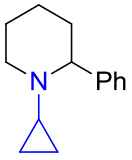
[a] All reactions were carried out under the standard conditions: **30** (0.5 mmol), $[Cp^*RhCl_2]_2$ (5 µmol), HCOOH (12 mmol), (*R*)-PEA (5 mmol), $[Cp^*RhCl_2]_2$ (5 µmol), CH_2Cl_2/H_2O (3.75/0.25 mL), 40 °C, 22 h, in air. [b] Isolated yields. [c] (*S*)-PEA was used. [d] The reaction was carried out in 2.5 mmol scale. [e] Reaction conditions were the same as standard conditions except for using HCOOH (24 mmol), (*R*)-PEA (10 mmol), $[Cp^*RhCl_2]_2$ (10 µmol), CH_2Cl_2/H_2O (7.5/0.5 mL).

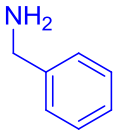
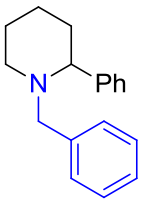
Notably the isolated yields approached 90% in some cases, which would be the maximum theoretical yield of the desired product if the transamination reaction had reached equilibrium, assuming a 10:1 ration of starting material and PEA.

Although the *in situ* incorporation of a PEA auxiliary and subsequent reduction to give chiral piperidines is the most immediate use of this *in situ* transamination-reduction reaction, it can also be used to furnish the alkylation of piperidines, starting from pyridinium precursors, using amines as the alkylating agent, as shown in Table 15. This offers an advantage in cases where an effective alkylating agent is not available due to its instability or lack of reactivity. For instance, *N*-cyclopropylpiperidine **38**, which is not obtainable by alkylation or reductive amination, was obtained in a yield of 64% using cheap reagents. In addition, due to the retention of the nitrogen atom in the reactant amine, the stereochemistry of this unit is completely conserved. Using this method, a variety of *N*-alkyl piperidines **34-38** and **20d** bearing cyclic and acyclic alkyl groups were synthesised in a single step, including those bearing optically active *N*-alkyl groups **34-36** (Table 15, entries 1-3).

Table 15. *In situ* transamination of 2-phenylpyridiniums with various primary amines.[a]



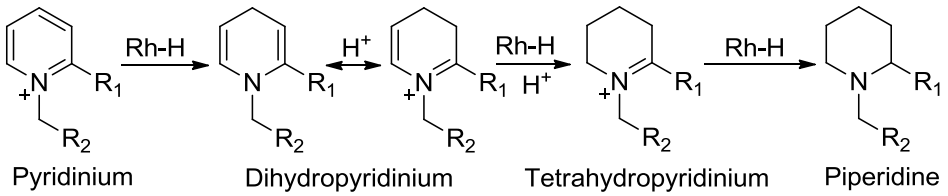
Entry	Amine	Product	Yield [%][b]
1		 **34**	78
2		 **35**	88
3		 **36**	77
4		 **37**	88
5		 **38**	64

6		 **20d**	83

[a] Reactions were carried out under the standard conditions given in Table 2 except for using different amines. [b] Isolated yield.

5.2.3 Mechanistic investigations

The $[Cp^*RhCl_2]_2$/KI-catalysed transfer hydrogenation of pyridnium salts to give piperidines occurs *via* successive hydride addition and protonation steps, and corresponding to the addition of 3 equivalents of dihydrogen (Scheme 55).



Scheme 55: Stepwise reduction of pyridinium salts by transfer hydrogenation reaction. The anionic counterions are omitted for clarity. Rh-H = Cp^*RhI_2H

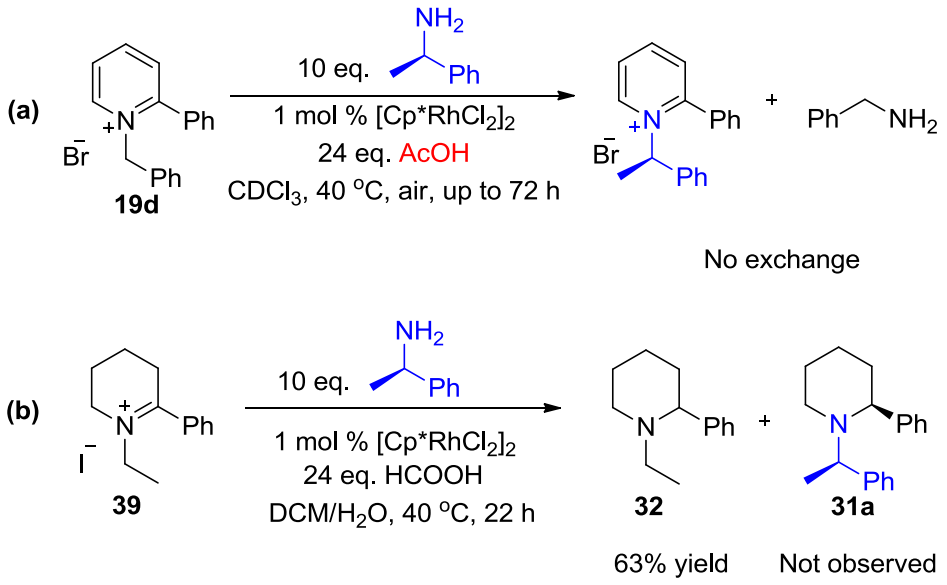
In order to pinpoint at which of the 3 possible oxidation states the transamination reaction occurs, model compounds were synthesised and reacted with PEA / acid mixtures under conditions closely related to the actual reaction conditions (Scheme 56, (a)-(c)). By replacing the formic

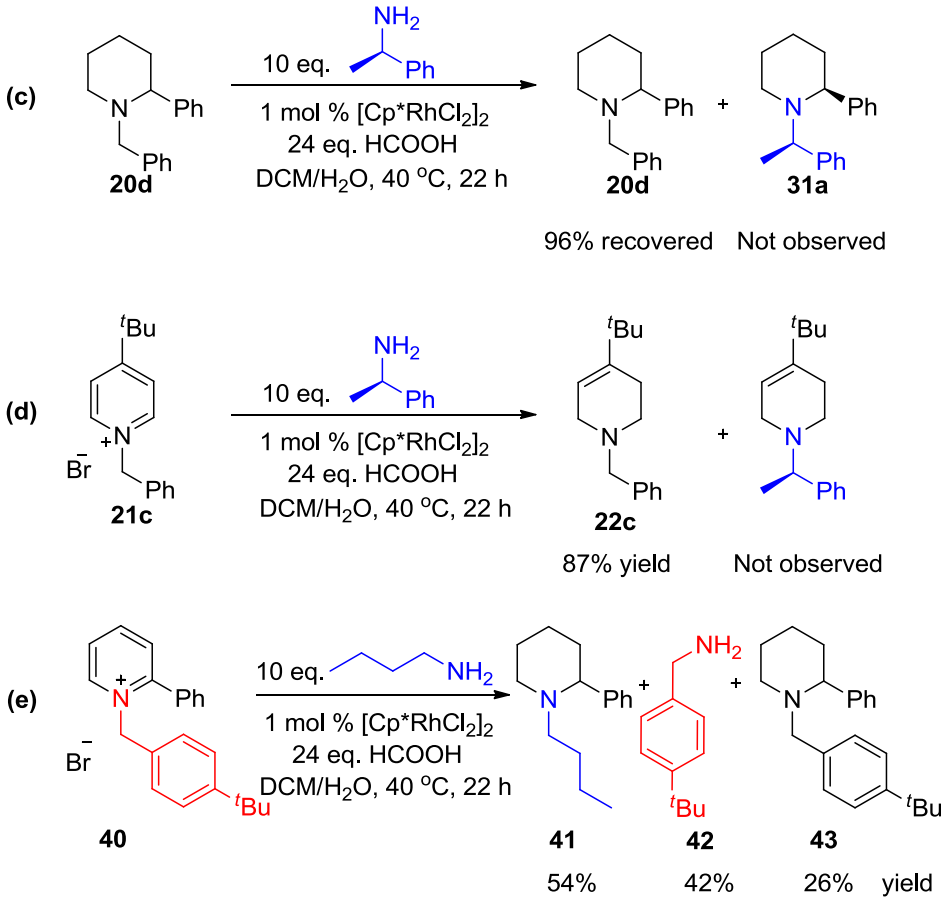
acid with acetic acid (which does not act as a hydrogen source), the reaction of compound **19d** with excess PEA could be studied in isolation without the reduction occurring. Chloroform-d ($CDCl_3$) was used in place of dichloromethane to allow for *in situ* analysis of the reaction by ^1H NMR. No exchange was observed in the reaction of the *N*-benzylpyridinium starting material **19d** (Scheme 56, (a)), suggesting that a Zincke[5] type mechanism was not in operation. The transfer-hydrogenated product **32** was isolated in high yield without observing any transamination product **31a** when tetrahydropyridinium **39** was employed in the identical conditions, indicating that the amine exchange does not happen on this possible intermediate (Scheme 56, (b)). The result together with the almost full recovery of **20d** (Scheme 56, (c)), hints that the amine incorporation probably takes place in the dihydropyridinium intermediate. Furthermore, blocking the 4-position of pyridines with a bulky substituent, which makes initial 1,4-hydride addition impossible, was found to totally hinder the transamination reaction, with transfer-hydrogenated product **22c** obtained in 87% yield (Scheme 56, (d)).

A possible mechanism explaining the transamination is shown in Scheme 57. The transamination reaction probably occurs after the initial reduction of the pyridinium salt to dihydropyridinium and before the subsequent reduction to give the piperidine product. The nucleophilic addition of amine to the dihydropyridinium leads to the formation of the enamine **44**, which after isomerisation could be hydrolysed to open the

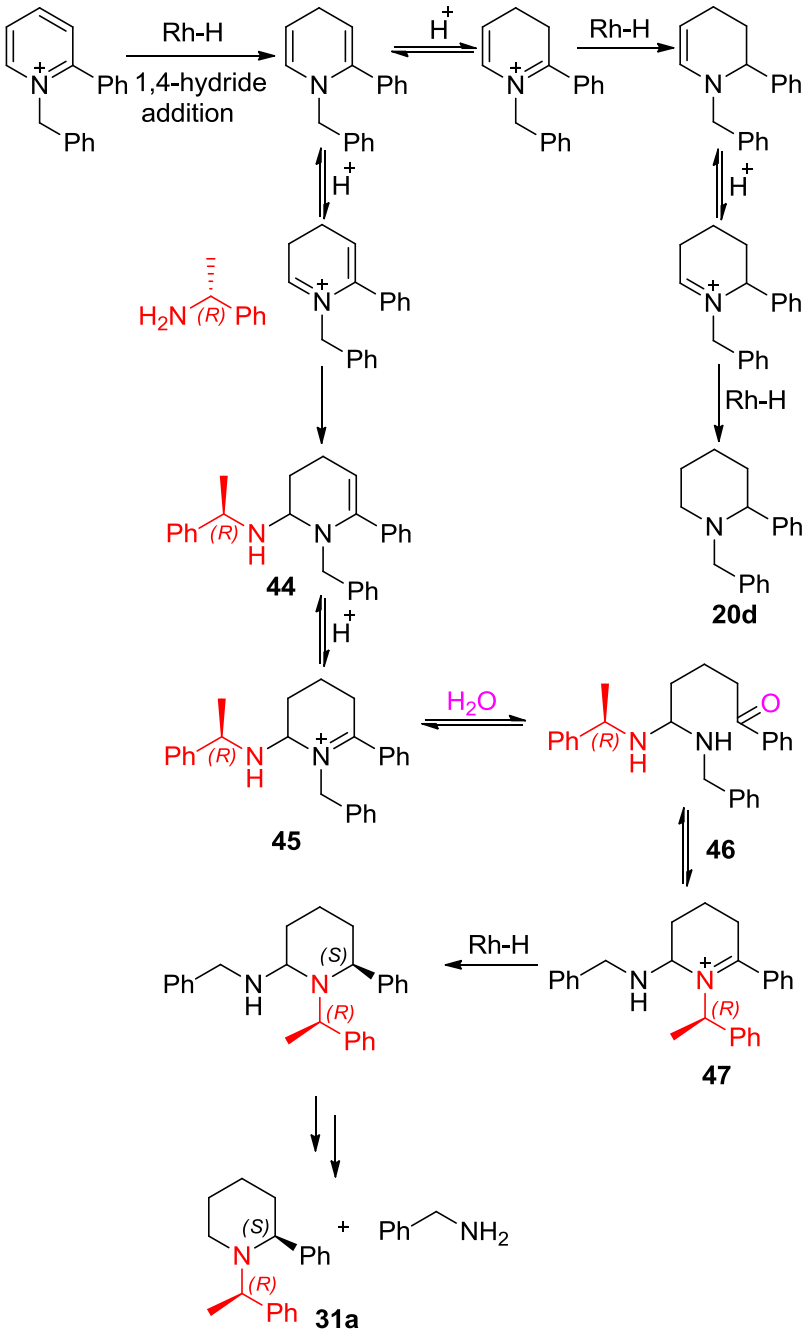
ring. As mentioned, the reaction was found to be aided by the presence of water, and was inhibited in a significant degree by the use of anhydrous reactants/solvents and the addition of 3Å molecular sieves. This is consistent with the proposed hydrolysis of **45** by water. The condensation of the ring opened product **46** with the chiral amine unit, followed by ring closure, would yield the amine exchange product **47** which may undergo further reduction to give the final products **31a**.

The formation of the amine product **42** from the pyridininium **40** in similar yield to the incorporated piperidine **41** also gave credit to the proposed mechanism (Scheme 56, (e)).





Scheme 56: Transamination reactions of model compounds with *(R)*-PEA. Reactions were performed under conditions given in the equations.



Scheme 57: Proposed mechanism for the *in situ* transamination of pyridinium and the formation of hydrogenated by-product.

5.3 Conclusions and future work

The use of chiral amines, in place of the commonly used triethylamine in the transfer hydrogenation of *N*-alkyl pyridinium salts, led to an unexpected and previously unknown method for the synthesis of chiral piperidine derivatives. The reaction requires no prior modification of the substrates, and offers an operationally simple, effective method for the synthesis of optically active piperidine derivatives.

Preliminary mechanistic investigations suggest that addition of a amine and water causes the usual transfer hydrogenation process to be interrupted after the initial reduction step by a ring opening / transamination / ring closing process. This process expands the scope of pyridine reduction chemistry and allows for a new method of *N*-alkylation of piperidine ring systems. Future work will focus on extending the substrate scope and gaining more mechanistic evidence by experimental investigations and computational calculations.

5.4 Experimental

5.4.1 General information

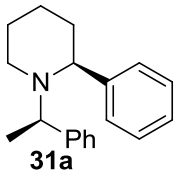
Unless otherwise specified, the chemicals were obtained commercially from Aldrich, Alfa Aesar, Apollo Scientific or TCI and used without further purification. Silica gel plates (GF_{254}) were used for TLC monitoring and silica gel (230-400 mesh) was used for running column chromatography. NMR spectra were recorded on a Bruker 400

MHz NMR spectrometer with TMS as the internal standard. The mass spectra were obtained by chemical ionization (CI) or electrospray ionization (ESI).

5.4.2 General procedure for *in situ* transamination of pyridiniums

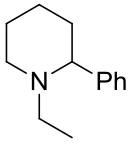
To a carousel reaction tube containing a magnetic stirring bar and (*R*)-(+)-α-methylbenzylamine (615 mg, 5 mmol) was added formic acid (564 mg, 12 mmol) dropwise at room temperature. After stirring the amine/acid mixture for 10 min, a pyridinium salt, *N*-ethyl-2-phenylpyridinium iodide (157 mg, 0.5 mmol), $[Cp^*RhCl_2]_2$ (3.1 mg, 5 μmol), 3.75 mL of CH_2Cl_2 and 0.25 mL of distilled H_2O were introduced into the mixture. The reaction system was placed in a carousel reactor. The mixture was stirred at 40 ^oC for 22 h, cooled to room temperature and then basified with an aqueous solution of KOH. The resulting mixture was extracted with ethyl acetate (3×10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane) to give the desired product **31a** in 86% yield.

5.5 Analytic data of isolated products



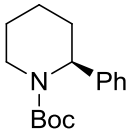
31a

(*S*)-2-Phenyl-1-((*R*)-1-phenylethyl)piperidine (31a):[8a] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.49-7.42 (m, 4H), 7.35-7.18 (m, 6H), 3.83 (q, *J* = 10.8 Hz, 1H), 3.50 (dd, *J* = 16.2, 4.6 Hz, 1H), 2.56 (dt, *J* = 18.6, 4.2 Hz, 1H), 2.22 (td, *J* = 17.8, 4.8 Hz, 1H), 1.80-1.26 (m, 6H), 1.18 (d, *J* = 10.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.4, 144.9, 128.6, 127.9, 126.68, 127.65, 127.0, 126.2, 65.7, 55.1, 45.2, 37.3, 26.4, 25.8, 8.2; HRMS for $C_{19}H_{24}N$ $[M+H]^+$: m/z calcd 266.1903, found 266.1906.



32

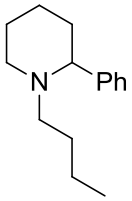
1-Ethyl-2-phenylpiperidine (32):[8b] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.37-7.20 (m, 5H), 3.17 (d, *J* = 11.2 Hz, 1H), 3.01 (dd, *J* = 11.2, 2.8 Hz, 1H), 2.57-2.49 (m, 1H), 2.10-1.95 (m, 2H), 1.81-1.53 (m, 5H), 1.41-1.31 (m, 1H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.4, 128.5, 127.6, 126.9, 68.9, 52.7, 49.2, 36.7, 26.2, 25.3, 11.1; HRMS for $C_{13}H_{20}N$ $[M+H]^+$: m/z calcd 190.1590, found 190.1589.



33

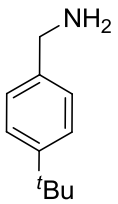
(*S*)-tert-Butyl 2-phenylpiperidine-1-carboxylate (33):[8c] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.34 (t, *J* = 8.0 Hz, 2H), 7.24-7.21 (m,

3H), 5.42 (brs, 1H), 4.05 (d, *J* = 13.6 Hz, 1H), 2.80-2.73 (m, 1H), 2.33-2.29 (m, 1H), 1.93-1.84 (m, 1H), 1.62-1.37 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 155.6, 140.3, 128.5, 126.5, 126.3, 99.9, 79.5, 40.1, 28.4, 28.1, 25.4, 19.3. HPLC (Chiralcel AD-H, hexane:isopropanol = 99:1, flow rate 1.0 mL/min, 220 nm): t_R = 7.3 min (minor), t_S = 8.0 min (major), 96.5% ee. The *S* configuration was determined by comparison with reported results in literature.



41

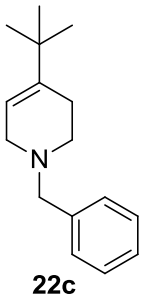
1-Butyl-2-phenylpiperidine (41):[8d] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.33-7.19 (m, 5H), 3.18 (d, *J* = 11.2 Hz, 1H), 2.98 (dd, *J* = 11.2, 2.8 Hz, 1H), 2.45-2.37 (m, 1H), 2.03 (td, *J* = 11.4, 3.4 Hz, 1H), 1.90-1.83 (m, 2H), 1.79-1.52 (m, 5H), 1.39-1.03 (m, 5H), 0.77 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.7, 128.4, 127.6, 126.8, 69.3, 55.3, 53.4, 36.9, 28.4, 26.3, 25.3, 20.7, 14.2; HRMS for $C_{15}H_{24}N$ $[M+H]^+$: m/z calcd 218.1903, found 218.1908.



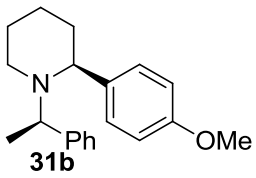
42

(4-(*tert*-Butyl)phenyl)methanamine (42):[8e] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.37 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 4.62 (brs, 2H), 3.84 (s, 2H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ

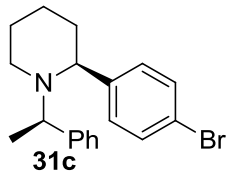
(ppm): 150.6, 136.9, 127.6, 125.8, 44.9, 34.6, 31.5; MS (CI, *m/z*, %) 147 (100) $[M+H-NH_3]^+$.



22c **1-Benzyl-4-(tert-butyl)-1,2,3,6-tetrahydropyridine (22c):**[8f] ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.36-7.22 (m, 5H), 5.41-5.39 (m, 1H), 3.57 (s, 2H), 3.02-3.00 (m, 2H), 2.52 (t, *J* = 5.8 Hz, 2H), 2.15 (br s, 2H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 144.6, 138.8, 129.6, 128.6, 127.4, 116.3, 63.3, 53.9, 50.6, 35.3, 29.2, 25.9; HRMS for $C_{16}H_{24}N$ $[M+H]^+$: m/z calcd 230.1903, found 230.1898.

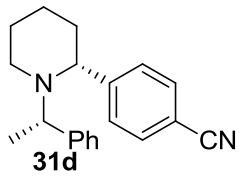


31b **(*S*)-1-((*R*)-1-Phenylethyl)-2-(4-(trifluoromethyl)phenyl)piperidine** (**31b**, unknown compound): ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.43 (d, *J* = 7.6 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 7.6 Hz, 2H), 7.17 (d, *J* = 7.4 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 3.83 (q, *J* = 6.8 Hz, 1H), 3.76 (s, 3H), 3.45 (dd, *J* = 10.8, 2.8 Hz, 1H), 2.55 (d, *J* = 11.6 Hz, 1H), 2.20 (td, *J* = 11.4, 2.6 Hz, 1H), 1.78-1.26 (m, 6H), 1.17 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 158.6, 145.0, 137.5, 128.6, 127.9, 127.6, 126.1, 114.0, 65.0, 55.4, 54.9, 45.3, 37.4, 26.6, 25.8, 8.2; HRMS for $C_{20}H_{26}NO$ $[M+H]^+$: m/z calcd 296.2009, found 296.2005.



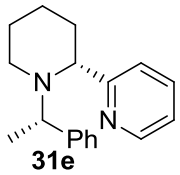
31c

(*S*)-2-(4-Bromophenyl)-1-((*R*)-1-phenylethyl)piperidine (**31c**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.46-7.34 (m, 6H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.19 (d, *J* = 7.2 Hz, 2H), 3.78 (q, *J* = 6.8 Hz, 1H), 3.48 (dd, *J* = 10.8, 2.6 Hz, 1H), 2.55 (d, *J* = 11.6 Hz, 1H), 2.21 (td, *J* = 11.6, 2.4 Hz, 1H), 1.79-1.72 (m, 2H), 1.66-1.28 (m, 4H), 1.18 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 144.47, 144.46, 131.8, 129.4, 128.0, 127.6, 126.3, 120.5, 65.0, 55.1, 45.1, 37.3, 26.3, 25.6, 8.3; HRMS for $C_{19}H_{23}BrN$ $[M+H]^+$: m/z calcd 346.0988, 344.1009, found 346.0987, 344.0995.



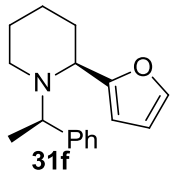
31d

4-((*R*)-1-((*S*)-1-Phenylethyl)piperidin-2-yl)benzonitrile (**31d**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.65-7.57 (m, 4H), 7.41 (d, *J* = 12.8 Hz, 2H), 7.34-7.18 (m, 3H), 3.71 (q, *J* = 10.8 Hz, 1H), 3.59 (dd, *J* = 16.8, 4.8 Hz, 1H), 2.58 (d, *J* = 19.0 Hz, 1H), 2.23 (td, *J* = 18.0, 4.6 Hz, 1H), 1.83-1.72 (m, 4H), 1.67-1.28 (m, 4H), 1.20 (d, *J* = 10.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 151.2, 144.0, 132.6, 128.3, 128.1, 127.4, 126.5, 119.1, 110.8, 65.3, 55.6, 44.9, 37.2, 26.1, 25.4, 8.5; HRMS for $C_{20}H_{23}N_2$ $[M+H]^+$: m/z calcd 291.1856, found 291.1854.



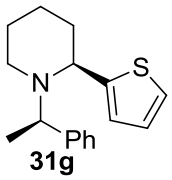
31e

2-((*R*)-1-((*S*)-1-phenylethyl)piperidin-2-yl)pyridine (**31e**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.53 (d, *J* = 4.8 Hz, 1H), 7.67-7.61 (m, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.13 (ddd, *J* = 7.2, 5.0, 1.8 Hz, 1H), 3.78 (dd, *J* = 10.8, 2.8 Hz, 1H), 3.72 (q, *J* = 6.8 Hz, 1H), 2.59 (d, *J* = 11.2 Hz, 1H), 2.28 (td, *J* = 11.2, 2.8 Hz, 1H), 1.91-1.86 (m, 1H), 1.81-1.77 (m, 1H), 1.70-1.33 (m, 4H), 1.26 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 164.9, 149.0, 144.5, 136.7, 128.0, 127.6, 126.3, 122.0, 121.9, 67.2, 56.0, 44.9, 35.8, 26.2, 25.2, 8.8; HRMS for $C_{18}H_{23}N_2$ $[M+H]^+$: m/z calcd 267.1856, found 267.1863.



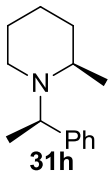
31f

(*S*)-2-(Furan-2-yl)-1-((*R*)-1-phenylethyl)piperidine (**31f**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.39 (t, *J* = 7.6 Hz, 3H), 7.27 (d, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 6.31 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.25 (d, *J* = 3.2 Hz, 1H), 3.79 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.66 (q, *J* = 6.8 Hz, 1H), 2.52 (dt, *J* = 11.2, 4.0 Hz, 1H), 2.55 (td, *J* = 10.4, 2.8 Hz, 1H), 1.97-1.72 (m, 3H), 1.54-1.30 (m, 3H), 1.26 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 157.2, 145.0, 141.3, 128.0, 127.8, 126.3, 110.0, 106.8, 57.3, 57.1, 45.4, 32.7, 26.0, 24.3, 11.2; HRMS for $C_{17}H_{22}NO$ $[M+H]^+$: m/z calcd 256.1696, found 256.1689.



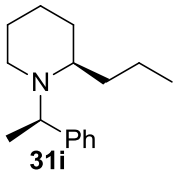
31g

(*S*)-1-((*R*)-1-phenylethyl)-2-(thiophen-2-yl)piperidine (**31g**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.42 (t, *J* = 7.6 Hz, 3H), 7.48-7.15 (m, 6H), 6.93-6.83 (m, 2H), 3.92-3.75 (m, 2H), 2.62 (dt, *J* = 11.2, 4.0 Hz, 1H), 2.18 (td, *J* = 10.4, 2.8 Hz, 1H), 1.88-1.27 (m, 6H), 1.20 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 149.5, 144.7, 127.9, 127.7, 126.3, 126.0, 124.4, 60.1, 55.4, 45.1, 37.9, 26.0, 25.3, 9.0; HRMS for $C_{17}H_{22}NS$ $[M+H]^+$: m/z calcd 272.1467, found 272.1463.



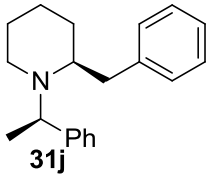
31h

(*R*)-2-Methyl-1-((*R*)-1-phenylethyl)piperidine (31h):[8g] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.42 (d, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 4.04 (q, *J* = 6.8 Hz, 1H), 2.84-2.77 (m, 1H), 2.36-2.31 (m, 1H), 2.15-2.09 (m, 1H), 1.72-1.56 (m, 2H), 1.43-1.28 (m, 4H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.9, 128.0, 127.8, 126.3, 56.7, 52.1, 45.0, 34.8, 26.5, 23.5, 17.2, 12.6; HRMS for $C_{14}H_{22}N$ $[M+H]^+$: m/z calcd 204.1747, found 204.1747.



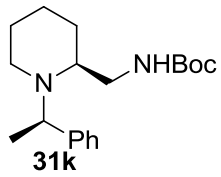
31i

(*R*)-1-((*R*)-1-Phenylethyl)-2-propylpiperidine (31i):[8g] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.41 (d, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 4.01 (q, *J* = 6.6 Hz, 1H), 2.72 (brs, 1H), 2.36 (ddd, *J* = 11.2, 8.0, 3.2 Hz, 1H), 2.23-2.18 (m, 1H), 1.69-1.28 (m, 10H), 1.25 (d, *J* = 6.4 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 146.4, 128.1, 127.6, 126.3, 56.9, 55.8, 45.2, 31.1, 29.7, 25.9, 22.8, 19.0, 14.9, 14.7; HRMS for $C_{16}H_{26}N$ $[M+H]^+$: m/z calcd 232.2060, found 232.2057.



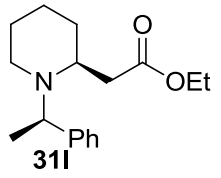
31j

(*S*)-2-Benzyl-1-((*R*)-1-phenylethyl)piperidine (**31j**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.40 (d, *J* = 7.2 Hz, 2H), 7.32-7.17 (m, 8H), 4.02 (q, *J* = 6.8 Hz, 1H), 3.19-3.14 (m, 1H), 3.01 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.75 (dd, *J* = 13.0, 10.6 Hz, 1H), 2.46-2.32 (m, 2H), 1.64-1.40 (m, 6H), 1.37 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 146.7, 141.0, 129.4, 128.4, 128.3, 127.5, 126.6, 125.8, 58.9, 57.0, 45.2, 32.8, 28.3, 25.9, 21.3, 17.8; HRMS for $C_{20}H_{26}N$ $[M+H]^+$: m/z calcd 280.2060, found 280.2062.



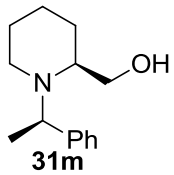
31k

***tert*-butyl (((*S*)-1-((*R*)-1-Phenylethyl)piperidin-2-yl)methyl)carbamate** (**31k**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.38 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 4.98 (s, 1H), 4.12 (q, *J* = 6.8 Hz, 1H), 3.40-3.35 (m, 1H), 3.29-3.23 (m, 1H), 2.72 (brs, 1H), 2.54-2.49 (m, 1H), 2.34 (ddd, *J* = 12.0, 8.8, 2.8 Hz, 1H), 1.71-1.64 (m, 3H), 1.44 (s, 10H), 1.38-1.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 156.5, 145.1, 128.3, 127.6, 126.7, 79.1, 56.0, 55.2, 44.1, 41.1, 28.6, 28.2, 24.7, 23.3, 13.4; HRMS for $C_{19}H_{31}N_2O_2$ $[M+H]^+$: m/z calcd 319.2380, found 319.2396.



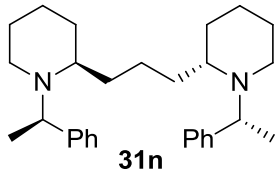
31l

Ethyl 2-((S)-1-((R)-1-phenylethyl)piperidin-2-yl)acetate (31l):[8h] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.35-7.21 (m, 5H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.86 (q, *J* = 6.4 Hz, 1H), 2.84-2.80 (m, 1H), 2.76-2.73 (m, 1H), 1.90-1.83 (m, 1H), 1.68-1.43 (m, 6H), 1.32-1.26 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 174.7, 146.6, 128.5, 126.9, 126.8, 60.1, 55.1, 53.5, 44.6, 30.0, 25.7, 24.8, 23.4, 23.0, 14.5; HRMS for $C_{17}H_{26}NO_2$ $[M+H]^+$: m/z calcd 276.1958, found 276.1965.



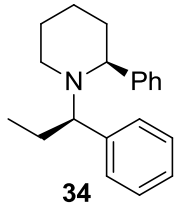
31m

((*S*)-1-((*R*)-1-Phenylethyl)piperidin-2-yl)methanol (31m)[8i] : ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.38-7.19 (m, 5H), 4.25 (q, *J* = 10.8 Hz, 1H), 3.62 (d, *J* = 10.8 Hz, 2H), 2.78-2.68 (m, 1H), 2.66-2.54 (m, 2H), 1.79-1.40 (m, 5H), 1.35 (d, *J* = 8.8 Hz, 3H), 1.31-1.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 144.9, 128.4, 127.6, 126.9, 61.2, 56.4, 56.2, 42.9, 25.6, 23.2, 22.7, 15.4; HRMS for $C_{14}H_{22}NO$ $[M+H]^+$: m/z calcd 220.1696, found 220.1692.



31n

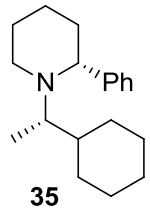
1,3-bis((*S*)-1-((*R*)-1-Phenylethyl)piperidin-2-yl)propane (**31n**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.41 (d, *J* = 7.0 Hz, 4H), 7.29 (t, *J* = 7.0 Hz, 4H), 7.23-7.15 (m, 2H), 4.00 (q, *J* = 6.8 Hz, 2H), 2.73-2.70 (m, 18H), 2.41-2.33 (m, 2H), 2.25-2.15 (m, 2H), 1.65-1.30 (m, 2H), 1.24 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 146.3, 128.1, 127.6, 126.6, 57.0, 56.1, 45.1, 29.7, 29.4, 25.9, 22.8, 22.0, 14.8; HRMS for $C_{19}H_{43}N_2$ $[M+H]^+$: m/z calcd 419.3421, found 419.3419.



34

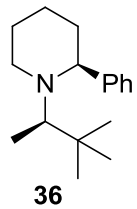
(*S*)-2-Phenyl-1-((*R*)-1-phenylpropyl)piperidine (**34**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.54 (d, *J* =

7.6 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.36-7.29 (m, 5H), 7.25 (t, *J* = 6.4 Hz, 1H), 3.62 (d, *J* = 10.4 Hz, 1H), 3.51 (dd, *J* = 9.6, 3.4 Hz, 1H), 2.78 (d, *J* = 11.6 Hz, 1H), 2.32 (t, *J* = 11.2 Hz, 1H), 1.93-1.30 (m, 8H), 0.68 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.3, 142.2, 128.9, 128.6, 128.0, 127.8, 127.1, 126.4, 65.8, 63.1, 45.5, 36.7, 26.4, 25.6, 15.3, 12.1; HRMS for $C_{20}H_{26}N$ $[M+H]^+$: m/z calcd 280.2060, found 280.2060.



35

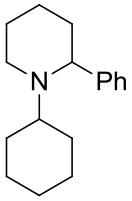
(*R*)-1-((*S*)-1-Cyclohexylethyl)-2-phenylpiperidine (35, unknown compound**)**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.30-7.16 (m, 5H), 3.32 (dd, *J* = 10.8, 2.8 Hz, 1H), 2.78 (d, *J* = 11.6 Hz, 1H), 2.25-2.09 (m, 3H), 1.76-1.49 (m, 9H), 1.35-1.00 (m, 5H), 0.73 (d, *J* = 6.4 Hz, 3H), 0.69-0.62 (m, 1H), 0.58-0.48 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.7, 128.2, 128.1, 126.6, 65.7, 57.5, 44.9, 41.1, 37.6, 31.2, 30.6, 26.9, 26.8, 26.6, 25.8, 8.4; HRMS for $C_{19}H_{30}N$ $[M+H]^+$: m/z calcd 272.2373, found 272.2378.



36

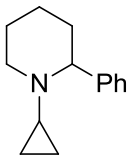
(*S*)-1-((*R*)-3,3-Dimethylbutan-2-yl)-2-phenylpiperidine (**36**, unknown compound): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.23-7.10 (m, 5H), 3.19-3.16 (m, 1H), 2.89 (d, *J* = 11.2 Hz, 1H), 2.20-2.11 (m, 2H), 1.69-1.47 (m, 5H), 1.27-1.16 (m, 1H), 0.73-0.71 (m, 12H); ^{13}C NMR

($CDCl_3$, 100 MHz) δ (ppm): 145.8, 128.5, 128.1, 126.8, 67.3, 60.2, 48.4, 37.2, 35.2, 28.9, 26.6, 25.9, 5.6; HRMS for $C_{17}H_{28}N$ $[M+H]^+$: m/z calcd 246.2216, found 246.2209.



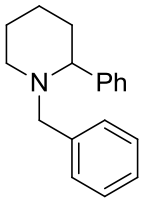
37

1-Cyclohexyl-2-phenylpiperidine (**37**, unknown compound): ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.32-7.19 (m, 5H), 3.41 (dd, *J* = 10.8, 2.8 Hz, 1H), 3.02 (d, *J* = 11.2 Hz, 1H), 2.32-2.25 (m, 2H), 1.77-1.25 (m, 12H), 1.14-0.73 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.6, 128.4, 127.5, 126.7, 65.7, 58.2, 46.4, 37.3, 31.8, 26.72, 26.68, 26.64, 26.0, 25.6, 23.8; HRMS for $C_{17}H_{26}N$ $[M+H]^+$: m/z calcd 244.2060, found 244.2063.



38

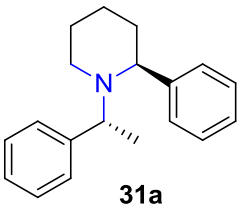
1-Cyclopropyl-2-phenylpiperidine (**38**, unknown compound): ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.31-7.21 (m, 5H), 3.17 (d, *J* = 11.6 Hz, 1H), 3.09 (dd, *J* = 10.4, 3.2 Hz, 1H), 2.25 (td, *J* = 11.8, 3.0 Hz, 1H), 1.85-1.51 (m, 5H), 1.45-1.26 (m, 2H), 0.28-0.13 (m, 2H), -0.01--0.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 144.4, 128.7, 127.9, 127.0, 71.3, 56.1, 39.1, 34.6, 26.1, 24.9, 9.6, 4.0; HRMS for $C_{14}H_{20}N$ $[M+H]^+$: m/z calcd 202.1590, found 202.1595.



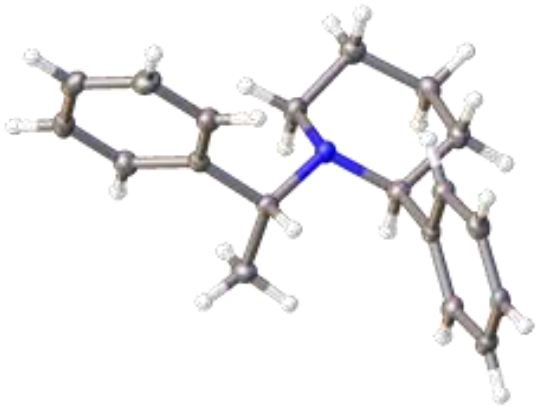
20d

1-Benzyl-2-phenylpiperidine (20d):[8f] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.46 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 4.4 Hz, 4H), 7.25-7.18 (m, 2H), 3.76 (d, *J* = 13.6 Hz, 1H), 3.11 (dd, *J* = 11.0, 2.6 Hz, 1H), 2.96 (d, *J* = 11.6 Hz, 1H), 2.81 (d, *J* = 13.2 Hz, 1H), 1.98-1.89 (m, 1H), 1.81-1.74 (m, 2H), 1.67-1.53 (m, 3H), 1.42-1.31 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.9, 140.0, 128.8, 128.6, 128.1, 127.6, 127.0, 126.6, 69.3, 59.9, 53.5, 37.2, 26.1, 25.4; HRMS for $C_{18}H_{22}N$ $[M+H]^+$: m/z calcd 252.1752, found 252.1748.

5.6 Crystallographic data of 31a



31a



$C_{19}H_{23}N$, M = 265.38, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 7.8158(6) Å, b = 10.3447(7) Å, c = 18.8075(14) Å, V = 1520.63(19) Å3, Z = 4, T = 100.0 K, μ(Mo kα) = 0.499 mm-1, *Dcalc* = 1.159 g/mm3, 13955 reflections measured ($9.4 \leq 2\Theta \leq 149.24$), 3073 unique ($R$int = 0.0281) which were used in all calculations. The final R1 was 0.0305 (>2sigma(I)) and wR2 was 0.0776 (all data).

5.7 References

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CHAPTER 6 CONCLUSIONS AND PERSPECTIVES

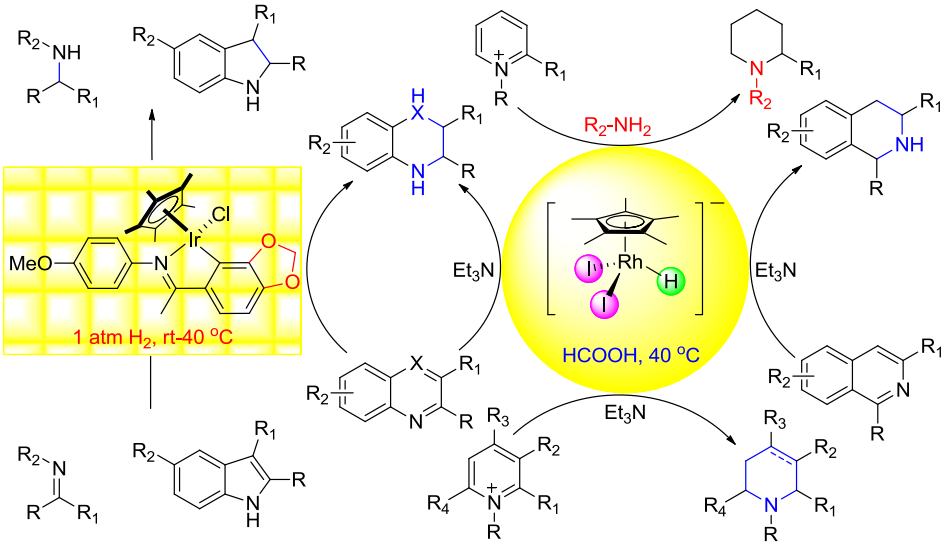
This thesis describes our contribution to TH of *N*-heteroaromatic compounds. In the previous chapters, we identified the challenges in the realm of TH and new protocols to tackle these problems were developed in our research.

An efficient and mild TH protocol was developed for the reduction of quinolines, isoquinolines and quinoxalines to the corresponding tetrahydro products. This system was also applied to the reduction of more challenging pyridines to afford not only piperidines but also the 3,4-unsaturated derivatives in a highly chemoselective manner. In this study, the remarkable accelerating effect of the iodide ion was discovered, which offers a solution for practical preparation of various *N*-heterocyclic compounds. The iodide-promoted system also found its use in the reduction of alkenes to alkanes, nitrobenzene to aniline, as well as alkynes to alkenes with an exclusively *trans* manner, which is not described in the thesis.

In the hydrogenation of *N*-heterocycles with H_2, a simple bridging electron-donor was found to convert an inactive cyclometalated iridium complex into a most active catalyst at ambient conditions without using any additives.

A new reaction was serendipitously discovered, leading to the direct preparation of a range of *N*-substituted piperidines, particularly the chiral versions from pyridines. The unprecedented diastereo- and enantioselectivities for a variety of substrates were demonstrated using this TH-transamination process.

A summary of the research in this thesis is shown in scheme 58.



Scheme 58: Schematic summary of the research of the thesis

Considering the high activity of iodide-accelerated TH of *N*-heteroaromatic compounds, future work could aim at developing chiral catalysts with more structurally rigid ligands, such as chiral Cp ligand,[1] which may resist the attack of excessive iodide, thereby achieving industrially viable ATH with a higher efficacy than currently available asymmetric methods.

Encouraged by recently arising iron-catalysed TH of carbonyls,[2] imines[2] and nitroarenes,[3a] and decomposition of formic acid,[3b] search for more cost-efficient metal catalysts, such as iron complexes, could be a future direction for a greener TH-transamination process.

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