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Borrowing Hydrogen in the Activation of Alcohols

Malai Haniti S. A. Hamid,[a] Paul A. Slatford,[a] and Jonathan M. J. Williams[a,*]

[a] Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, U.K.
Fax: (+ 44)-1225-386-231; e-mail: j.m.j.williams@bath.ac.uk

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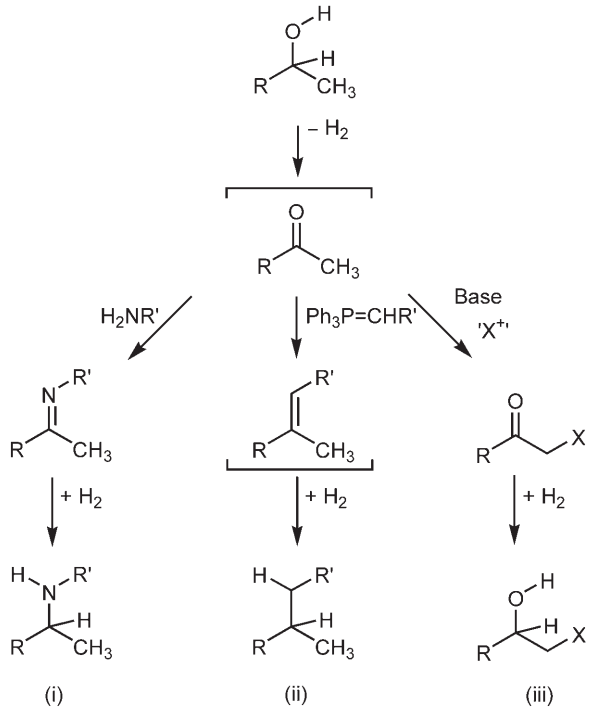
Abstract: Alcohols can be temporarily converted into carbonyl compounds by the metal-catalysed removal of hydrogen. The carbonyl compounds are reactive in a wider range of transformations than the precursor alcohols and can react *in situ* to give imines, alkenes, and α-functionalised carbonyl compounds. The metal catalyst, which had borrowed the hydrogen, then returns it to the transformed carbonyl compound, leading to an overall process in which alcohols can be converted into amines, compounds containing C–C bonds and β-functionalised alcohols.

Keywords: alcohols; amines; catalysis; transfer hydrogenation; transition metals

1 Introduction

In general, alcohols have a limited reactivity without some type of activation. Activation can be as simple as the addition of base, forming a nucleophilic alkoxide, or the addition of an acid to provide an electrophilic species. However, there is an alternative activation pathway, which involves the temporary oxidation of an alcohol into the corresponding aldehyde or ketone. Carbonyl compounds usually have a much wider range of reactivity than alcohols, and are amenable to nucleophilic addition reactions, as well as acting as nucleophiles themselves (as the corresponding enol or enolate). Using oxidation as an activation process for alcohols can become a catalytic process when the carbonyl compound, or its derivative, is subsequently reduced under the reaction conditions. The main reactions that have employed this activation strategy are identified in Scheme 1. The additional reactivity of the ketone over the alcohol is exploited by (i) imine formation and reduction to an amine, (ii) alkene formation and reduction to a C–C bond and (iii) enolisation, electrophilic trap and reduction back to a functionalised alcohol. In all cases there is, ideally, no net hydrogen loss or gain during the reaction sequence.



Scheme 1. Activation of alcohols by borrowing hydrogen.

Jonathan Williams (centre) was born in Worcestershire, England in 1964, and graduated from the University of York in 1986. He completed his DPhil in organic chemistry at the University of Oxford in 1989 under the supervision of Professor Stephen G. Davies. After a two year post-doctoral stay with Professor David A. Evans at Harvard University, he was appointed to a Lectureship in Organic Chemistry at Loughborough University. In 1996, he moved to the University of Bath as a Professor of Organic Chemistry. His research interests are mainly centred on the use of transition metal-catalysed reactions, and recent work in the area of borrowing hydrogen has been recognised by the award of the AstraZeneca, GlaxoSmithKline and Pfizer UK Prize for Process Chemistry in 2005.

M. Haniti Sh. Abd. Hamid (left) was born in Bandar Seri Begawan, Brunei Darussalam. She completed her BSc in chemistry at the University of Nottingham in 1998. After she had received her MSc in advanced organic chemistry in 1999 at the University of East Anglia, she worked as a lecturer in organic chemistry at the Universiti Brunei Darussalam. She is now a second year PhD student at the University of Bath working on the synthetic applications of borrowing hydrogen under the supervision of Professor Jonathan Williams.

Paul Slatford (right) was born in Hornchurch, England in 1977, and graduated from the University of Bristol in 2000. He completed his PhD under the supervision of Professor Guy Lloyd-Jones, also at the University of Bristol, in 2004. He is currently working as a post-doc at the University of Bath under Professor Jonathan Williams. His research interests are based upon the development of new methodology utilising transition metal catalysis.

Recent research in this area has benefited from developments in the area of transfer hydrogenation chemistry. Along with the classical aluminium-based reagents used for the Oppenauer oxidation of alcohols by ketones, and the Meerwein–Pondorff–Verley reduction of ketones by alcohols, many other metals have been shown to be catalytically competent for the reversible transformation of alcohols into carbonyl compounds. In particular, late transition metal catalysts have been widely investigated, including examples of imine and alkene reduction using alcohols as hydrogen donors.[1] Transfer hydrogenation reactions,[2] and their asymmetric variants[3] have been well reviewed, along with a detailed analysis of the mechanisms involved in these processes.[4]

In the transfer hydrogenation of alcohols with carbonyl compounds, several mechanisms are possible, depending on the nature of the metal and its associated ligands. During the catalytic cycle, the metal may react without forming a metal hydride at all, or react *via* a mono-hydride or di-hydride complex.

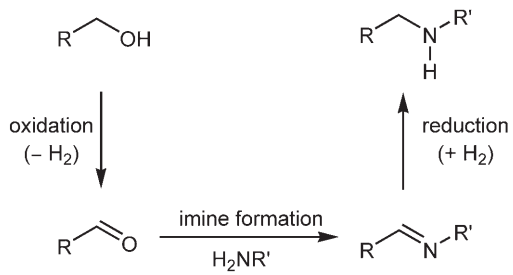
2 Amination of Alcohols

Traditionally, the alkylation of amines is achieved using conventional alkylating agents, such as alkyl halides. There can be selectivity problems in such reactions when control of multiple alkylation can be difficult. For example, the reaction of a primary amine with an alkyl halide may provide secondary amine, tertiary amine, quaternary ammonium salt along with recovered starting material in varying amounts depending on the reaction conditions and relative reactivities of the species involved. A review of the methods available for the synthesis of secondary amines has been published,[5] and in some instances, mono-alkylation can be controlled by using alkyl halides under appropriate conditions.[6] Microwave irradiation has been used in the selective synthesis of tertiary amines from secondary amines and alkyl halides.[7] However, many alkyl halides have toxic or even mutagenic properties and an alternative to using such reagents is therefore advantageous.

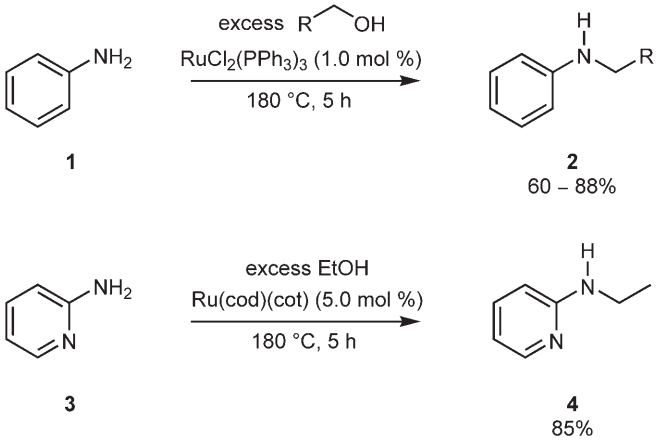
Alcohols have been used directly in the synthesis of amines by using acid catalysts including solid acid catalysts[8] and alumina.[9] Direct *N*-alkylation has also been reported with the use of supercritical methanol providing methylation of aniline, although high temperatures (350 °C) are required.[10]

The amination of alcohols by borrowing hydrogen involves three well-known reactions; the oxidation of an alcohol into a carbonyl compound with a transition metal catalyst,[11] imine formation between an amine and a carbonyl compound,[12] and the reduction of an imine to an amine with a transition metal catalyst.[13] The reaction sequence is identified in Scheme 2.

Amination reactions of alcohols which proceed *via* the borrowing hydrogen route have been known for many years, including a report on the use of heterogeneous nickel catalysts in 1932.[14] In 1981, Grigg and co-workers reported homogeneous catalysts for the amination of alcohols using rhodium-, iridium- and ruthenium-based catalysts,[15] and other metals have also been used in this transformation.[16]



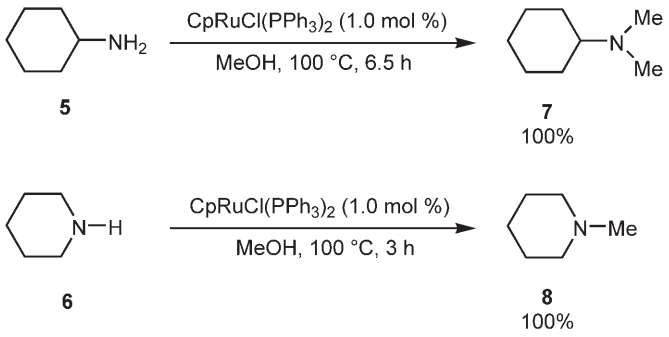
Scheme 2. Conversion of alcohols into amines by 'borrowing hydrogen'.



Scheme 3. Ruthenium catalysed *N*-alkylation of amines.

Several ruthenium catalysts have been used for the formation of secondary amines from primary amines and alcohols, although the reaction conditions are often harsh. Typical reactions, as shown in Scheme 3, include the use of $RuCl_2(PPh_3)_3$ in the alkylation of aniline **1** which gave secondary amines **2** as the major product along with some tertiary amine arising from di-alkylation.[17] The same catalyst has also been reported to work in other *N*-alkylation reactions.[18] Selectivity for mono-alkylation was improved using the ruthenium complex Ru(cod)(cot), where the ethylation of 2-aminopyridine **3** was achieved to give the product **4** in 85% yield.[19] The addition of phosphines and phosphites to this complex increased the amount of di-alkylation. Other ruthenium catalysts have been used successfully,[20] including $[Ru(cymene)Cl_2]_2$ with dppf [bis(diphenylphosphino)ferrocene] which has been used to effect the *N*-alkylation of aromatic and aliphatic amines by primary alcohols at 110 °C.[21]

Del Zotto and co-workers have used the ruthenium complex $RuClCp(PPh_3)_2$ as a catalyst for the methylation of amines with methanol. It is particularly effective for the formation of tertiary aliphatic amines, although aniline was unreactive under the reported reaction conditions. The catalyst was successful for the methylation of a range of amines including cyclohexylamine **5** and piperidine **6** as shown in Scheme 4.[22]



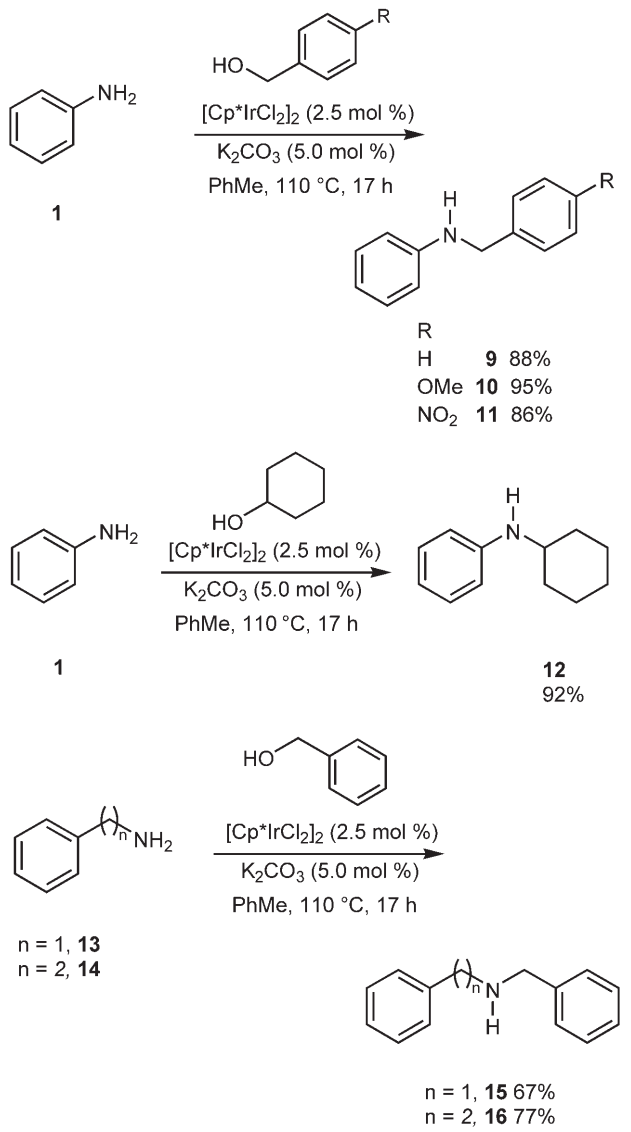
Scheme 4. *N*-Methylation of primary and secondary amines.

The iridium catalyst $[Cp^*IrCl]_2$ has been shown by Fujita, Yamaguchi and co-workers to be an efficient catalyst for the *N*-alkylation of amines with alcohols.[23] They have successfully used benzylic alcohols with either electron-wthdrawing or electron-donating groups as well as other primary and secondary alcohols. The reaction is particularly effective for the *N*-alkylation of anilines, but also gives good yields with aliphatic primary amines. Examples shown in Scheme 5 include the alkylation of aniline **1** to give products **9**, **10**, **11**, and **12**, as well as the alkylation of benzylamine **13** and β-phenethylamine **14** with benzyl alcohol providing the corresponding secondary amines **15** and **16**.

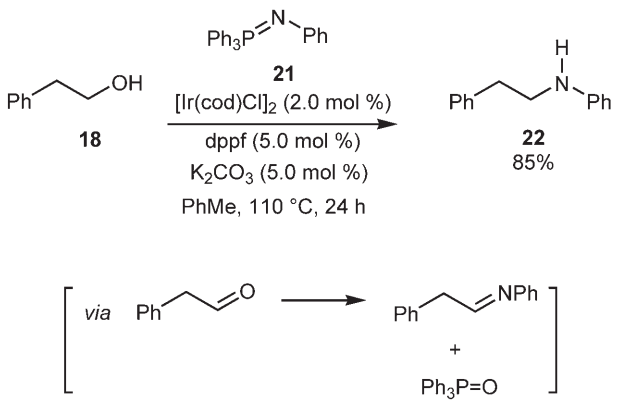
An alternative iridium complex derived from $[Ir(cod)Cl]_2$ and bis(diphenylphosphino)ferrocene (dppf) has also been shown to be effective for the mono-alkylation of primary amines with alcohols (Scheme 6).[24] The secondary amine **19** was prepared in good yield by the reaction of tryptamine **17** with phenethyl alcohol **18**. Employing the alternative combination of alcohol **20** and amine **14** was also successful, although the use of benzyl alcohol led to the formation of non-reduced imine as a significant by-product.

Recently, Beller and co-workers have reported a method for the *N*-alkylation of primary amines with primary and secondary alcohols. Use of $Ru_3(CO)_{12}$ as catalyst combined with tri-*o*-tolylphosphine as ligand produces excellent conversions with a range of amines and alcohols.[25] For example, hexylamine was alkylated with 1-phenylethanol with complete consumption of starting materials with the product recovered in 97% yield. Other secondary alcohols were also successfully aminated under these conditions.

The oxidation, imine formation and reduction steps can all be carried out as independent reactions in order to achieve the same outcome, although the borrowing hydrogen approach is more efficient since there is no net hydrogen gain or loss. However, the performance of sequential reactions in one pot is synthetically useful and the amination of alcohols using a stoichiometric oxidising agent (MnO_2) and reducing agent ($NaBH_4$) has been reported.[26]



Scheme 5. *N*-Alkylation with $[Cp^*IrCl]_2$ as the catalyst.

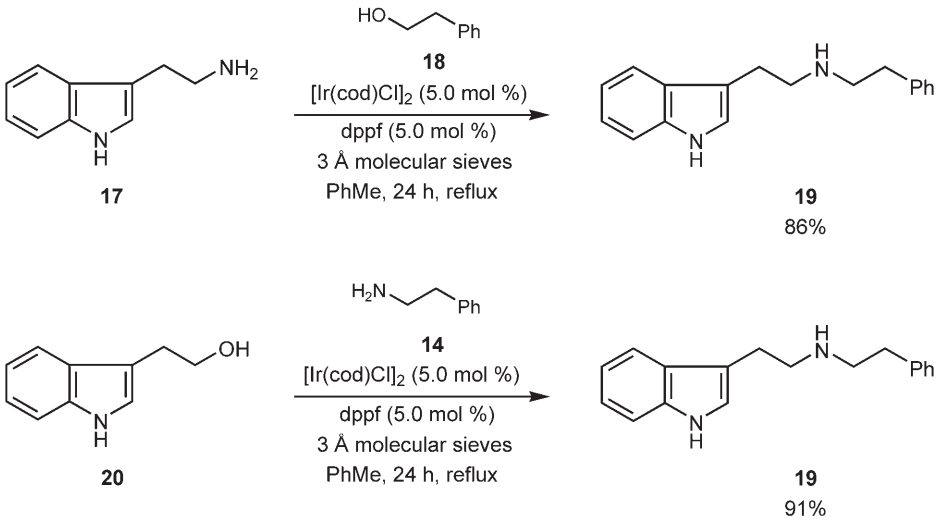


Scheme 7. Use of iminophosphorane in an indirect aza-Wittig reaction.

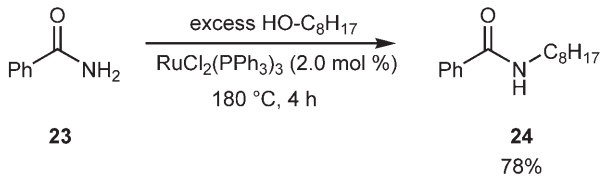
The conversion of alcohols into amines has been achieved using a related strategy employing an iminophosphorane as the reagent for forming an imine from the intermediate aldehyde. Alcohol **18** is converted into the aniline **22** with an iridium catalyst and the iminophosphorane **21**. The overall process is an indirect aza-Wittig reaction on an alcohol, which is assumed to proceed *via* the same oxidation, imine formation, reduction sequence as other alcohol amination reactions (Scheme 7).[27]

As well as the alkylation of amines with alcohols, amides have also been shown to undergo *N*-alkylation on treatment with alcohols and a ruthenium complex. For example, the primary amide **23** has been converted into the secondary amide **24**, as illustrated in Scheme 8.[28]

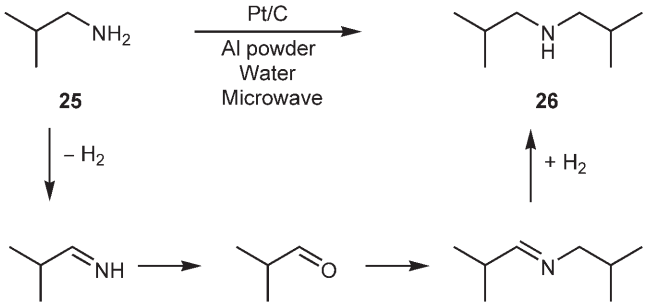
A related process involving the formation of secondary amines from primary amines is also known. In a recent example reported by Miyazawa and co-workers, platinum on carbon was used as the catalyst.[29] The reaction was most successful for primary amines



Scheme 6. Formation of an alkylated tryptamine.



Scheme 8. *N*-Alkylation of an amide.



Scheme 9. Conversion of a primary amine into a secondary amine.

adjacent to a methylene group, as illustrated for the conversion of primary amine **25** into secondary amine **26**. The reaction was believed to proceed *via* oxidation of the amine into an imine. The imine was hydrolysed to an aldehyde and then reformed an imine with more amine, which was reduced to give the final product as indicated in Scheme 9. For some substrates, the formation of tertiary amines was a problem, and with amines attached to a secondary alkyl group, the main product was the ketone.

Many other catalysts have been reported to be able to facilitate alkyl transfer between amines, including palladium black,[30] ruthenium phosphine complexes[31] and osmium, ruthenium and iridium carbonyl complexes.[32]

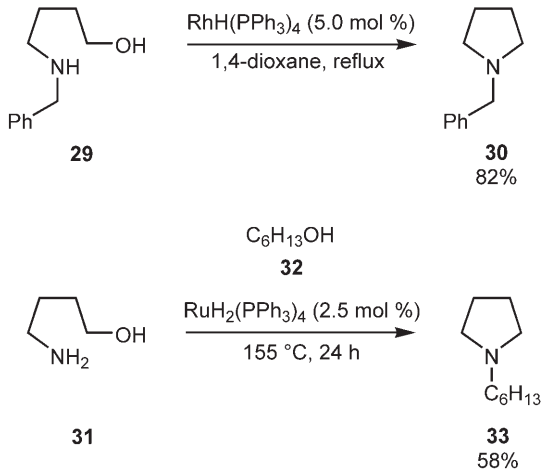
Amine redistribution has been combined with *N*-alkylation by controlling the reaction conditions.[33] The reaction of hexylamine with excess methanol provided the *N,N*-dimethylamine **27** as the major product (Scheme 10). However, using fewer equivalents of methanol afforded *N,N*-dihexylamine **28** as the major product (trihexylamine and dihexylamine were also identified as minor by-products).

3 Formation of Nitrogen Heterocycles

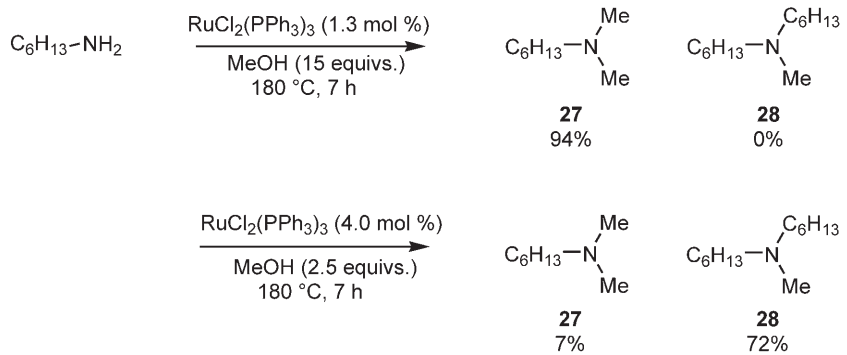
Nitrogen heterocycles are common synthetic targets due to their common occurrence in natural products and pharmaceutically interesting structures. The amination of alcohols has been successfully extended into cyclisation reactions by appropriate choice of substrate.

3.1 Cyclisation of Amino Alcohols

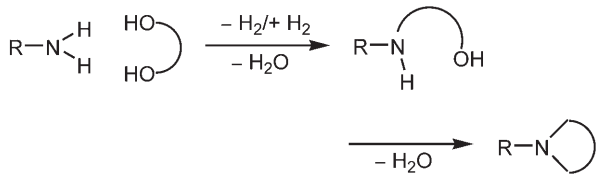
Amino alcohols have been converted into cyclic amines using transition metal catalysts. For example, amino alcohol **29** underwent cyclisation into the pyrrolidine **30** on treatment with a rhodium catalyst.[15] Presumably, the reaction proceeds by oxidation of the



Scheme 11. Cyclisation reactions of amino alcohols.



Scheme 10. Amine redistribution and *N*-alkylation.



Scheme 12. General strategy for the formation of N-heterocycles from primary amines.

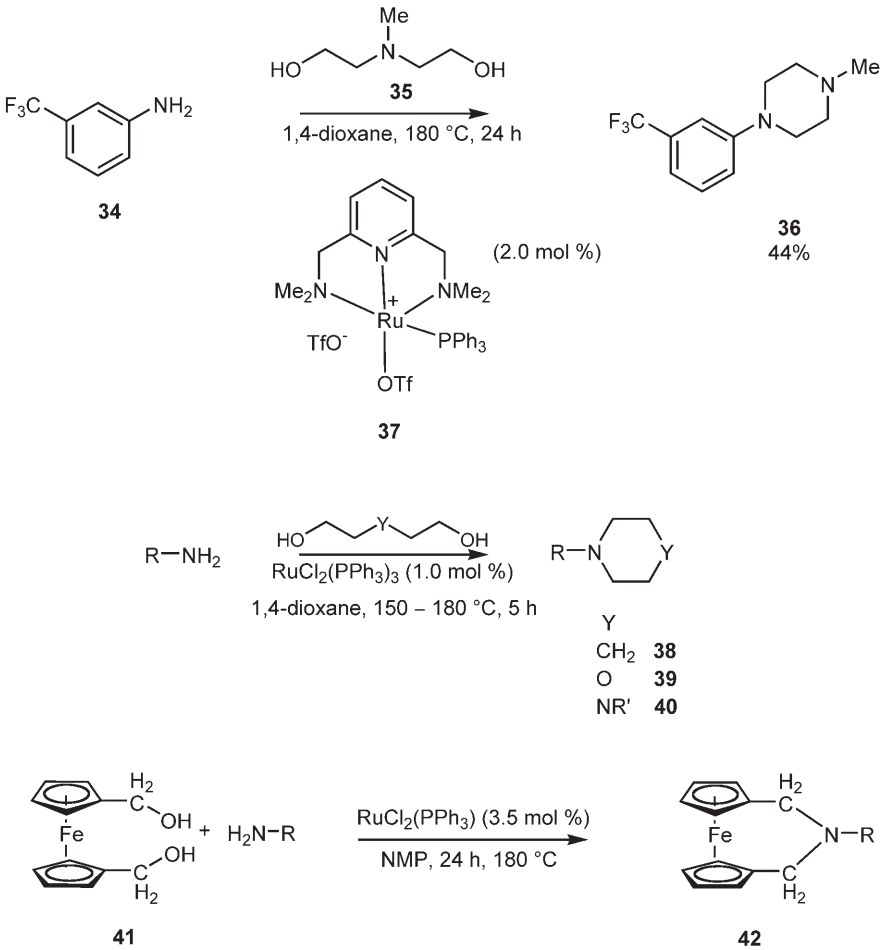
alcohol to an aldehyde, formation of a cyclised iminium or enamine species and then reduction to the saturated amine. $RuH_2(PPh_3)_4$ has also been used to catalyse similar cyclisation reactions, as well as cyclisation/alkylation reactions such as the conversion of amino alcohol **31** and alcohol **32** into the cyclic product **33** (Scheme 11).[34]

3.2 Condensation of Amines with Diols

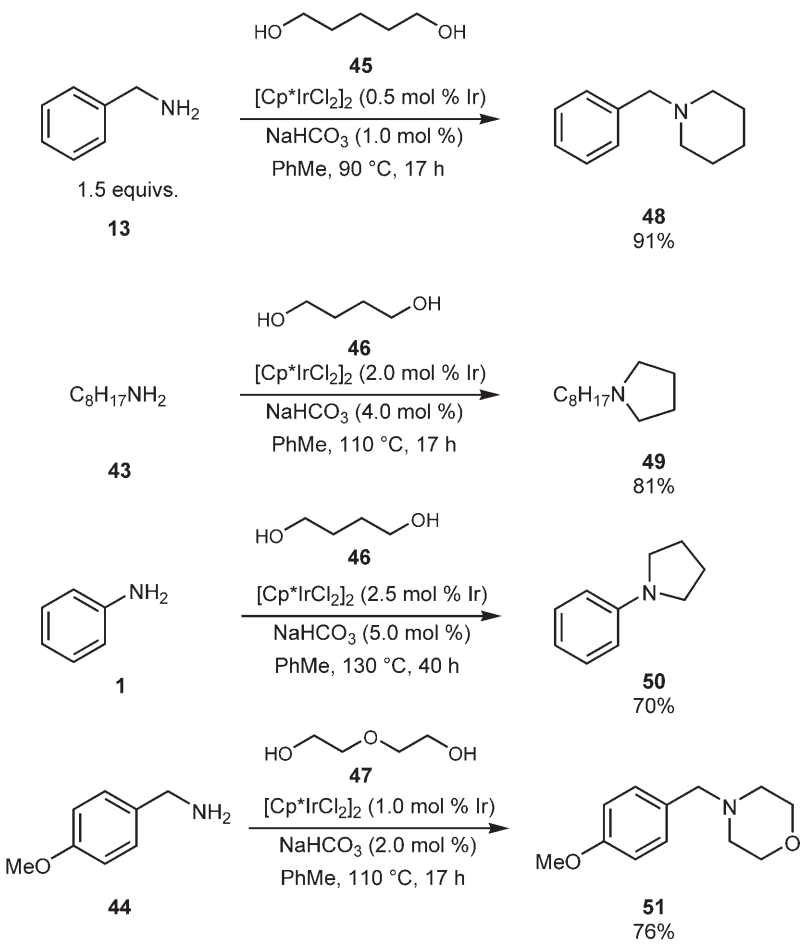
The reaction of a primary amine with a diol to form a cyclic amine is a useful method for the preparation of this compound class. Suitable transfer hydrogenation catalysts have been employed for this process, which involves a double alkylation of the primary amine, with the second alkylation being an intramolecular step (Scheme 12).

Many early examples of this transformation required forcing conditions, and include the examples given in Scheme 13. For example, van Koten and co-workers have prepared piperazine **36**, which is a potent serotonin agonist, by the reaction between aniline **34** and aminodiol **35** using a ruthenium pincer complex **37**.[35] Watanabe and co-workers have demonstrated that primary amines can be converted into piperidines **38**, morpholines **39** and piperazines **40** by condensation with suitable diols in the presence of ruthenium/phosphine complexes.[36] Cyclisation of 1,1′-ferrocenedimethanol **41** with primary amines provides access to the *N*-substituted 2-aza[3]ferrocenophanes **42** which were of interest for their electrochemical properties.[37]

Yamaguchi and co-workers have demonstrated that the iridium complex $[Cp^*IrCl_2]_2$ is again a highly competent catalyst for this heterocyclisation process.[38] Representative examples include the use of benzyl-



Scheme 13. Examples of ruthenium-catalysed N-heterocyclisation reactions.



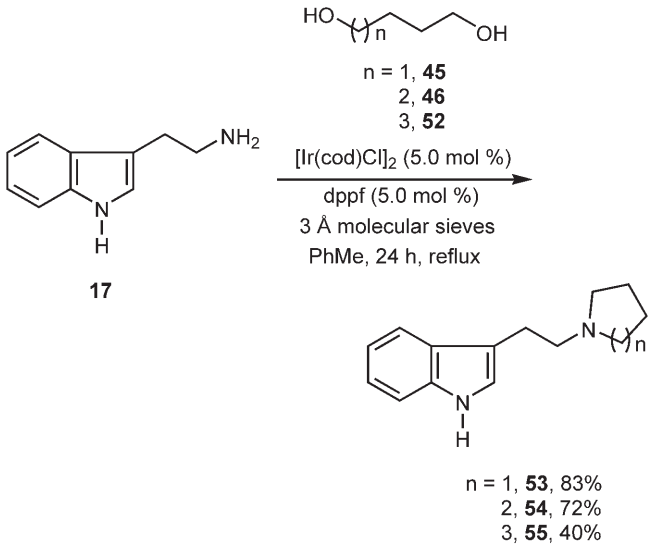
Scheme 14. Use of $[Cp^*IrCl_2]_2$ in the formation of nitrogen heterocycles.

amine **13**, aliphatic amine **43** and aniline **1** as the primary amine substrate (Scheme 14). The reaction was successful for various diols, including compounds **45** and **46**, as well as diol **47** which also provides an interesting route to the morpholine **51**.

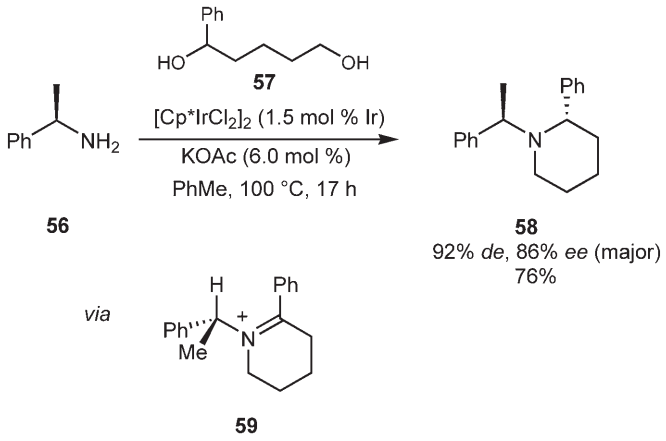
The formation of 5-, 6-, and 7-membered cyclic amines **53**–**55** from tryptamine **17** has been achieved using suitable diols (Scheme 15).[24] It is interesting to note that these reactions to form cyclic tertiary amines are performed under identical conditions to the reactions involving mono-alkylation to give secondary amines described in Scheme 6. Presumably, the intramolecular nature of the subsequent alkylation renders the process more favourable.

Reasonable levels of diastereoselectivity have been achieved in the formation of *N*-heterocycles. As shown in Scheme 16, amine **56** (99% *ee*) was reacted with the racemic diol **57** in the synthesis of the heterocycle **58**.[38] The major diastereomer was formed with 92% *de*, attributed to the selective reduction of the iminium intermediate **59**. There was some loss of enantiomeric excess, with the major diastereomer having 86% *ee*, which it was suggested occurred *via* isomerisation of intermediate **59**.

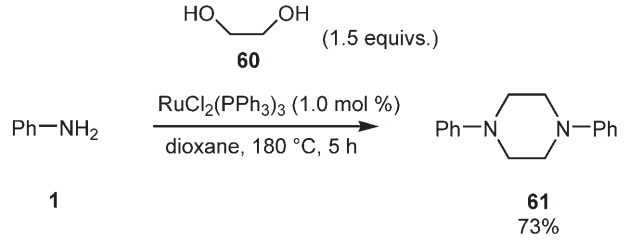
Using ethylene glycol as the diol component, cyclisation has been reported to give symmetrical piperazines such as compound **61** by the combination of two



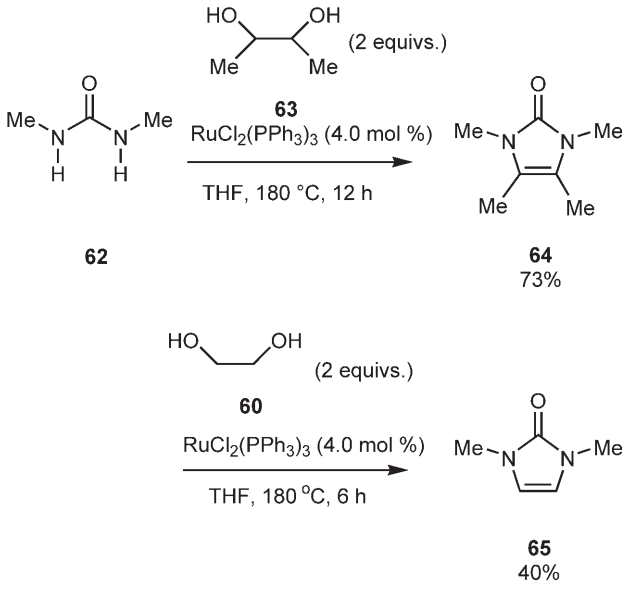
Scheme 15. Formation of cyclic amines from tryptamine.



Scheme 16. Diastereoselective formation of a cyclic amine.



Scheme 17. Formation of symmetrical piperazines.



Scheme 18. Cyclisation of 1,2-diols with a urea.

equivalents of aniline **1** and two of ethylene glycol **60** (Scheme 17). The reaction of diols with secondary amines under similar conditions afforded diamino compounds.[39] The mono-amination of ethylene glycol has been reported by Marsella.[40]

Ureas undergo cyclisation reactions with 1,2-diols with the loss of one equivalent of hydrogen to provide a synthesis of the dihydroimidazolones.[41] For example, the urea **62** could be converted into the cyclised products **64** and **65** by ruthenium-catalysed condensation with diol **63** or **60** (Scheme 18).

4 C–C Bond Formation from Alcohols

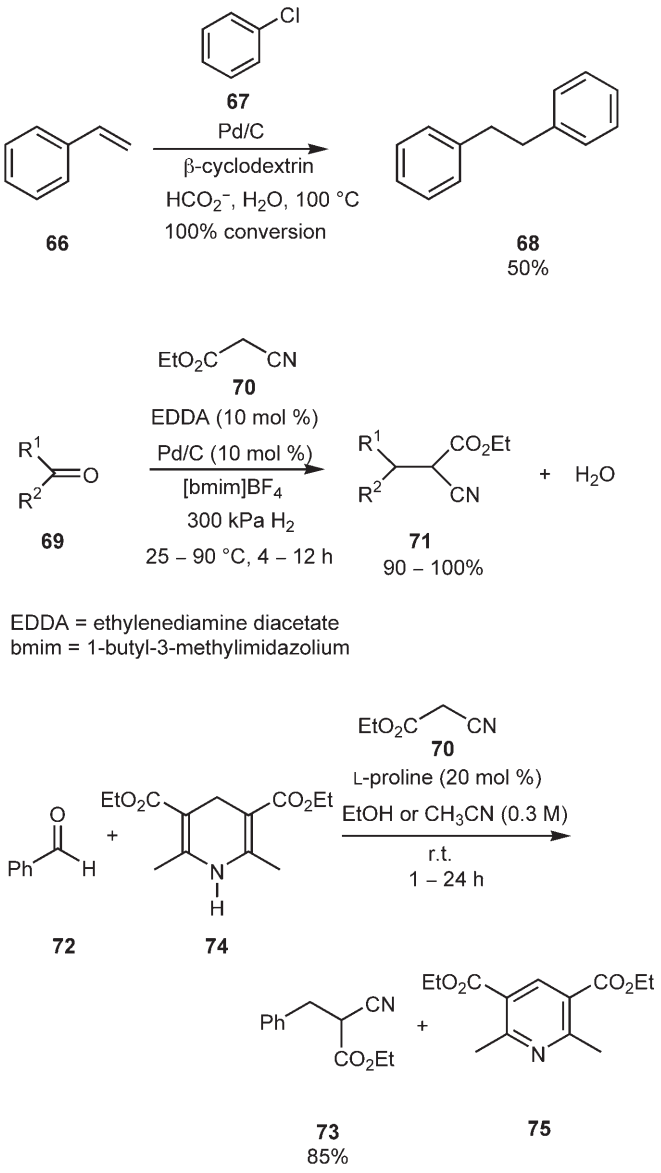
The direct formation of C–C bonds from alcohols is generally disfavoured due to the poor leaving group ability of hydroxide. However, there have been several approaches to the formation of C–C bonds that involve alkene formation followed by *in situ* reduction. A few of these reactions will be considered before returning the borrowing hydrogen approach to C–C bond formation.

For example, Sasson and co-workers have combined a Heck reaction with a hydrogenation process to yield 1,2-diphenylethane **68** starting from styrene **66** and chlorobenzene **67** (Scheme 19).[42] The same authors have more recently reported on the combination of a Knoevenagel condensation reaction with a hydrogenation in an ionic liquid.[43] Motokura and co-workers have described a related one-pot synthesis of α-alkylated nitriles with carbonyl compounds through a consecutive aldol reaction–hydrogenation using hydrotalcite-supported palladium nanoparticles as catalyst. A wide range of nitrile compounds and carbonyl compounds are compatible with this chemistry.[44]

A similar, non-transition metal system has been studied by Ramachary and co-workers. A wide range of activated methylene compounds and aldehydes were reacted together with Hantzsch esters and L-proline to give the reduced aldol product in good to excellent yields. For example, benzaldehyde **72** and ethyl cyanoacetate **70** underwent a condensation/reduction reaction to give the alkylated product **73**.[45]

Breit and Zahn have published an interesting report of a domino hydroformylation/Wittig/hydrogenation reaction.[46] In this chemistry, an alkene **76** undergoes a rhodium-catalysed hydroformylation reaction to give an intermediate aldehyde which, in turn, undergoes a Wittig reaction to form a new alkene. This alkene is then hydrogenated to give the elaborated product **77** (Scheme 20). The same authors subsequently reported a related domino hydroformylation/Knoevenagel//hydrogenation reaction.[57]

Wittig reactions have also been used in a borrowing hydrogen strategy for the synthesis of C–C bonds from alcohols.[48] Edwards and Williams used an iridium catalyst which was believed to remove hydrogen from the alcohol substrate **78** to generate benzaldehyde **72** which underwent an *in situ* Wittig reaction to give the alkene **79**. The iridium catalyst then returns the borrowed hydrogen to give the product **80** where



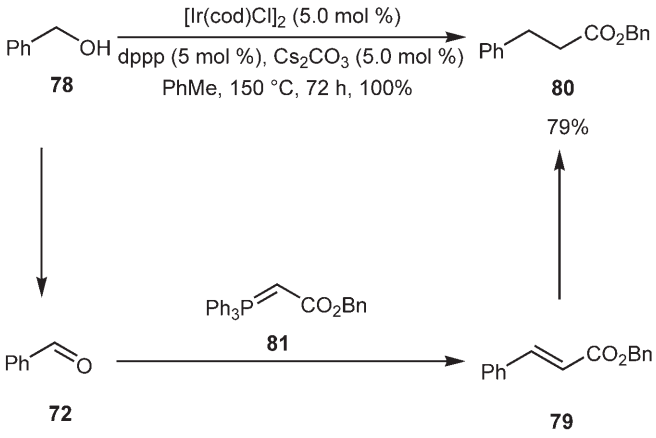
Scheme 19. Examples of reductive alkylation reactions.

a new C–C bond has been generated from the starting alcohol (Scheme 21). The Wittig reagent **81** could also be replaced by a phosphonate ester to give an indirect Horner–Wadsworth–Emmons reaction of alcohols.

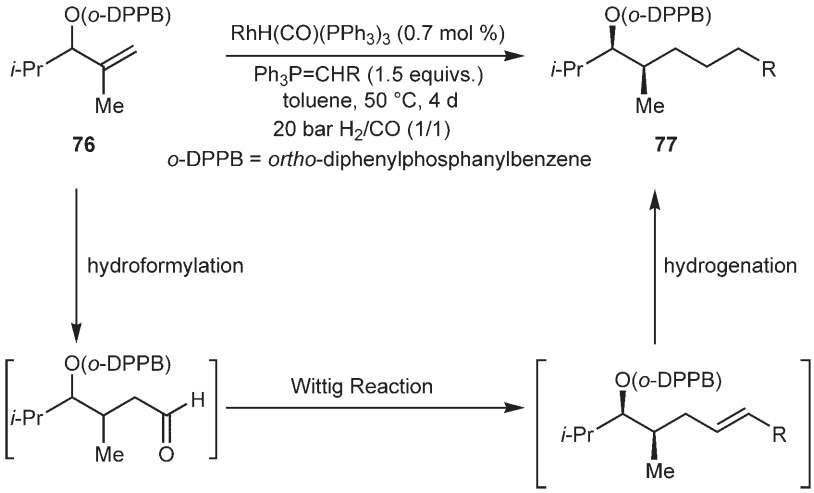
A dramatic improvement to this system was observed when the ruthenium complex **82** was employed as catalyst (Scheme 22).[49] The reaction proceeded smoothly at 80 °C to 100 % conversion in 24 h showing a much higher activity than previously observed.

The α-alkylation of ketones with primary alcohols has been reported by several research groups. The reaction proceeds *via* an oxidation/aldol condensation/reduction pathway, as shown in Scheme 23.

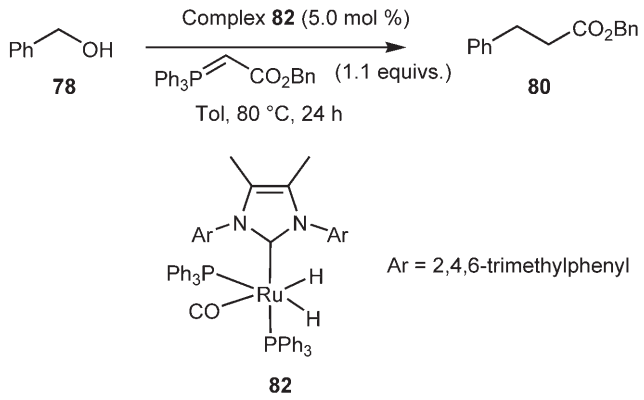
In 2001, Cho, Shim and co-workers used a range of ruthenium complexes to effect this oxidation/aldol condensation/reduction approach.[50] For example, acetophenone **83** was alkylated with various alcohols including benzyl alcohol **78** and butanol **84** to generate products **85** and **86** in good yields (Scheme 24). The same research group later reported that lower catalyst loadings and the use of only one equivalent



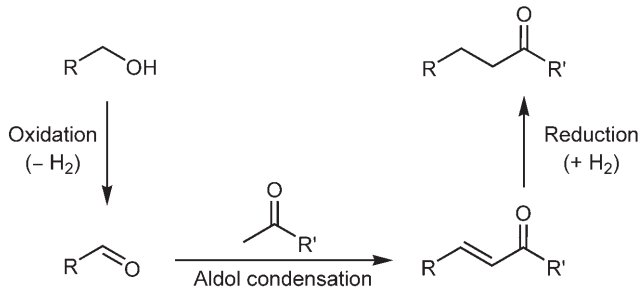
Scheme 21. Indirect Wittig reaction on alcohols.



Scheme 20. A domino hydroformylation/Wittig/hydrogenation reaction.



Scheme 22. An improved catalyst for the indirect Wittig reation on alcohols.



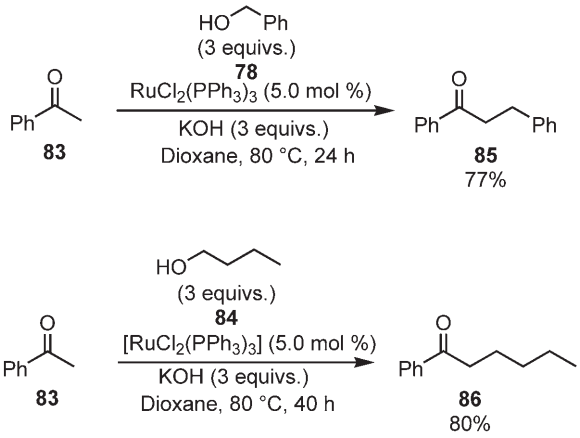
Scheme 23. The α-alkylation of ketones by an oxidation/aldol/reduction sequence.

of alcohol was possible when 1-dodecene was added as a hydrogen acceptor.[51]

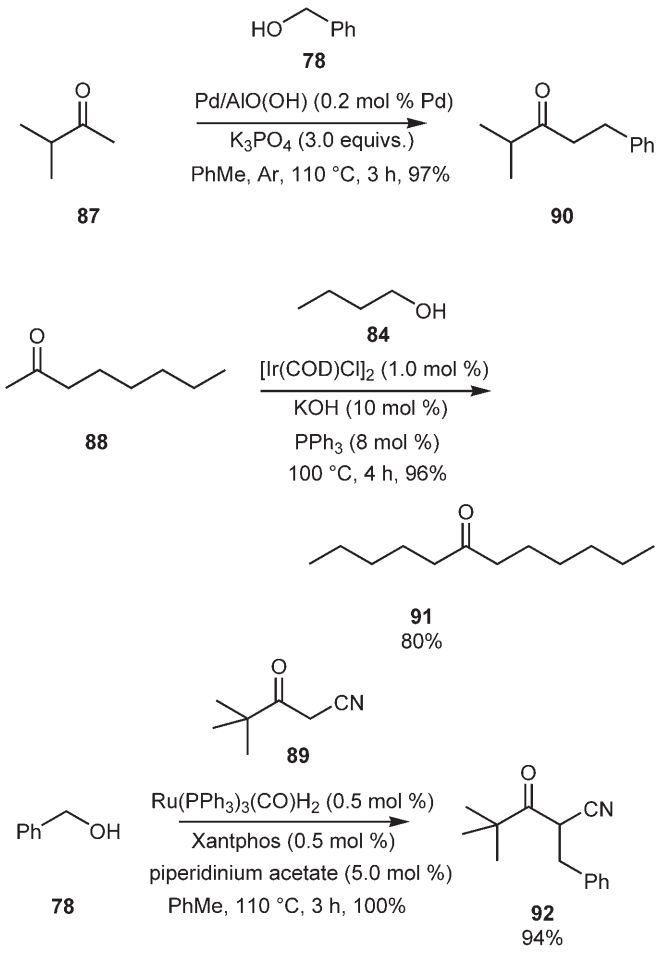
Alternative catalysts for the α-alkylation of ketones with alcohols have been reported, including the use of the phosphine free catalyst $Ru(DMSO)_4Cl_2$ reported by Martinez and co-workers.[52]

Palladium catalysts have been used for the α-alkylation of ketones, with reports of palladium on carbon[53] and of palladium nanoparticles[54] being able to catalyse this reaction. Particularly efficient palladium catalysts for this type of process were developed by Park and co-workers.[55] The authors optimised the conditions for the alkylation of acetophenone with benzyl alcohol through variation of the base, temperature, and solvent using a heterogeneous palladium catalyst, Pd/AlO(OH) that is composed of palladium nanoparticles entrapped in aluminium hydroxide. The choice of K_3PO_4 as the base was important, since stronger bases were found to dissolve the aluminium hydroxide matrix, and no alkylation product was detected with weak bases. Only 0.2 mol% of this catalyst was required to alkylate ketone **87** with benzyl alcohol **78** to give the alkylation product **90** as a single regiosiomer (Scheme 25).

Excellent regioselectivity was also observed by Ishii and co-workers, who used an iridium-based catalyst



Scheme 24. Alkylation of acetophenone with alcohols.



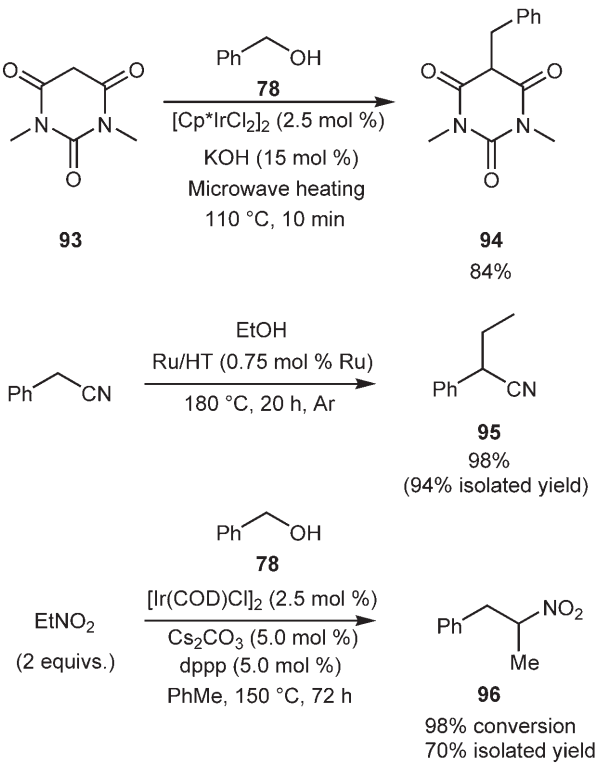
Scheme 25. More examples of the α-alkylation of ketones.

for the α-alkylation of ketones. In one example, ketone **88** was reacted with butanol **84** to give the alkylated ketone product **91** selectively (Scheme 25).[56]

The ketonitrile **89** has been alkylated with alcohols using a ruthenium catalyst to give the product **92** when benzyl alcohol is used as the alkylating agent.[57]

The use of Xantphos as a ligand was important for high reactivity, and allowed the reactions to be run with a catalyst loading of 0.5 mol% and still obtain 100% conversion in 3 h.

The borrowing hydrogen approach to the α-alkylation of ketones has been applied to the α-alkylation of other functional groups. In 1981, Grigg and co-workers reported a ruthenium-catalysed α-alkylation of nitriles by alcohols.[58] More recently they have reported an improved alkylation of nitriles using $[Cp^*IrCl_2]_2$, allowing the mono-alkylation of arylacetonitriles with a wide range of aromatic, heteroaromatic and aliphatic alcohols. Alkylation of bis- and tris-primary alcohols also proceeded efficiently.[59] The same catalyst was also used in the alkylation of the barbituric acid **93**. A range of alcohols, including benzyl alcohol, was used in the alkylation of the barbituric acid, and the reactions could be completed in 10 min under microwave irradiation to give the alkylated product **94**.[59] In 2004 Kaneda and co-workers reported the α-alkylation of nitriles with primary alcohols using a ruthenium grafted hydrotalcite catalyst. The reaction proceeded *via* ruthenium-catalysed oxidation of the alcohol, followed by condensation catalysed by basic sites of the hydrotalcite. Several aromatic nitriles and aliphatic alcohols were combined to give the alkylated products, such as nitrile **95**, in excellent yields (Scheme 26).[60]



Scheme 26. α-Alkylation of other functional groups.

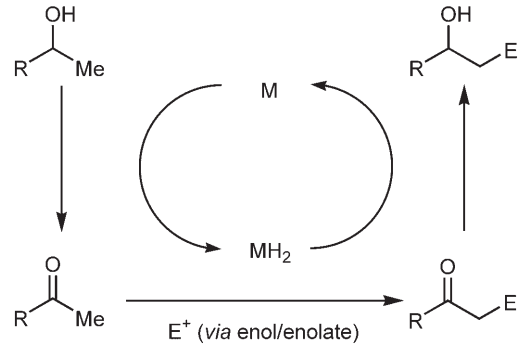
Williams et al. have also reported[61] on some indirect condensation reactions with activated methylene compounds. The indirect nitro-aldol reaction (Henry reaction) has been studied using both iridium and ruthenium catalyst systems, to give alkylation of simple nitroalkanes leading to products including compound **96**. The iridium system depended heavily on the base (Cs_2CO_3) used to activate $[Ir(COD)Cl]_2$ to the active catalyst, as well as choice of ligand (dppp or dppf) and required high temperatures (150 °C) and long reaction times (72 h).

5 β-Functionalisation of Alcohols

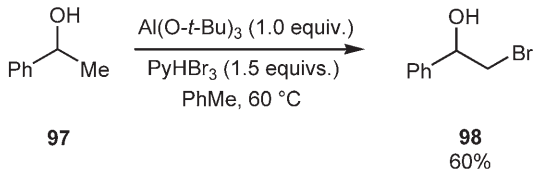
When an alcohol is oxidised to the corresponding aldehyde or ketone, this enables nucleophilic addition to take place more rapidly, and this formed the basis of imine formation and alkene formation prior to reduction to give the C–N and C–C bonds outlined in the earlier sections. However, temporary oxidation of an alcohol to a carbonyl compound also provides an opportunity to access enol/enolate chemistry.

Scheme 27 represents the possibility for the β-functionalisation of alcohols by temporarily borrowing hydrogen from the alcohol. Addition of an electrophile to the enol or enolate prior to reduction back to the alcohol allows the overall process to proceed.

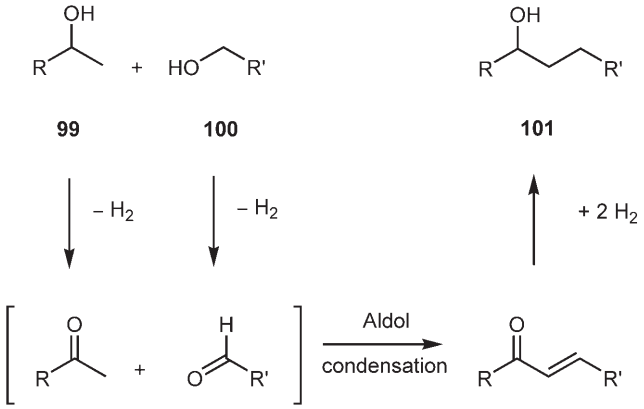
This strategy has been applied to the bromination of alcohols, including 1-phenylethanol **97**.[62] In the presence of an aluminium alkoxide, bromination with pyridinium tribromide occurred to provide the brominated product **98** (Scheme 28). The reaction condi-



Scheme 27. Borrowing hydrogen in the β-functionalisation of alcohols.



Scheme 28. Bromination of alcohols *via* temporary oxidation.



Scheme 29. C-C Bond formation between two alcohols.

tions also led to some irreversible oxidation promoted by direct interaction of the alcohol with the brominating agent.

The activation of two alcohols by borrowing hydrogen can lead to an interesting coupling process. Typically, a secondary (or primary) alcohol **99** and a primary alcohol **100** react with formation of a new C–C bond to generate the product **101**. Mechanistically, such reactions are believed to involve oxidation of both alcohols to form a ketone and an aldehyde, which undergo an aldol condensation giving an α,β-unsaturated ketone, which is reduced to give the saturated alcohol **101** (Scheme 29).

The reaction between *n*-propanol **102** and methanol **103** has been achieved with a variety of transition metal catalysts, generating isobutyl alcohol **104** as the main product (Scheme 30).[63] Isobutyl alcohol is of interest as a precursor to gasoline additives.

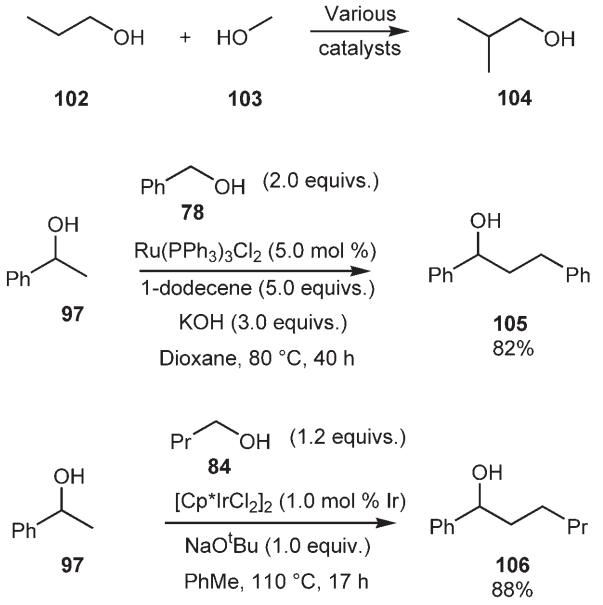
Following their original report in 2001 Cho et al. designed a one-pot β-alkylation of secondary alcohols with primary alcohols.[64] 1-Dodecene was added as a sacrificial hydrogen acceptor, allowing 1-phenylethanol **97** to be alkylated by benzyl alcohol **78** in good overall yield.

Yamaguchi has reported the β-alkylation of secondary alcohols with primary alcohols using $[Cp^*IrCl_2]_2$ (0.5 mol%) as catalyst.[65] For example, alcohol **97** could be alkylated with primary alcohols such as butanol **84** with this catalyst.

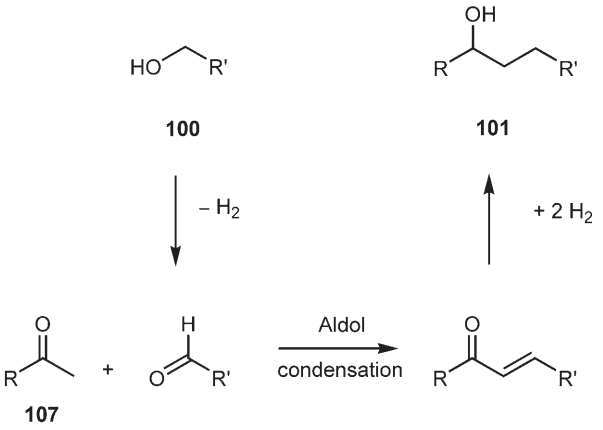
The α-alkylation of ketones has also been combined with a reduction process, as outlined in Scheme 31. The reaction pathway is broadly similar to that outlined in Scheme 29, with the exception that the ketone **107** is already present. This means that additional hydrogen is then required to reduce the intermediate α,β-unsaturated ketone all the way down to the saturated alcohol **101**. The hydrogen can originate from the presence of additional alcohol or some other hydrogen source.

This strategy was employed in 2001 by Cho and coworkers when they reported the observation of unexpected C–C bond formation during a ruthenium-catalysed transfer hydrogenation of ketones with alcohols. Upon further investigation they determined that under optimum conditions this C–C bond formation could proceed as the major pathway.[49] Thus acetophenone **83** was converted into alcohol **106**. A related strategy was used by Yus and co-workers in the conversion of acetophenone **83** into alcohol **105**. This group has used $RuCl_2(DMSO)_4$ very effectively in a range of alkylation reactions involving alcohols.[52]

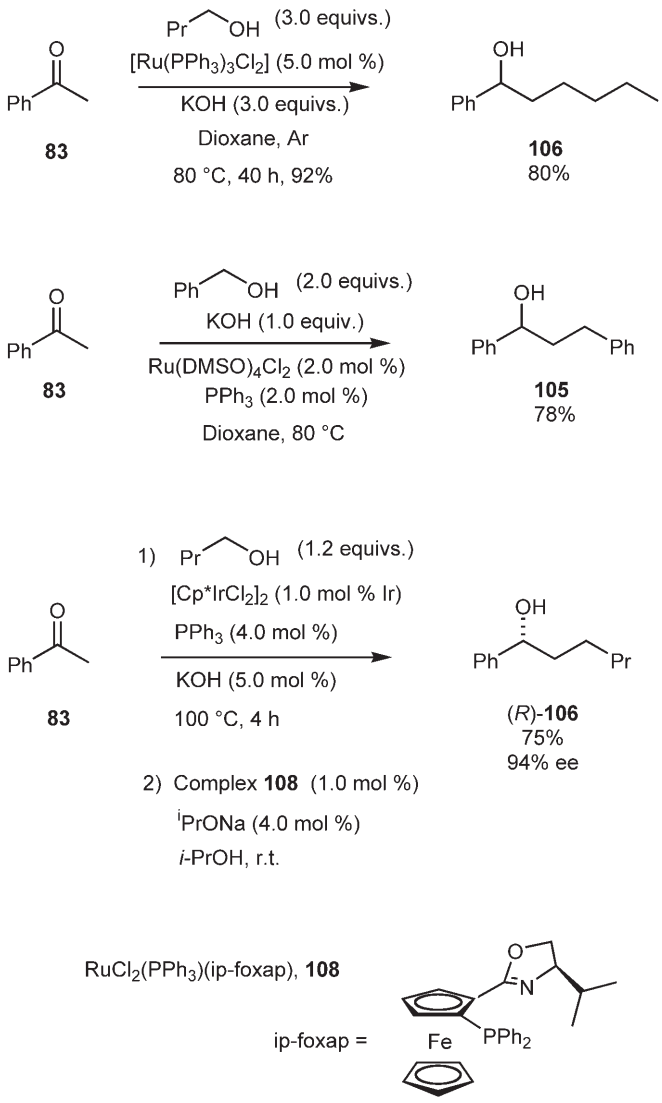
Nishibayashi et al. have reported the first enantioselective version of this reaction.[66] In a one-pot procedure a ketone and a primary alcohol are reacted under $[Cp^*IrCl_2]_2$ conditions at 110 °C for 4 h, followed by cooling to room temperature, addition of a ruthenium catalyst, *i*-PrONa, and *i*-PrOH for 2 h (Scheme 32).[66]



Scheme 30. Alkylation of alcohols with another alcohol.



Scheme 31. Alkylation and reduction of ketones.



Scheme 32. Alkylation of ketones with alcohols followed by reduction.

6 Formation of Aromatic N-Heterocycles

There are several reported reactions which combine C–C and C–N bond formation using a borrowing hydrogen strategy. These reactions have been of particular importance in the formation of aromatic nitrogen-containing heterocycles.

Amine scrambling has been used effectively in the synthesis of indoles[67] and quinolines[69] from anilines. The reaction pathway is initiated by a transfer of the hydroxyalkyl group on to the aniline providing the intermediate alcohols **109** and **110**, which then undergo oxidative cyclisation, possibly *via* the amine or imine, leading ultimately to the indole **111** and quinoline **112** (Scheme 33).

Diols have been used in the ruthenium-catalysed conversion of 2-aminopyridines into imidazopyridines and of *o*-phenylenediamines into quinoxalines.[69]

An interesting extension of this work which incorporates a cyclisation step has been reported by several people. In 2001, Cho reported that quinolines could be formed by the oxidative cyclisation of 2-aminobenzyl alcohol with ketones under ruthenium catalysis.[70] After further research the same group reported that the same transformation could be obtained when employing secondary alcohols in place of ketones, with 1-dodecene added as a sacrificial hydrogen acceptor (Scheme 34).[71] A later communication reported that aldehydes could be used in such reactions to give 3-substituted quinolines.[72]

Similarly, Kaneda et al. have reported that substituted quinolines **114** can be formed from 2-aminobenzyl alcohol **113** using a ruthenium-grafted hydrotalcite catalyst under an oxygen atmosphere (Scheme 35). Ketones, aldehydes, and nitriles can all be used as substrates in the reaction and give good yields of quinolines.[73]

The synthesis of quinolines by the coupling of 2-aminobenzyl alcohol and acetophenone has been reported by Ishii and co-workers.[74] In the model reaction between 2-aminobenzyl alcohol and acetophenone, quinoline **114** was obtained in 90% yield in 3 h using an iridium-based catalyst without solvent. An interesting addition to this paper was the use of aliphatic amino alcohols to form pyrroles. When *N*-methyl-2-aminoethanol **115** was reacted with **116** in the presence of an iridium catalyst and base under solvent-free conditions pyrrole **117** was formed in 70% yield (Scheme 36).

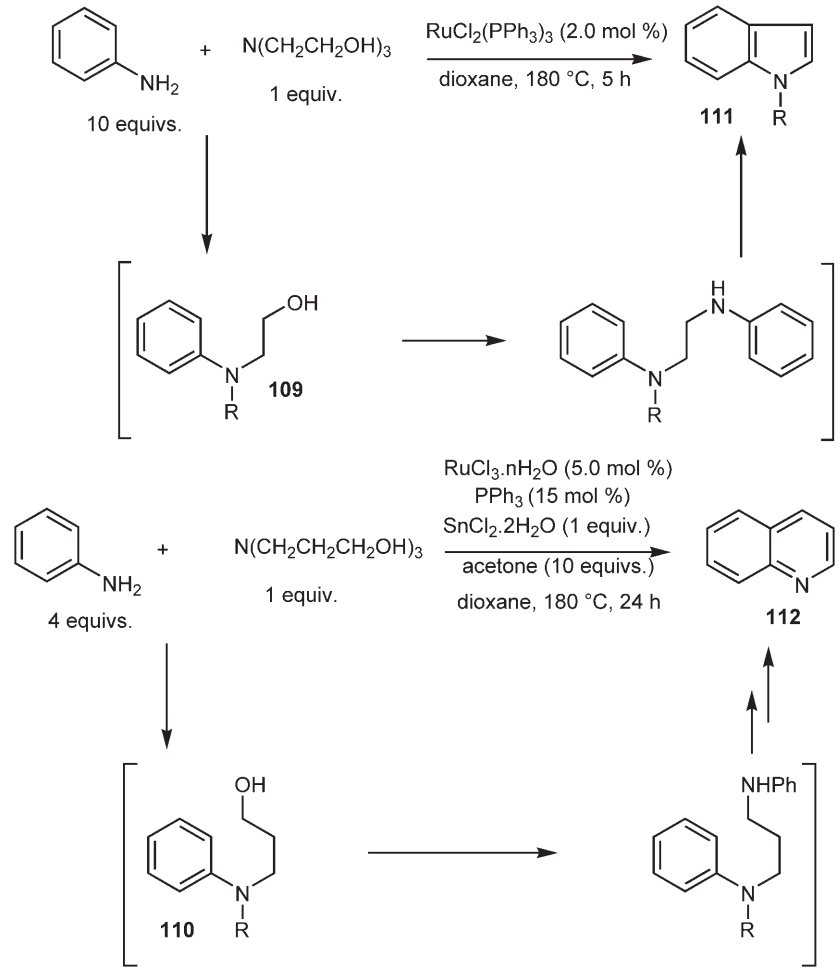
Yus and co-workers have also used their standard conditions employing $[Ru(DMSO)_4]Cl_2$ as catalyst to form quinolines. Good to excellent yields (67–96%) from 2-aminobenzyl alcohol and a range of ketones have been achieved using only 2 mol% catalyst.[52]

7 Other Reactions Involving Temporary Oxidation

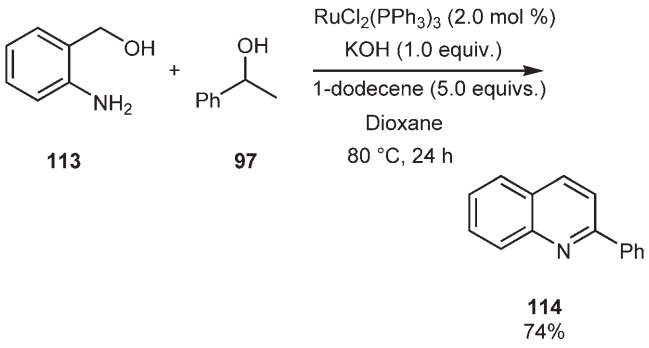
7.1 Electronic Activation of Alkenes

The chemistry of alkenes is strongly linked to the nature of adjacent functional groups. A typical alkene is electron-rich and prefers to undergo reaction with electrophiles, as seen in the addition of H-Hal and halides across alkenes. However, alkenes become susceptible to reaction with nucleophiles when the alkene is conjugated to an electron-withdrawing group. For example, conjugate addition reactions and Diels–Alder reactions are usually more favoured for electron-deficient alkenes (Scheme 37).

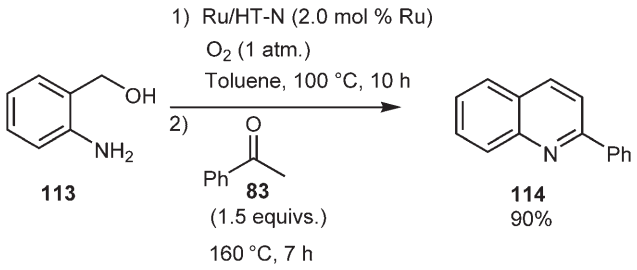
The interconversion of allylic alcohols with α,β-unsaturated carbonyl compounds can be achieved by transfer hydrogenation, temporarily altering the elec-



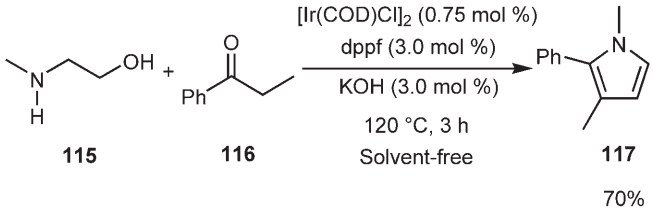
Scheme 33. Synthesis of indoles and quinolines by initial amine exchange.



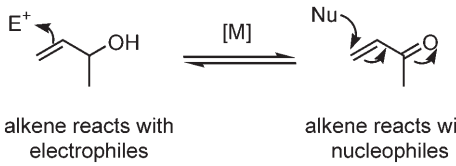
Scheme 34. Quinoline synthesis from alcohols.



Scheme 35. Quinoline synthesis from nitriles.

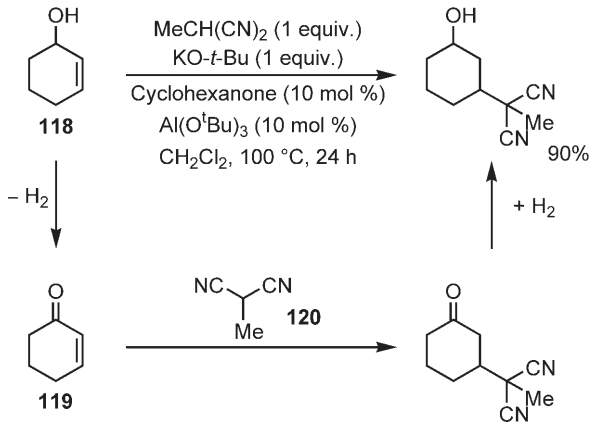


Scheme 36. Pyrrole synthesis by borrowing hydrogen.



Scheme 37. The reactivity of different classes of alkene.

tronic nature of the alkene. In principle, this approach could be exploited for electron-deficient alkenes to undergo reactions with electrophiles,[75] but to date, only the activation of allylic alcohols has been reported.[76] Cyclohexenol **118** is inert to reaction with nu-

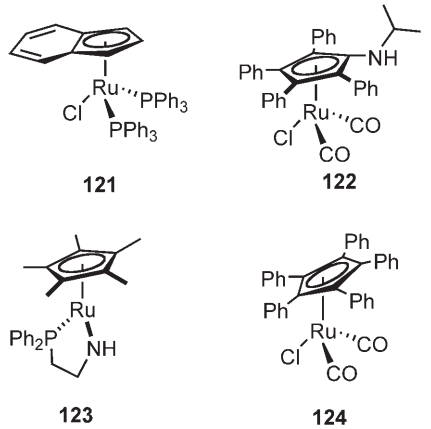


Scheme 38. Indirect conjugate addition of a nucleophile to an allylic alcohol.

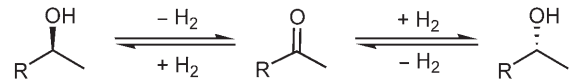
cleophiles, whereas cyclohexenone **119** readily undergoes conjugate addition with suitable nucleophiles such as the anion derived from methylmalononitrile **120** (Scheme 38).[77]

7.2 Racemisation and Dynamic Kinetic Resolution

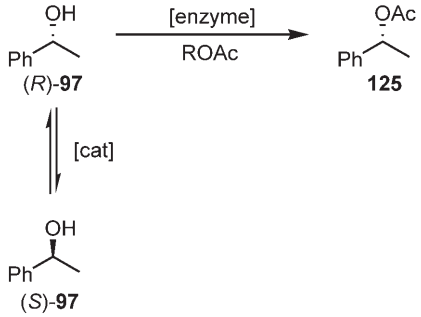
The racemisation of secondary alcohols has been achieved by reversible oxidation to the corresponding ketone. The oxidation of a simple enantiomerically pure secondary alcohol leads to an achiral ketone. Reduction of the ketone back to the alcohol then occurs to give a racemic product. Since racemisation reactions are usually thermodynamically favoured, transfer hydrogenation catalysts are expected to be able to racemise secondary alcohols, and this has been reported by several research groups, with ruthenium complexes **121**,[78] **122**,[79] **123**[80] and **124**[81] being especially successful (Scheme 39). The latter complex is able to racemise enantiomerically pure phenethyl



Scheme 39. Some ruthenium complexes for racemisation.



Scheme 40. Racemisation of alcohols by temporary oxidation.



Scheme 41. Dynamic kinetic resolution of alcohols.

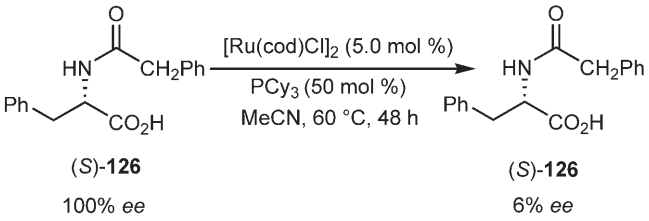
alcohol within 10 min at room temperature at just 0.5 mol % catalyst loading (Scheme 40).

Pàmies and Bäckvall have analysed the level of deuterium incorporation during the racemisation process for a range of catalysts, including rhodium, ruthenium and iridium complexes, as well as samarium and aluminium complexes. Distinct mechanistic pathways were suggested to explain the differences in the observed deuterium incorporation observed once racemisation was complete.[82]

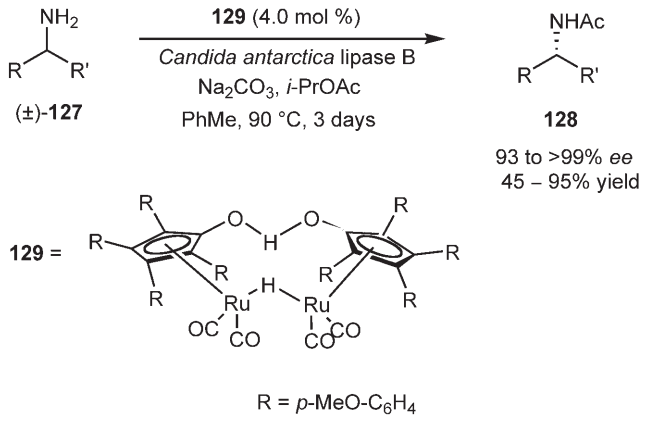
The combination of a transition metal complex to achieve racemisation of an alcohol coupled with an enzymatic resolution process to achieve a dynamic resolution reaction has been investigated by several groups and reviewed.[83] The basic principle uses the reversible removal of hydrogen to maintain a racemic mixture of alcohol, whilst the enzyme enantioselectively acylates one enantiomer of the alcohol.[84] Thus, racemic alcohol **97** can be converted into enantiomerically enriched ester **125** in high enantiomeric excess and high yield under optimised conditions (Scheme 41).[85]

In addition, the racemisation of amines has been achieved by reversible oxidation into an imine. In one example, Beller and co-workers have used rhodium catalysts to racemise *N*-acyl α-amino acids, as shown in Scheme 42 for the racemisation of compound **126**.[86] It was suggested that the racemisation pathway involved dehydrogenation to the imine followed by non-selective hydrogenation.

The racemisation of amines has also been developed into a dynamic kinetic resolution reaction when coupled with an enzyme-catalysed acylation reaction.[87] For example, racemic amines **127** could be enantioselectively acylated with *Candida antarctica* lipase B (CAL-B), with the unwanted enantiomer of



Scheme 42. Racemisation of an *N*-acyl α-amino acid.

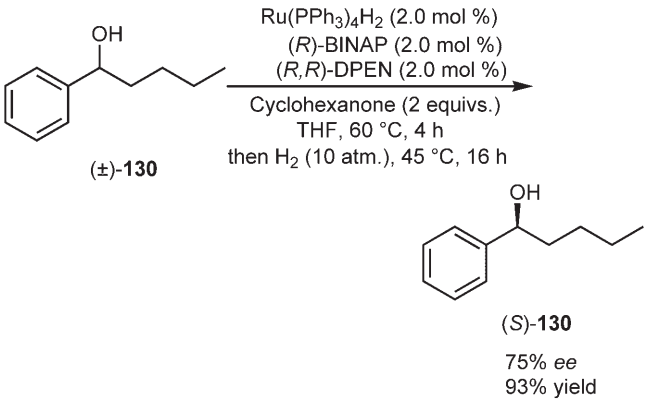


Scheme 43. Dynamic kinetic resolution of amines

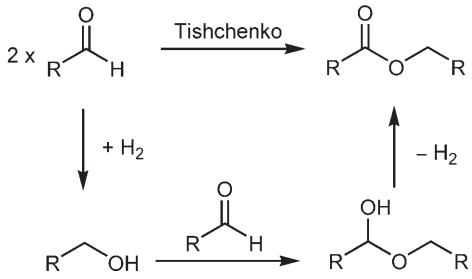
the amine being racemised *in situ* with the catalyst (Scheme 43).[88]

7.3 Deracemisation

Racemisation reactions are thermodynamically favoured for simple non-aggregated molecules, because of the increase in entropy. Therefore, a general deracemisation of racemic secondary alcohols is difficult to achieve unless coupled with a second process, such as the dynamic kinetic resolution reactions discussed in the earlier section.



Scheme 44. Deracemisation of a secondary alcohol by hydrogen loss/hydrogen addition.



Scheme 45. The Tishchenko reaction of aldehydes.

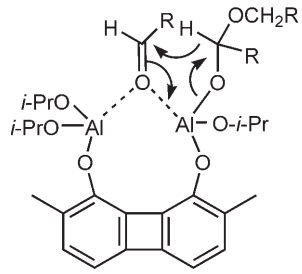
Adair and Williams have reported a two-stage dehydrogenation/rehydrogenation process which provides a strategy to overcome this problem.[89] Racemic alcohol **130** underwent oxidation by transfer hydrogenation with cyclohexanone using a ruthenium hydride complex with (*R*)-BINAP and (*R,R*)-DPEN (1,2-diphenylethylenediamine) ligands, based on the Noyori hydrogenation catalyst. Once oxidation was complete, the alcohol was regenerated by the enantioselective addition of hydrogen, as shown in Scheme 44.

Nishibayashi and co-workers have reported an alternative approach to the deracemisation of secondary alcohols using two different ruthenium complexes. One catalyses the oxidation step and the other the reduction step.[90]

7.4 Tishchenko Reaction

The Tishchenko reaction is related to the Cannizzaro reaction, and involves the dimerisation of an aldehyde to give an ester. In general terms the reaction can be considered to be a reduction of an aldehyde to give an alcohol (or alkoxide) which then combines with another aldehyde to give a hemi-acetal, which in turn undergoes oxidation to the ester. The overall process is redox neutral (Scheme 45). Aluminium and lanthanide complexes catalyse the reaction by hydrogen transfer from the metal alkoxide to the co-ordinated carbonyl compound, whereas late transition metal complexes usually proceed *via* the metal hydride or metal dihydride.[4] Bosnich has suggested that some cationic rhodium catalysts catalyse a different mechanism involving oxidative addition into the C–H bond of the aldehyde.[91] An osmium complex has also been reported to have a mechanistic pathway involving C–H insertion.[92]

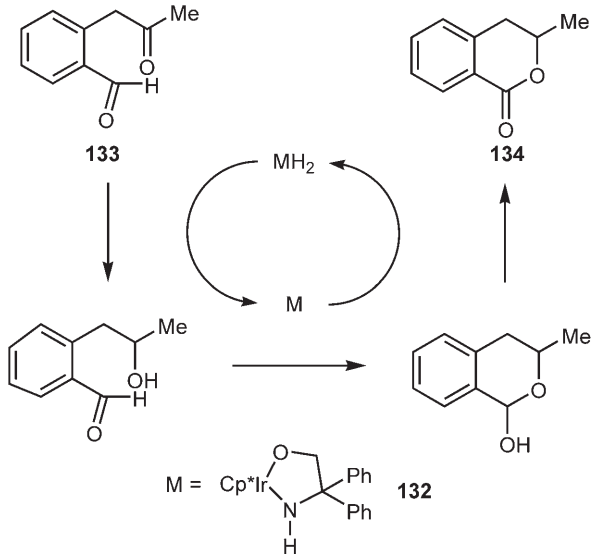
Many metal complexes have been reported to catalyse the Tishchenko reaction,[93] along with various solid phase catalysts.[94] The bidentate aluminium complex **131** (Scheme 46) is a particularly efficient room temperature catalyst for the Tishchenko reaction.[95] The high reactivity is attributed to the double activation of the aldehyde by the two Lewis acid groups, although some other aluminium complexes



Scheme 46. Bidentate catalysis in the Tishchenko reaction.

which do not appear to act as bidentate catalysts can also give rapid reaction.[96]

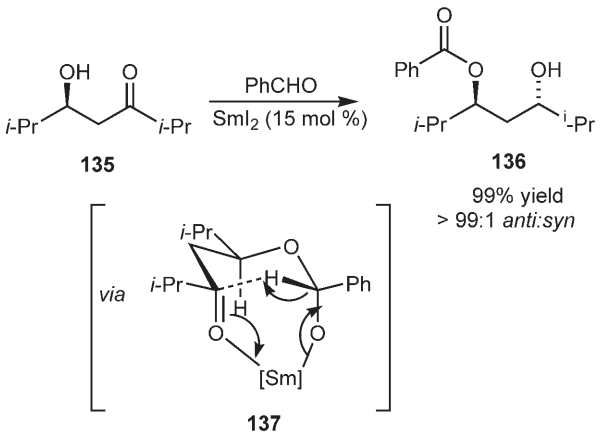
The iridium catalyst **132** is also an efficient room temperature catalyst for the Tishchenko reaction.[97] The same iridium complex has also been used for an intramolecular Tishchenko reaction of ketoaldehyde **133**. The reaction is believed to proceed *via* a borrowing hydrogen route as shown in Scheme 47.



Scheme 47. Iridium-catalysed intramolecular Tishchenko reaction.

Evans and Hoveyda have demonstrated that the intramolecular Tishchenko reaction of β-hydroxy ketones occurs with excellent diastereocontrol.[98] For example, the reduction of ketone **135** proceeded with essentially complete stereocontrol to give the mono-protected diol **136**. The selectivity was attributed to the chelation by the catalyst and the intramolecular hydrogen transfer (Scheme 48).

The first example of a catalytic asymmetric aldol-Tishchenko reaction was reported by Morken using a metal alkoxide $[Y_5O(O\text{-}i\text{-}Pr)_{13}]$ coupled with a salen



Scheme 48. Diastereoselective Tishchenko reaction of a β-hydroxy ketone.

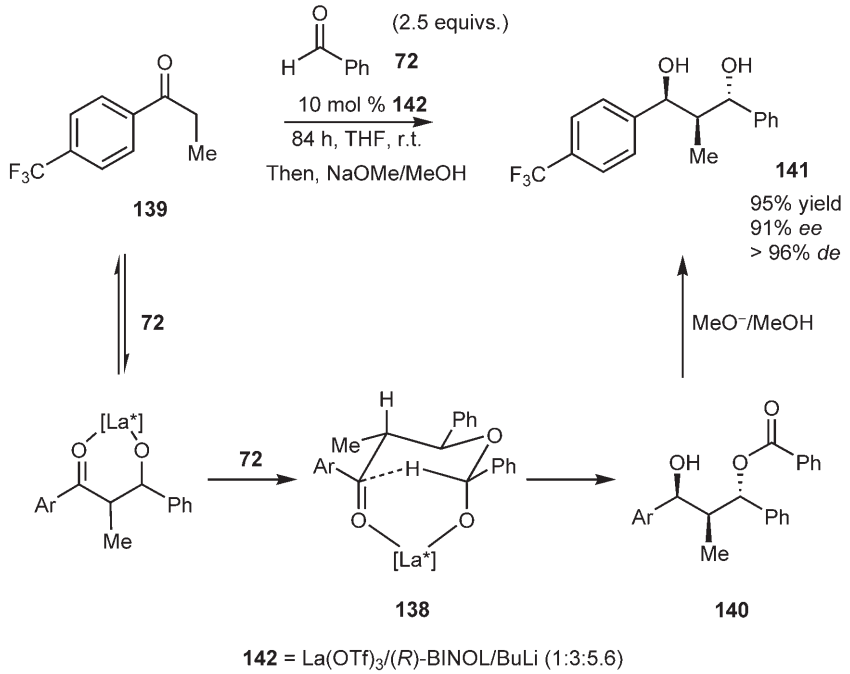
ligand.[99] Moderately good yields and enantiomeric excesses were obtained and mechanistic investigations enabled a predictive model for enantioselection in the aldol-Tishchenko reaction to be proposed. These ideas were developed by Shibasaki and co-workers who used a single catalyst for an asymmetric aldol-Tishchenko reaction sequence.[100] The lanthanum catalyst firstly effects the aldol condensation of ketone **139** with benzaldehyde **72** to give an intermediate aldolate with little selectivity. One of the aldolate stereoisomers selectively undergoes a Tishchenko reaction to give the mono-ester **140**, which is isolated as the diol **141** in excellent selectivity and yield (Scheme 49).

Other tandem reactions involving a Tishchenko reaction have also been reported,[101] including a tandem semipinacol rearrangement/Tishchenko reaction of α-hydroxy aldehydes catalysed by samarium(II) iodide.[102]

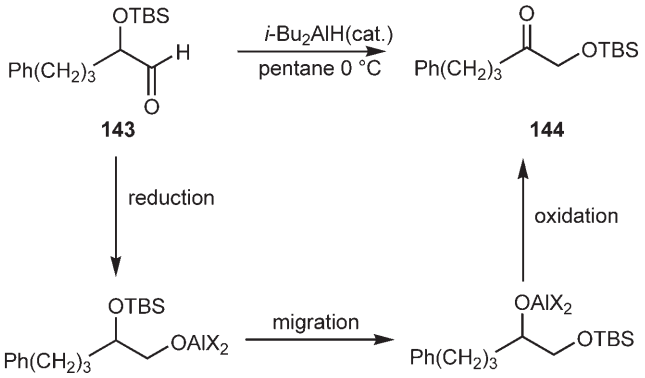
An interesting rearrangement of α-silyloxy aldehyde **143** into the corresponding α-silyloxy ketone **144** catalysed by di-isobutylaluminium hydride (DIBAL) has been reported by Hon and co-workers.[103] The reaction probably proceeds *via* an initial reduction of the aldhyde, silyl migration and then re-oxidation (Scheme 50). DIBAL was also shown to catalyse conventional Tishchenko reactions.

In a process closely related to the Tishchenko reaction, Fang and co-workers have used a combination of samarium iodide and a thiol as the catalyst.[104] The role of the thiol is to add to one of the carbonyl groups facilitating hydride transfer, as indicated in Scheme 51. A range of δ-lactones was prepared in good yields and with good diastereocontrol in some examples.

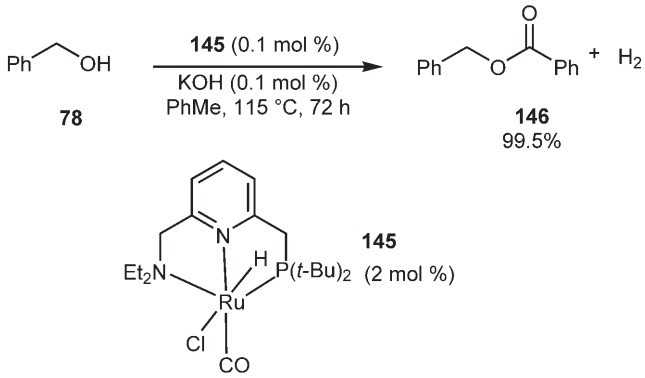
In some cases, alcohols are converted into esters without the addition of an oxidant. The reactions are believed to proceed by the loss of dihydrogen, which in these cases is not returned to the reaction prod-



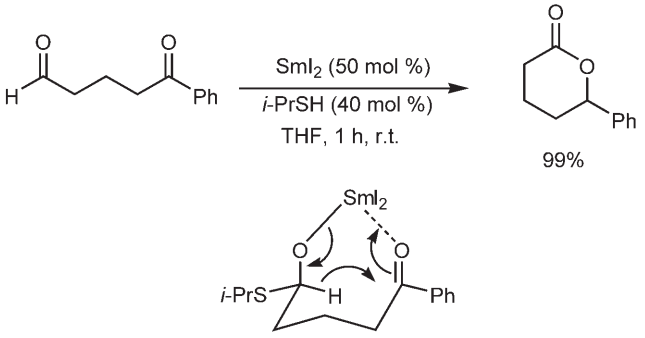
Scheme 49. Aldol Tishchenko reaction.



Scheme 50. DIBAL catalysed rearrangement of an α-silyloxy-aldehyde.



Scheme 52. Acceptorless oxidation of alcohol into ester.



Scheme 51. Lactonisation with a samarium iodide/thiol combination.

uct.[105] A recent example by Milstein and co-workers used the ruthenium complex **145** to achieve the oxidation of benzyl alcohol **78** into benzyl benzoate **146** (Scheme 52).[106]

8 Conclusion

The 'borrowing hydrogen' strategy has been exploited in the synthesis of C–C and C–N bonds from alcohols, allowing alcohols to be employed as benign alkylating agents. Reactions proceed by oxidation of the alcohol to an intermediate carbonyl compound, which can form alkenes or imines *in situ* before reduction occurs. Temporary oxidation of an alcohol into a car-

bonyl compound also allows access to enol/enolate chemistry before restoration of the alcohol moiety.[107]

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