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Ruthenium-catalysed synthesis of tertiary amines from alcohols

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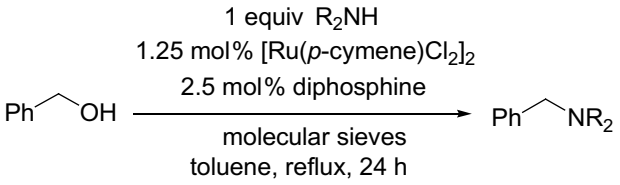
Abstract—Secondary amines have been converted into tertiary amines by reactions with primary alcohols. A catalytic system of $[Ru(cymene)Cl_2]_2$ with dppf has been shown to be effective for this transformation for a range of primary alcohols and secondary amines. The methodology has been applied to the one pot synthesis of Piribedil and other piperazine and morpholine-containing products.

The alkylation of amines is a widely used process, typically involving the reaction of an amine with a conventional electrophilic alkylating agent such as an alkyl halide.[1] However, such alkylation reactions can lead to multiple alkylations, including the formation of quaternary ammonium salts. Several transition metal complexes have been identified that allow amines to be alkylated by alcohols using an oxidation/imine formation/reduction sequence. Early examples included the use of $RhH(PPh_3)_4$ and $RuCl_2(PPh_3)_3$.[2,3] More recent examples include the iridium complexes $[Cp^*IrCl_2]_2$ and $[IrCl(cod)]_2$/dppp[4,5] along with alternative Ru complexes.[6,7] Many of these catalysts require forcing conditions or high catalyst loadings. We have found that the combination of $[Ru(p\text{-cymene})Cl_2]_2$ with bidentate phosphines is a convenient and effective catalyst for the alkylation of primary amines to secondary amines.[8] Herein, we report the development of this process into a synthesis of tertiary amines from secondary amines and primary alcohols.

Benzyl alcohol was chosen as a model starting material and was reacted with a range of secondary amines using 1.25 mol% $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol% of Ru) with either dppf, 1,1′-bis(diphenylphosphinoferrocene) or DPEphos, bis(2-diphenylphosphinophenyl)ether as the diphosphine ligand (Scheme 1). The products were isolated and purified by column chromatography in good yields (Table 1). The reactions were successful for the alkylation of both cyclic (entries 1–4) and acyclic (entries 5–6) amines.



Scheme 1. Amination of benzyl alcohol with secondary amines.

Having shown that several amines could be successfully used in the amination of benzyl alcohol, we wished to explore the range of alcohols that could be used. We chose to examine the alkylation of morpholine with a range of alcohols (Scheme 2, Table 2). We were pleased to find that benzylic alcohols (entries 1–5) were all cleanly alkylated under these conditions. All of these reactions, including the formation of *ortho*-substituted benzylamine (entry 2) proceeded essentially to completion, the variation in yield simply being a consequence of the relative ease of isolation. The aliphatic amines (entries 7 and 8) were also formed with 100% conversion, although the branched product (entry 6) only proceeded to 75% conversion under these reaction conditions, leading to a lower isolated yield.

There are many target molecules of pharmaceutical interest that contain tertiary amines,[9] and we chose to apply this chemistry to the synthesis of Piribedil (Scheme 3). Piribedil is a piperazine dopamine agonist used in the treatment of Parkinson's disease,[10] and is

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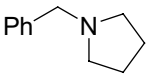
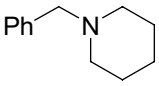
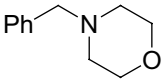
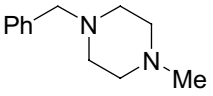
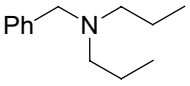
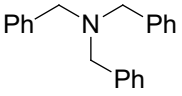
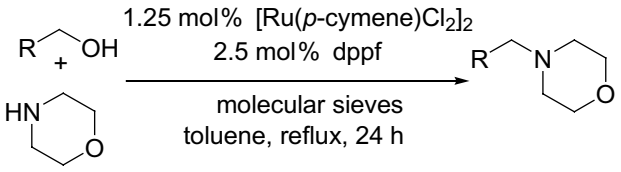
Table 1. Benzylation of secondary amines

Entry	Product	Isolated yield[a] (%)
1		71
2		72
3		84
4		97[b]
5		87
6		73[b]

[a] Reactions were performed using 1 mmol of amine and 1 mmol of benzyl alcohol using dppf as the ligand.
[b] Reactions run using DPEphos. The values given are conversions.



Scheme 2. Alkylation of morpholine with alcohols.

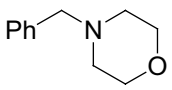
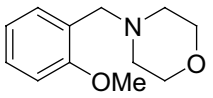
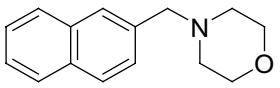
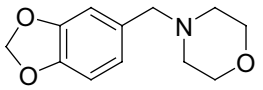
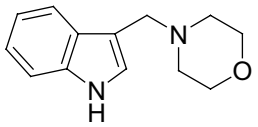
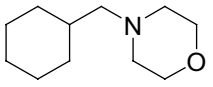
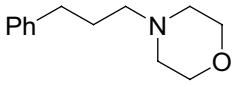
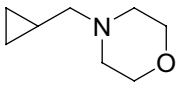
one example of a larger class of pharmaceutically important *N*-arylpiperazines.[11,12]

Under the standard amination conditions, commercially available 1-(2-pyrimidyl)piperazine and piperonyl alcohol underwent clean conversion to provide Piribedil in good isolated yield in a single synthetic operation.

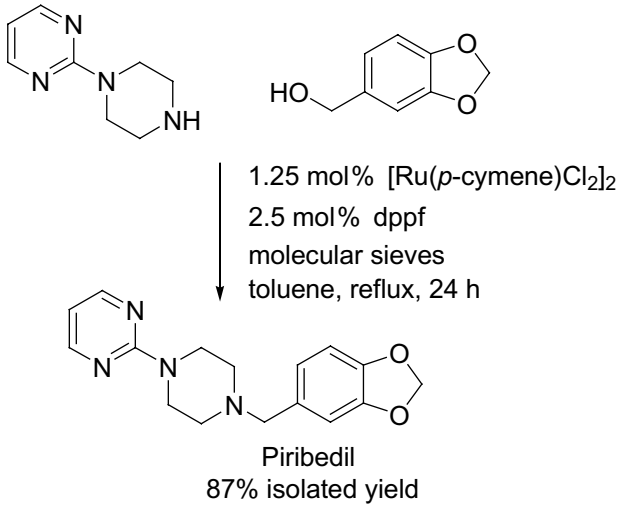
Given the common occurrence of the dimethylamino group in pharmaceutical compounds, we also wished to examine the viability of converting benzyl alcohol into *N,N*-dimethylbenzylamine. Because of the volatility of dimethylamine (bp 7 °C), we successfully used dimethylammonium acetate for this transformation (Scheme 4). The use of ammonium acetate led to the formation of tribenzylamine in acceptable isolated yield.

Whilst we have not performed any detailed mechanistic experiments, we assume that the reactions proceed by the borrowing hydrogen pathway suggested for C–C and C–N bond formation from alcohols.[13,14] Temporary removal of hydrogen from the alcohol affords an aldehyde, which undergoes reaction with the amine to give an intermediate iminium species, which is converted into the tertiary amine by the return of the hydrogen

Table 2. Formation of *N*-substituted morpholines

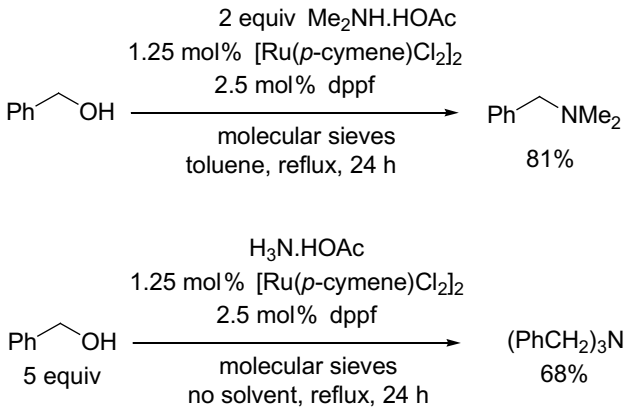
Entry	Product	Isolated yield[a] (%)
1		84
2		74
3		78
4		89
5		85
6		62
7		77
8		85

[a] Reactions were performed using 1 mmol of amine and 1 mmol of benzyl alcohol using dppf as the ligand.

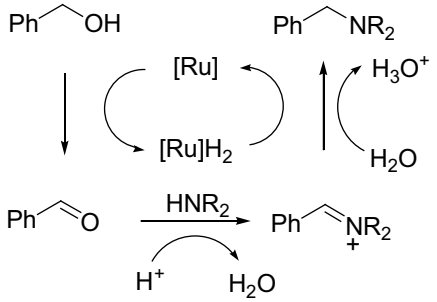


Scheme 3. Synthesis of Piribedil.

(Scheme 5). It is possible that the enamine is also involved as an intermediate. However, in some cases (e.g., R = Me or Bn), it is not possible to form an enamine. Further studies into the nature of the ruthenium catalyst are currently underway.



Scheme 4. Alkylation of ammonium acetates.



Scheme 5. Presumed mechanism of tertiary amine formation.

In summary, we have shown that the combination of $[Ru(p\text{-cymene})Cl_2]_2$ with dppf provides a useful catalyst for the alkylation of secondary amines with alcohols.[15] The use of potentially harmful alkyl halides is therefore avoided, and this chemistry has been applied to the synthesis of Piribedil.

Acknowledgements

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15. *Typical experimental procedure*: $[Ru(p\text{-cymene})Cl_2]_2$ (7.7 mg, 0.0125 mmol), dppf (13.9 mg, 0.025 mmol) and activated 3 Å molecular sieves (0.52 g) were added to a carousel tube and the mixture was exposed to a nitrogen atmosphere for 10 min. Morpholine (87 μL, 1 mmol) and benzyl alcohol (103 μL, 1 mmol) followed by anhydrous toluene (1 mL) were added dropwise. The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature for 10 min and then heated to reflux for 24 h. The resulting crude was evaporated in vacuo. Purification by column chromatography eluting with petroleum ether (bp 40–60 °C)/ethyl acetate (4:1) gave a colourless liquid (0.150 g, 84%).