

Ruthenium catalysed *N*-alkylation of amines with alcohols

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Received (in Cambridge, UK) 17th November 2006, Accepted 14th December 2006

First published as an Advance Article on the web 16th January 2007

DOI: 10.1039/b616859k

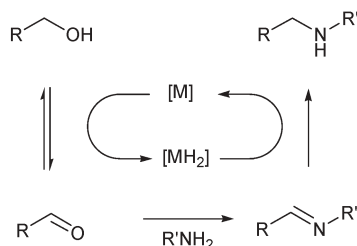
The conversion of primary amines into secondary amines has been achieved using alcohols as the alkylating agent, catalysed by $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ and a bidentate phosphine ligand.

The alkylation of amines often involves treatment of the amine with an alkyl halide or similar alkylating agent. However, there can be problems with the toxicity of such alkylating agents and control of mono-alkylation can be problematic.¹ An alternative approach to the synthesis of secondary amines involves reductive amination of carbonyl compounds.² An attractive combination of these methods employs alcohols as the starting materials, which undergo loss of hydrogen to provide carbonyl compounds that form an imine which is reduced to an amine (Scheme 1). This 'borrowing hydrogen' approach is redox neutral overall and also avoids the use of conventional alkylating agents.

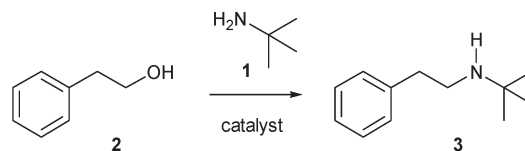
Several ruthenium catalysts have been investigated for this oxidation/imination/reduction sequence,³ but have suffered from the need for high temperatures (typically 180–200 °C). Very recently, Beller and co-workers have reported the use of $\text{Ru}_3(\text{CO})_{12}$ combined with bulky phosphines under less forcing conditions.⁴ Iridium catalysts have been reported by Yamaguchi⁵ and ourselves⁶ to be more effective, but are significantly more expensive.

We have recently reported that ruthenium complexes in the presence of bidentate phosphines are particularly effective for the formation of C–C bonds from alcohols, with the reactions similarly proceeding *via* intermediate carbonyl compounds.⁷ We therefore wished to investigate the utility of such catalysts for the *N*-alkylation of amines with alcohols, and report our findings herein.

We were especially interested in the synthesis of phenethylamine derivatives because of the range of neurotransmitters, and their agonists and antagonists, that possess this structure.⁸ Specifically, we chose the alkylation of *tert*-butylamine **1** with phenethyl alcohol **2** as our model reaction (Scheme 2).



Scheme 1 Borrowing hydrogen in amine alkylation.



Scheme 2 *N*-alkylation of amine **1**.

The combination of dppf (1,1'-bis(diphenylphosphino)ferrocene) with $\text{Ru}(\text{CO})(\text{PPh}_3)_3\text{H}_2$ was unsuccessful for this reaction, despite its use in C–C bond formation.⁷ $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$ -dppf provided some product, but the combination of bidentate phosphines⁹ with $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ was particularly effective (Table 1). With the exception of dppf, the bidentate phosphines led to appreciable quantities of ester formation, presumably from addition of alcohol to the intermediate aldehyde and oxidation of the so-formed hemi-acetal.¹⁰

We chose to use the $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ -dppf combination as the preferred catalyst for *N*-alkylation of amines, applying this to the synthesis of other amines.[†] We were able to use a catalyst loading of only 0.5 mol% $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ in the absence of base to achieve the formation of **3** in 77% conversion. However, the addition of potassium carbonate was a requirement when less basic amines were used. We chose to employ 2.5 mol% $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ for other reactions to ensure good conversions into product.

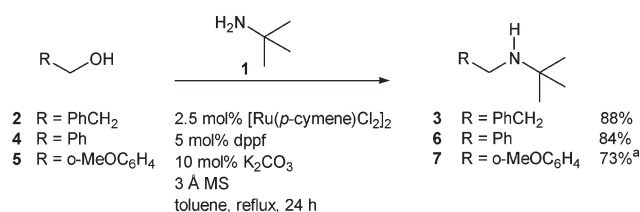
The alkylation of *tert*-butylamine **1** with alcohols **2**, **4** and **5** was achieved in good yields (Scheme 3). In the case of the more hindered *ortho*-substituted alcohol **5**, the reaction did not reach completion under the reaction conditions.

Table 1 Catalyst/ligand evaluation for formation of amine **3**^a

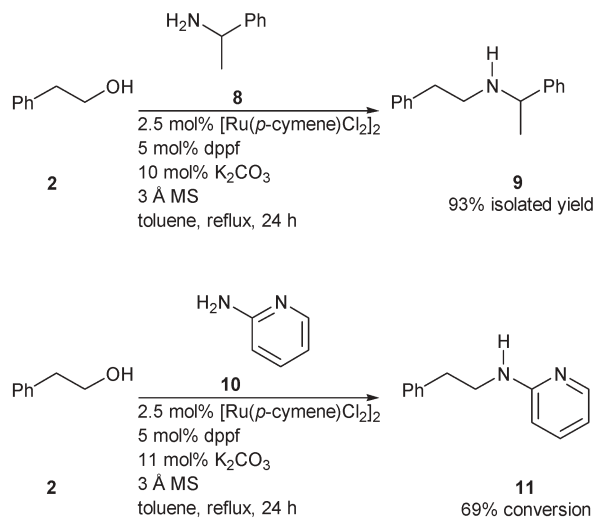
Catalyst (5 mol% in Ru)	Ligand (5 mol%)	Unreacted alcohol 2 (%)	Amine 3 (%)	Ester ^b (%)
$\text{Ru}(\text{CO})(\text{PPh}_3)_3\text{H}_2$	dppf	74	0	26
$\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$	dppf	65	35	0
$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$	none	92	0	8
$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$	PCy_3 (10 mol%)	90	0	10
$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$	PPh_3 (10 mol%)	54	36	10
$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$	Xantphos	0	39	61
$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$	rac-BINAP	12	35	53
$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$	2,2'-Bipyridine	99	0	1
$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$	dppf	0	80	20
$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$	dppe	80	20	0
$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$	dppp	42	52	6
$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$	dppf	0	100	0
$[\text{Ru}(\text{benzene})\text{Cl}_2]_2$	dppf	5	88	7
none	dppf	100	0	0

^a Alcohol : amine (1 : 1), 10 mol% K_2CO_3 , 3 Å molecular sieves, toluene, 110 °C, 24 h. Conversions are based on alcohol. Conversion to ester (two alcohols) is given by the amount of alcohol consumed to form it. ^b $\text{PhCH}_2\text{CO}_2\text{CH}_2\text{CH}_2\text{Ph}$.

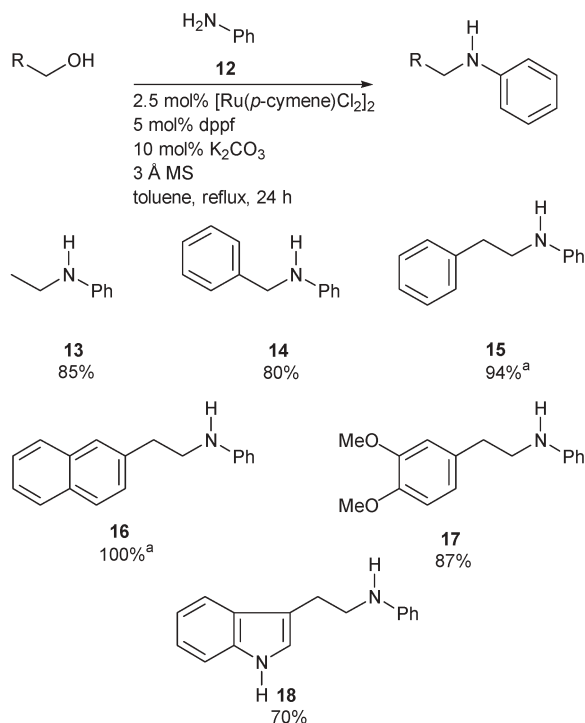
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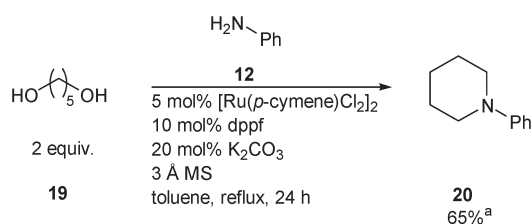
Scheme 3 *N*-alkylation of amine **1** with other alcohols. ^aConversion was determined by ¹H NMR analysis; other examples are isolated yields.



Scheme 4 *N*-alkylation of amines with phenethyl alcohol.



Scheme 5 *N*-alkylation of aniline with different alcohols. ^aConversion was determined by ¹H NMR analysis; other examples are isolated yields.



Scheme 6 Formation of *N*-phenylpiperidine.

Other amines were also amenable to *N*-alkylation (Scheme 4). The racemic amine **8** was converted into product **9** and the use of enantiomerically pure (*S*)-**8** afforded enantiomerically pure (*S*)-**9** (> 97 ee), as determined from the ¹H NMR spectrum in the presence of (*S*)-acetylmandelic acid.

Alkylation of aminopyridine **10** was successful, although in this case, some amide (PhCH₂CONHPy) was formed, presumably due to oxidation of the relatively stable intermediate hemi-aminal.

Nevertheless, the use of anilines in alkylation reactions with alcohols is usually unsuccessful, and we were pleased to discover that the [Ru(*p*-cymene)Cl₂]₂-dppf combination was successful for the formation of a range of *N*-phenylamines **13**–**18** (Scheme 5).

Cyclisation of diol **19** with aniline afforded *N*-phenyl heterocycle **20** (Scheme 6). However, a greater catalyst loading was needed to avoid formation of the lactone and other side products.

In summary, we report a method for the *N*-alkylation of amines with alcohols using a commercially available ruthenium catalyst–ligand combination. The reaction conditions are relatively mild and are applicable to the alkylation of anilines as well as aliphatic amines.

We thank His Majesty's Government of Brunei Darussalam and Universiti Brunei Darussalam for funding MHSAH under the in-service and training scheme.

Notes and references

[†] Typical experimental procedure: [Ru(*p*-cymene)Cl₂]₂ (15.3 mg, 0.025 mmol), dppf (27.7 mg, 0.05 mmol), K₂CO₃ (13.8 mg, 0.1 mmol) and activated molecular sieves (0.52 g, 3 Å) were added to a carousel tube and the mixture was exposed to a nitrogen atmosphere for 10 minutes. *tert*-Butylamine (105 μL, 1 mmol), phenethyl alcohol (119 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 minutes and then heated to reflux for 24 hours. The reaction mixture was filtered through Celite[®] and washed with dichloromethane. The filtrate was collected and the solvents were evaporated *in vacuo* to yield a reddish-brown crude mixture. Purification by column chromatography on silica gel eluting with diethyl ether gave the title compound **3** (0.16 g, 88% yield) as a pale yellow liquid. ¹H NMR (300 MHz, CDCl₃) δ = 1.01 (9H, s), 2.68–2.80 (4H, m), 7.10–7.25 (5H, m). ¹³C NMR (75.4 MHz, CDCl₃) δ = 29.4 (CH₃), 37.6 (CH₂), 44.5 (CH₂), 50.7 (C), 126.5 (CH), 128.8 (CH), 129.1 (CH), 140.6 (C). This is consistent with literature data.¹¹

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- 9 Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene, rac-BINAP = racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, dippf = 1,1'-bis(diisopropylphosphino)ferrocene, dppe = 1,3-bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenylphosphino)propane.
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