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Ruthenium-catalysed oxidation of alcohols to amides using a hydrogen acceptor

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ABSTRACT

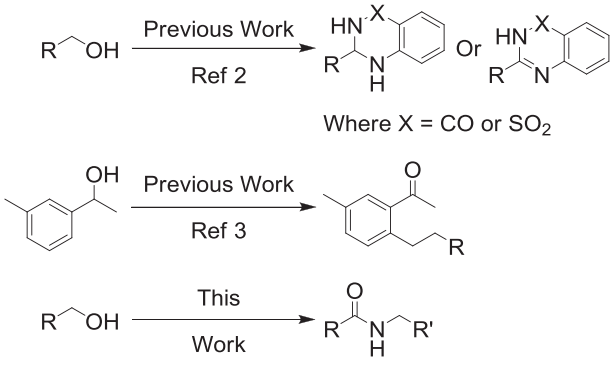
A wider investigation into the synthesis of secondary amides from primary alcohols using a hydrogen acceptor using commercially available $[Ru(p\text{-cymene})Cl_2]_2$ with bis(diphenylphosphino)butane (dppb) as the catalyst. The report looks at over 50 examples with varying functionality and steric bulk, whilst also covering the first reported results using microwave heating to effect the transformation.

1. Introduction

Amides are present in many molecules throughout the chemical industry, appearing in polymers, pharmaceuticals, agrochemicals, fragrances and dyes. However, the synthesis of these important functional groups often relies on stoichiometric activation of carboxylic acids, generating large amounts of waste material and solvent, making them expensive to produce.[1] An alternative is to use pre-activated carboxylic acid derivatives such as acid chlorides, however, these are often not available and have to be synthesised by the user. To illustrate how important this bond formation is, a recent poll on green chemistry in the pharmaceutical industry voted that amide formation avoiding poor atom economy was the highest priority area of research.[1]

Our previous work has investigated ruthenium-catalysed oxidations in tandem processes (Scheme 1). We have developed routes to access heterocyclic scaffolds from alcohols,[2] and developed a tandem oxidation/C–H activation protocol.[3]

Many recent publications have focused on a wide range of metal-catalysed amide formations.[4] One such metal-catalysed approach that has seen significant research in the past 6 years has been the oxidation of alcohols to amides using ruthenium catalysts.[5] Since Milstein's early work, demonstrating that a ruthenium catalyst was capable of oxidising an alcohol to an amide by removing two molecules of dihydrogen,[6] the area of ruthenium-catalysed amide formation from alcohols has seen considerable research activity with publications from Madsen,[7] ourselves,[8] Hong[9] and more recent contributions from Crabtree,[10] Milstein[11] and others[12] continuing to expand the applications of the original work.



Scheme 1. Examples of ruthenium-catalysed tandem oxidative reactions.

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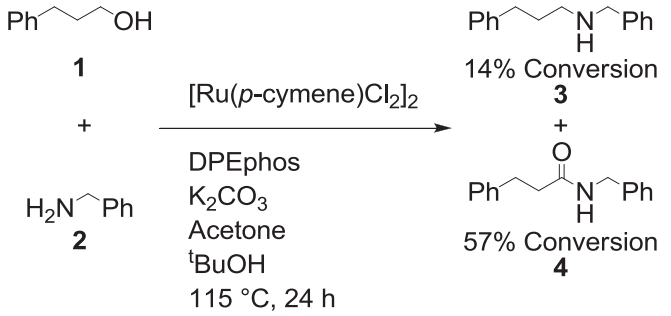
In this article we wish to present the full extent of our work showing how the catalytic system was developed and highlighting its substrate scope and limitations.

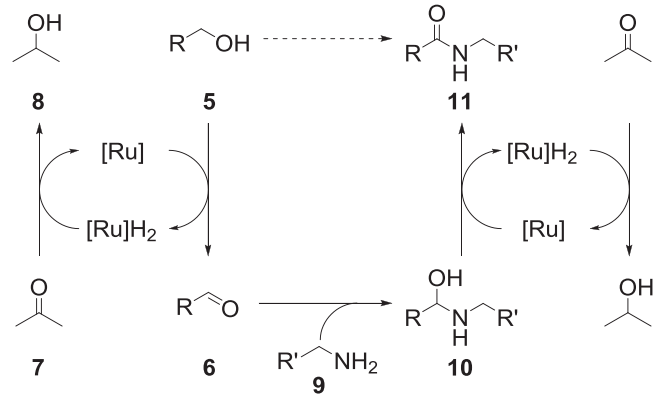
2. Results/discussion

Amide formation was initially observed as a by-product in the borrowing hydrogen[13] reaction of 3-phenyl-1-propanol (**1**) and benzylamine (**2**).[14] The formation of this product was unexpected, and it was later determined that the reaction had been contaminated with acetone, which led to the formation of the amide via oxidation of the hemi-aminal. The same amide (**4**) was formed again in the absence of acetone when screening different solvents for the same reaction, with the largest amount formed when using ^{t}BuOH. Considering that the addition of both acetone and ^{t}BuOH favoured amide formation, the combination of both was trialled in one reaction (Scheme 2) and led to an increased conversion to amide.



Scheme 2. Initial results.

In this case the amide was the major product, with 57% conversion. This result led to us proposing the following mechanism for formation of the amide (Scheme 3).



Scheme 3. Proposed mechanism.

The alcohol (**5**) is initially oxidised to the aldehyde (**6**) via hydrogen transfer to acetone (**7**) forming 2-propanol (**8**). The aldehyde is then intercepted by an amine (**9**) forming a hemi-aminal (**10**). Before the hemi-aminal can dehydrate to the imine, the catalyst oxidises it to the amide (**11**), again via hydrogen transfer to acetone. Whilst the first two steps are at equilibrium, the second oxidation step from the hemi-aminal to the secondary amide is effectively irreversible and drives the reaction.

To improve further upon the initial results (Scheme 2), and make the reaction more viable as a synthetic method a screen of the reaction conditions was undertaken (Table 1, Scheme 4).

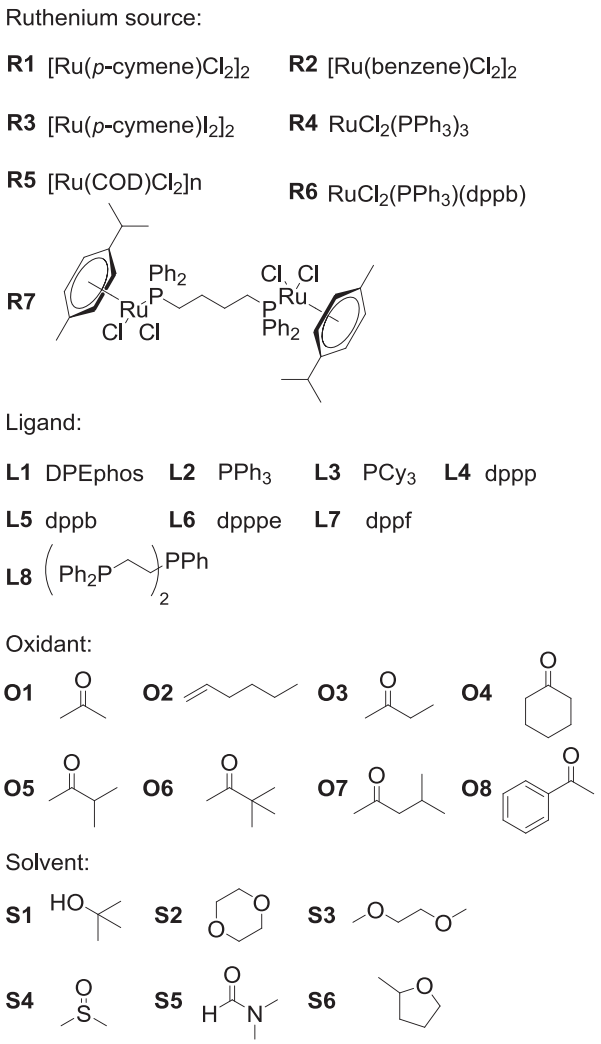
Table 1
Selected catalyst optimisation results

Entry[a]	Ru Source	Ligand	Oxidant	Solvent	Amide[b] (**4**) (%)
1[c]	**R1**	**L1**	**O1**	**S1**	57
2[d]	**R1**	**L1**	**O1**	**S1**	0
3	**R1**	**L1**	**O1**	**S1**	67
4	**R1**	**L1**	**O1**	**S2**	45
5	**R1**	**L1**	**O1**	**S3**	50
6	**R1**	**L1**	**O1**	**S4**	47
7	**R1**	**L1**	**O1**	**S5**	47
8	**R1**	**L1**	**O1**	**S6**	66
9	**R1**	**L1**	**O2**	**S1**	45
10	**R1**	**L1**	**O3**	**S1**	62
11	**R1**	**L1**	**O4**	**S1**	69
12	**R1**	**L1**	**O5**	**S1**	63
13	**R1**	**L1**	**O6**	**S1**	39
14	**R1**	**L1**	**O7**	**S1**	55
15	**R1**	**L1**	**O8**	**S1**	80
16	**R2**	**L1**	**O8**	**S1**	74
17	**R3**	**L1**	**O8**	**S1**	64
18	**R4**	**L1**	**O8**	**S1**	42
19	**R5**	**L1**	**O8**	**S1**	62
20	**R6**	—	**O8**	**S1**	69
21	**R7**	—	**O8**	**S1**	56
22[e]	**R1**	**L2**	**O8**	**S1**	79
23	**R1**	**L3**	**O8**	**S1**	43
24	**R1**	**L4**	**O8**	**S1**	86
25	**R1**	**L5**	**O8**	**S1**	93
26	**R1**	**L6**	**O8**	**S1**	86
27	**R1**	**L7**	**O8**	**S1**	83
28	**R1**	**L8**	**O8**	**S1**	20
29	**R1**	**L5**	**O1**	**S1**	80
30	**R1**	**L5**	**O3**	**S1**	82
31	**R1**	**L5**	**O4**	**S1**	79
32	**R1**	**L5**	**O5**	**S1**	85
33[f]	**R1**	**L5**	**O5**	**S1**	72
34[g]	**R1**	**L5**	**O5**	**S1**	85

[a] Reaction conditions: 3-phenyl-1-propanol (1 mmol), benzylamine (1.1 mmol), oxidant (2.5 mmol), [Ru] (5 mol % in Ru), ligand (5 mol %), Cs_2CO_3 (10 mol %), solvent (1 mL), 125 °C, 24 h.
[b] Determined by ^{1}H NMR.
[c] K_2CO_3 used as the base.
[d] No base.
[e] Ligand of 15 mol % added.
[f] H_2O of 20 mol % added.
[g] Acetophenone of 10 mol % added.

Variation of the activating base showed carbonates to be superior over hydroxide, phosphate, hydrogen carbonate and *tert*-butoxide, with caesium carbonate being the most effective (entry 3, Table 1). In the presence of weak organic bases such as triethylamine the reaction did not proceed and the use of a group 2 base ($MgCO_3$) was also less efficient (neither shown in the table). It should also be noted that with no base, the reaction did not proceed (entry 2, Table 1). Hong and co-workers[9f] have recently shown that for sterically demanding amines, their catalyst works better in the presence of an activating base as it proceeds via the ester, which then acylates the amide. However, throughout this work, the ester was never isolated or seen in any crude reaction mixture, even in the case of sterically hindered amines, thus it can be speculated that this is not the case here.

As previously mentioned, using ^{t}BuOH (entry 3, Table 1) as the solvent gave the highest conversion (67%) of the solvents screened (entries 3–8, Table 1), with 2-methyltetrahydrofuran (entry 8, Table 1) also giving a similarly high conversion (66%) the high conversion using these solvents may be due to the stabilisation of the intermediate hemi-aminal via hydrogen bonding. A wide variety of hydrogen acceptors was screened (entries 9–15, Table 1) with acetophenone (entry 15, Table 1) working over 10% better than the next best choice cyclohexanone (entry 11, Table 1). Alkenes would be a more desirable oxidant, as the reduction would be



Scheme 4. Materials present in Table 1.

irreversible, however, significantly lower conversions were obtained when tested (entry 9, Table 1).

The choice of ruthenium pre-catalyst was also analysed (entries 15–21, Table 1) indicating that $[Ru(p\text{-cymene})Cl_2]_2$ was the best option, over other similar choices such as $[Ru(benzene)Cl_2]_2$, and $[Ru(p\text{-cymene})I_2]_2$. Analysis of the phosphine ligand (entries 22–28, Table 1) indicated that the use of simple triphenylphosphine (entry 22, Table 1) in at least threefold excess (15 mol %) was just as effective as the original DPEphos. By tethering two phosphines together with a three carbon linker (dppp, entry 24, Table 1) it was possible to obtain the same result, without the higher loading of ligand, and by extending the linker to four carbons, as in dppb (entry 25, Table 1), a greater conversion was achieved. Other ligands with longer chains (entry 26, Table 1), or other functionality separating the phosphines (entry 27, Table 1) gave lower conversions.

Consideration of the improved catalytic system suggested that the use of acetophenone may not be considered atom efficient. As such, a variety of ketones were re-screened under the reaction conditions (entries 29–32, Table 1). 3-Methyl-2-butanone (entry 32, Table 1) was the next most effective, and can be considered slightly more atom economic than acetophenone.

Final screening of further additives such as water to re-hydrate the imine (entry 33, Table 1) or a catalytic amount of acetophenone (entry 34, Table 1) to aid in the hydrogen transfer[15] did little to improve the conversion.

A range of alcohols was then screened (Table 2). Butanol (entry 1, Table 2) gave a disappointing result with only 42% yield, however, on extending the chain length, thus increasing the boiling point of the alcohol, the yield rose, to 70% and 71% in the cases of hexanol (entry 2, Table 2) and nonanol (entry 3, Table 2), respectively. Phenyl-substituted aliphatic alcohols also gave good results (entries 4–6, Table 2) although a drop in yield was obtained with 3-phenyl-1-butanol (entry 7, Table 2). This was not due to steric reasons, as the corresponding 3,3-diphenyl-1-propanol (entry 8, Table 2) gave a similar result to the unsubstituted examples mentioned earlier with 72% yield. Introduction of steric bulk at the β-position did have a small effect, with 2-methyl-1-butanol (entry 9, Table 2) returning a slightly lower yield.

Phenethyl alcohols also worked in this reaction, but showed a larger variation in yields. Both electron rich (entries 12–14, Table 2) and electron poor (Table 2, entry 16) analogues gave similar results to that obtained with phenethyl alcohol (Table 2, entry 10). However, the use of the 4-chloro-substituted variant (entry 15, Table 2) gave a lower yield than expected. As before, the introduction of steric hindrance at the β-position led to a low yield (entry 11, Table 2). However, it was pleasing to see that the unprotected tryptophol (entry 17, Table 2) was tolerated, although the pyridyl variant (not shown) led to a far lower conversion (11%), presumably due to catalyst inhibition by complexation to the pyridine. In all these cases an average 10% drop in yield was observed compared with the previous aliphatic alcohols, which can be attributed to the increased steric demands on the catalyst.

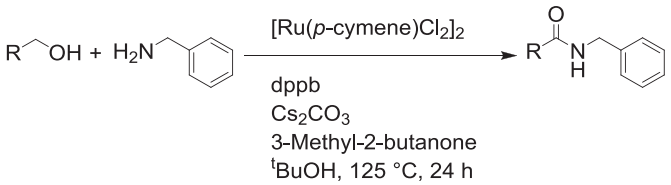
In the case of benzylic examples (rntry 18, Table 2), the yields were significantly lower (20–40%).[16] Whilst there is again an increased steric demand, in these cases a by-product was present in the reaction mixture accounting for another 20–50% of the alcohol. Isolation and characterisation of an example showed it to be the reduced aldol product from the reaction of the intermediate aldehyde and the ketone oxidant (Scheme 5). This transformation is already known under Borrowing Hydrogen conditions,[17] however, it was unexpected here.

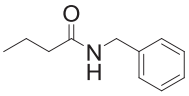
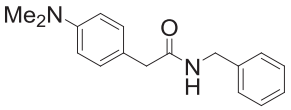
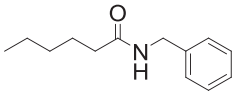
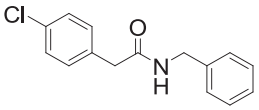
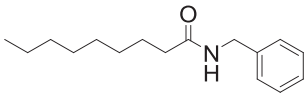
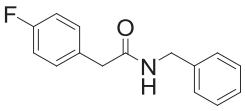
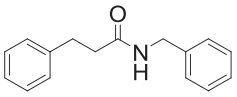
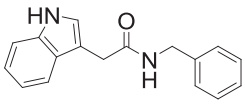
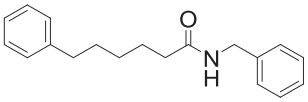
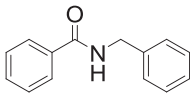
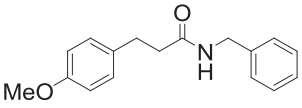
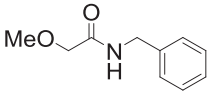
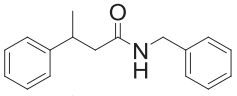
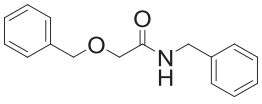
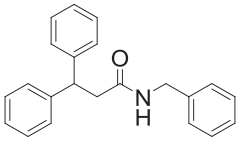
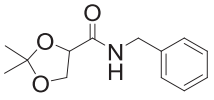
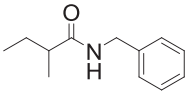
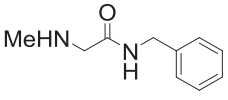
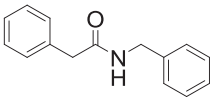
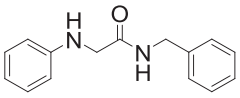
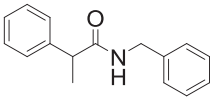
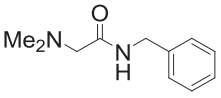
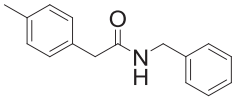
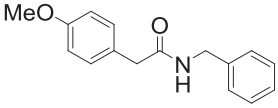
Once the alcohol is oxidised to the aldehyde, it is expected to react with the amine to form the hemi-aminal and proceed to the amide. However, in the case of benzylic alcohols, the aldehyde also reacts with the enolate of the ketone forming a by-product. It should be noted that it is only observed for benzylic alcohols.

This is probably due to several factors. The benzylic hemi-aminal is severely sterically hindered, thus the rate of oxidation would be low, allowing for the elimination back to the aldehyde, which can then undergo the aldol reaction. The aldol reaction could be occurring reversibly in all the reactions. If this is the case then the by-product is only observed in these cases due to the aldol product eliminating water to form the thermodynamically favourable α,β-unsaturated ketone, which forms an extended conjugated system with the aromatic ring. This can then be reduced either by direct reduction of the double bond[18] or via reduction of the ketone and isomerisation of the double bond,[19] both of which result in the same product.

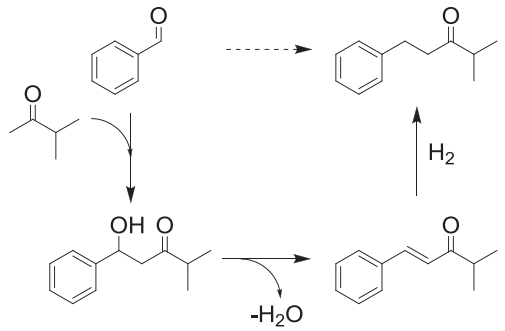
A series of alcohols with functionality attached to the β-atom was also trialled (entries 19–24, Table 2). The use of ethers such as methoxy (entry 19, Table 2) and benzoxy (entry 20, Table 2) both gave good results, however, the use of a phenoxy ether resulted in no conversion. The use of amino-substituted alcohols gave varying results. Secondary amine results depended upon how electron rich the nitrogen atom was, with electron rich methylamine (entry 22, Table 2) giving poor results, and the electron poor phenylamine (entry 23, Table 2) returning almost twice the yield. Tertiary amines, such as the dimethylamine (entry 24, Table 2) also worked well.

Table 2
Alcohol variation



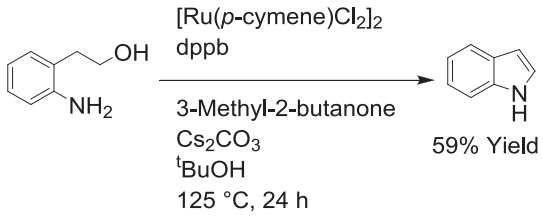
Entry[a]	Amide	Isolated yield (%)	Entry	Amide	Isolated yield (%)
1		42	14		57
2		70	15		49
3		71	16		60
4		68	17		36
5		67	18		24
6		72	19		73
7		62	20		81
8		72	21		40
9		65	22		37
10		58	23		63
11		45	24		63
12		57	25		49
13		52	26		63

[a] Reaction conditions: alcohol (3 mmol), benzylamine (3.3 mmol), 3-methyl-2-butanone (7.5 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %), dppb (5 mol %), Cs_2CO_3 (10 mol %), ^{t}BuOH (1 mL), 125 °C, 24 h.



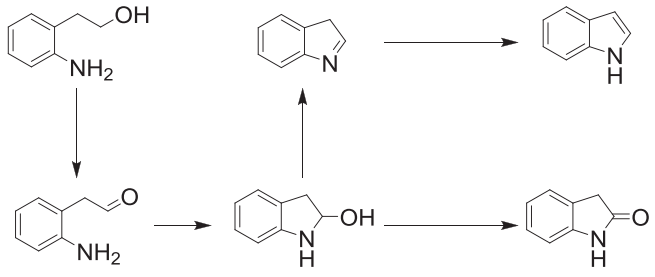
Scheme 5. Benzyl alcohol aldol product.

Amino alcohols were also tolerated as substrates with both five- and six-membered lactams being formed in fair yields (entries 25 and 26, Table 2), with the lower yield of the five-membered ring being due to its lower boiling point during isolation. However, the use of 2-aminophenethylalcohol under the reaction conditions, did not form the oxindole and only the indole was isolated (Scheme 6).



Scheme 6. Indole formation.

In this case, the alcohol is oxidised to the aldehyde, which then undergoes rapid cyclisation to form the cyclic hemi-aminal, at which point, as discussed previously, it can be further oxidised to the amide, in this case oxindole, or it can eliminate to form the cyclic imine. Whilst Yamaguchi and co-workers have reported the synthesis of similar cyclic oxindoles using a rhodium catalyst,[20] under these conditions the elimination to the cyclic imine was clearly the favoured pathway, before isomerisation to form the indole occurred, as no trace of the oxindole was present in the ^{1}H NMR of the reaction mixture. Again, this transformation has been reported by Grigg and co-workers[21] (Scheme 7).



Scheme 7. Possible routes for 2-aminophenethyl alcohol.

Having screened a series of alcohols, variation of the amine component was investigated (Table 3). Starting with a selection of benzylic amines, electron rich aromatics (entries 2–4, Table 3) generally gave good results, except for piperonylamine (entry 4, Table 3), whilst electron poor aromatics also gave reasonable results (entries 5–7, Table 3) except for the trifluoromethyl example (entry 7, Table 3). The structurally similar cyclohexyl example (entry 9, Table 3) also worked, although returning a low yield (44%). Heterocyclic amines were also tolerated with furfuryl (entry 9, Table 3) and 3-picolylamine (entry 10, Table 3) returning 54% and 93% isolated yields, respectively. However, the use of 2-picolylamine gave no product. This was attributed to the substrate binding to the catalyst preventing reaction. Considering the wide variation in results obtained with both 3- and 2-picolylamine from 93% isolated yield to 0%, 4-picolylamine was tested, and whilst returning a good conversion (78%), the isolation proved difficult.

Having observed the effect of substitution on the benzylic amines, aliphatic amines were studied next (entries 11–15, Table 3). These generally gave good results, except in the cases of tryptamine and cyclohexylamine, the latter being due to the steric bulk around the nitrogen atom.

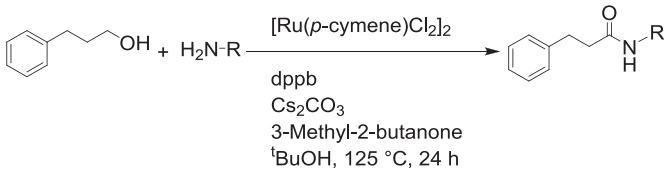
The use of acyclic examples such as diethylamine and dibenzylamine led to no product being formed under the reaction conditions. Even *N*-methyl-benzylamine (entry 16, Table 3), which is very similar to the benzylic amines previously used, was not successful in returning any product. However, cyclic secondary amines (entries 17–20, Table 3), where the lone pair is more exposed due to the alkyl chains being tied back, did form amides although in low yields (20–30%). Both pyrrolidine and piperidine formed the tertiary amide (entries 17 and 18, Table 3) and the scope could also be expanded to include heterocycles such as morpholine and *N*-methylpiperazine (entries 19 and 20, Table 3).

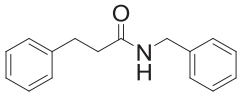
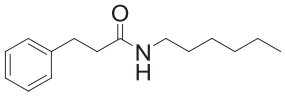
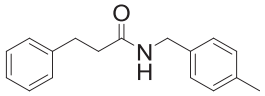
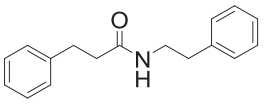
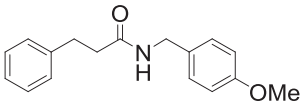
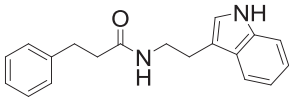
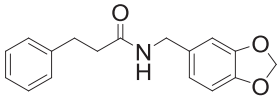
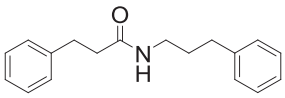
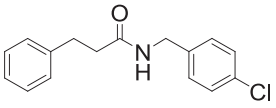
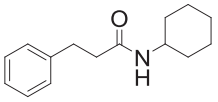
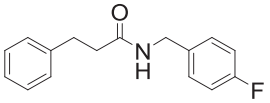
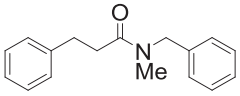
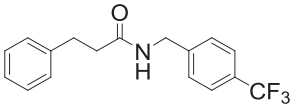
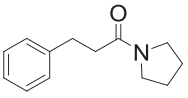
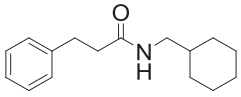
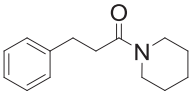
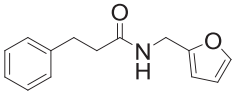
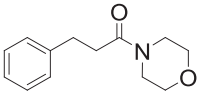
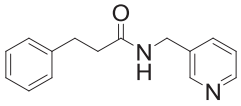
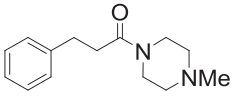
Recently published work by us, demonstrated the use of microwave heating to achieve C–N bond formation using Borrowing Hydrogen methodology.[22] The oxidation of alcohols we to amides using a ruthenium catalyst under microwave conditions has not to the best of our knowledge been reported, so proceeded to examine this further with our system. Initial work focused on replicating the thermal conditions used previously in this article (entry 19, Table 1). After 60 min 41% conversion to products was obtained of which 39% was amide, indicating that the reaction was working. The other 2% was the secondary amine. Extending the reaction to 90 min (entry 2, Table 4) did not lead to any further conversion and analysis of the reaction revealed that after 60 min no amine was left to continue the reaction, despite a slight excess being present (1.1 equiv). This is due to the benzylamine self-condensing to form dibenzylamine with release of ammonia, which is well reported in the literature.[23] As such, additional benzylamine was added (1.4 equiv) and the reaction repeated with an identical result obtained after 60 min and an improved conversion of 52% with 50% amide obtained after 90 min (entry 2, Table 4). Further extended heating to 120 and 180 min showed no further improvement, and in both cases sufficient primary amine was left in solution to push the reaction further.

Believing the catalyst to be decomposing under the conditions, the reaction was pulsed, heating to 125 °C for 30 min before allowing the reaction to cool and then repeating (entry 3, Table 4), again this led to no significant gain in conversion. Reducing the temperature and increasing the time (entry 5, Table 4) did improve the conversion, however, again further extension of the reaction time beyond 240 min did not improve the conversion further. Increased heating also improved the conversion (entry 6, Table 4), but again only to a point. Further increases in reaction time or temperature (entry 7, Table 4) did not further improve the conversion. Other options such as increasing the amount of oxidant (entry 8, Table 4) or increasing the amount of catalyst (entry 10, Table 4) did not improve upon previous results. As expected, removing the oxidant (entry 9, Table 4) led to a significantly lower conversion. The final result (entry 11, Table 4) did provide some insight into why the reaction was not proceeding further. After the first 90 min an extra portion of catalyst, ligand and base was added under N_2 before the reaction mixture was heated for a further 90 min. As no further reaction occurred, it can therefore be assumed that a material is being formed during the reaction that is inhibiting the reaction.

The major difference between the catalyst system reported here, and others present in the literature is the requirement for an

Table 3
Amine variation



Entry[a]	Amide	Isolated yield (%)	Entry	Amide	Isolated yield (%)
1		68	11		69
2		76	12		67
3		66	13		24[b]
4		45	14		68
5		51	15		33[b]
6		63	16		0[b]
7		43	17		23
8		44	18		35[b]
9		54	19		31
10		93	20		22

[a] Reaction conditions: alcohol (3 mmol), benzylamine (3.3 mmol), 3-methyl-2-butanone (7.5 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %), dppb (5 mol %), Cs_2CO_3 (10 mol %), ^{t}BuOH (1 mL), 125 °C, 24 h.
[b] Conversion determined by ^{1}H NMR.

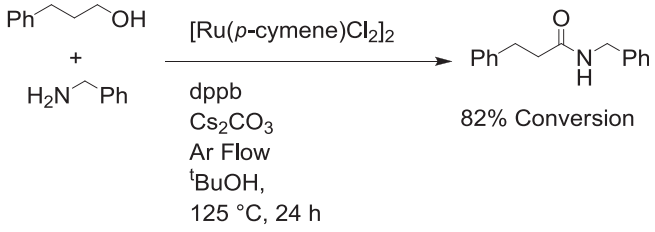
oxidant. Most other systems rely on using a flow of inert gas to remove the hydrogen formed. This approach also works for this catalyst system with both nitrogen and argon (Scheme 8). However, this method suffers from several issues making it less easy to repeat including flow rate of the gas, reaction vessel shape and size, stirring rate and whether the gas is bubbled through the solution or passed over the top. To this end, the use of oxidant-free amide formation was not pursued further.

Of the results obtained and reported in this paper, the reaction between 3-picolylamine and 3-phenyl-1-propanol (entry 10, Table 3), gave the highest yield (93%). This prompted further investigation. Attempts to form *ortho*-metallated ruthenium complexes with the picolylamine similar to those already reported in the literature[24] were unsuccessful. Similarly discounted was the picolylamine acting as a bi-dentate ligand similar to the catalyst used by Crabtree,[10] due to the large degree of separation between the two nitrogen atoms. Inclusion of pyridine as an organocatalyst or ligand similar to Madsen[7] also of had little effect. Whilst the reaction still continued in the presence of a catalytic amount of pyridine (73% conversion), it did not improve upon previous results. An alternative idea as to why 3-picolylamine gave such a good result would follow on from a similar effect observed in the Borrowing Hydrogen

Table 4
Microwave heating results

Entry[a]	Amine (equiv)	Temp (°C)	Time (min)	Conversion[b] (%)	Amide[c] (%)
1	1.1	125	90	41	39
2	1.4	125	90	52	50
3[d]	1.4	125	3×30	53	51
4	1.4	115	90	41	39
5	1.4	115	240	60	57
6	1.4	150	90	63	58
7	1.4	175	90	36	24
8[e]	1.4	125	90	45	44
9[f]	1.4	125	90	13	11
10[g]	1.4	125	90	54	52
11[h]	1.4	125	2×90	57	54

[a] Reaction conditions: 3-phenyl-1-propanol (1 mmol), benzylamine, 3-methyl-2-butanone (2.5 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %), dppb (5 mol %), Cs_2CO_3 (10 mol %), ^tBuOH (1 mL).
[b] Conversion of the alcohol determined by ^1H NMR.
[c] Determined by ^1H NMR.
[d] Reaction heated to 125 °C for 30 min, allowed to cool then re-heated.
[e] 3-Methyl-2-butanone (4 equiv).
[f] No oxidant used.
[g] $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), dppb (10 mol %), Cs_2CO_3 (20 mol %).
[h] After 90 min the reaction mixture was allowed to cool to room temperature before another equivalent of catalyst, ligand and base were added.

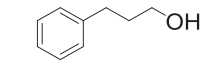
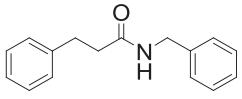
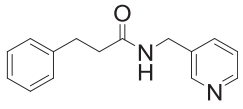
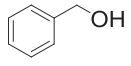
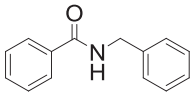
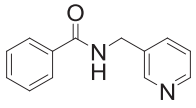
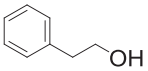
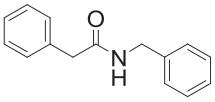
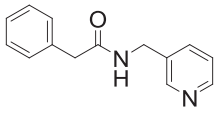
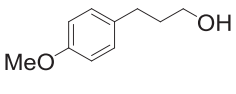
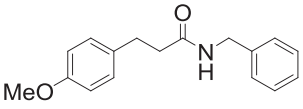
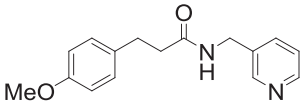
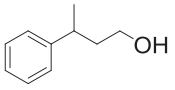
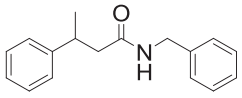
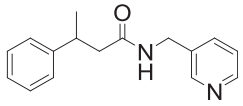
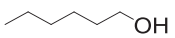
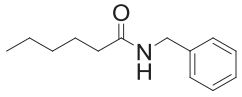
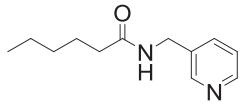
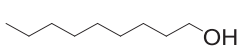
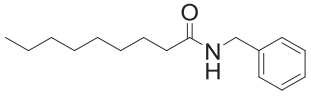
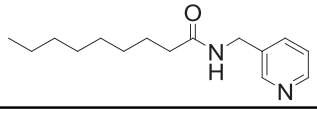


Scheme 8. Amide formation via dehydrogenation.

reaction of 2-phenylethanol of 2-aminopyridine.[25] The amine might be involved in either stabilising the intermediate through hydrogen bonding or aiding in the deprotonation of the hemi-aminal at the catalyst to increase the rate of oxidation.

A screen of alcohols (Table 5) highlighted that when poor results had been obtained previously (entry 2, Table 5) the yield was increased when 3-picolylamine was used, with benzyl alcohol doubling in isolated yield. This was encouraging suggesting that whilst the effect might be specific to the 3-picolylamine, it could be exploited advantageously with other alcohols. However, when

Table 5
Comparison of 3-picolylamine

Entry[a]	Alcohol	Amide	Isolated yield (%)	Amide	Isolated yield (%)
1			68		93
2			24		48
3			58		53
4			72		45
5			62		52
6			70		48
7			71		45

[a] Reaction conditions: alcohol (3 mmol), benzylamine (3.3 mmol), 3-methyl-2-butanone (7.5 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %), dppb (5 mol %), Cs_2CO_3 (10 mol %), ^tBuOH (1 mL), 125 °C, 24 h.

higher yields were obtained with benzylamine, the yields were not as good with the 3-picolylamine (entries 4–7, Table 5).

3. Conclusion

To conclude, the discovery, optimisation, evaluation and further development of a ruthenium-catalysed formation of amides from alcohols has been reported and discussed. Whilst the isolated yields vary, this can generally be explained by the relative steric bulk causing crowding around the catalytic centre. The reaction success also hinges upon the fine balance between the primary alcohol, ketone, and resulting aldehyde and secondary alcohol presence of the amine as a nucleophile, the irreversible oxidation to the amide drives the reaction. In summary this article expands upon our original report[8] of an operationally straightforward process using commercially available materials.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.04.017.

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