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ARTICLE TYPE

Ruthenium-Catalysed oxidative synthesis of heterocycles from alcohols

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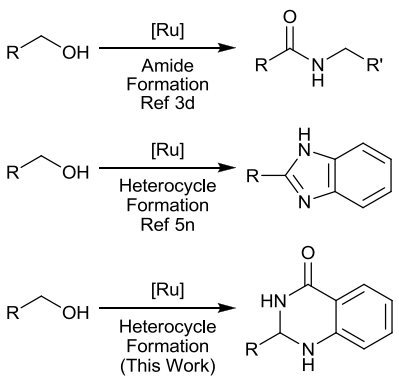
Ruthenium-catalysed hydrogen transfer has been successfully used for the conversion of alcohols into either 2,3-dihydroquinazolines or quinazolines. The choice of reaction conditions allows for the selective formation of either heterocycle and the methodology can also be applied to the sulfonamide analogue.

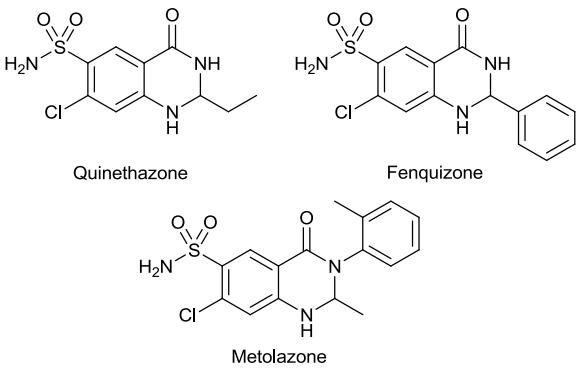
Ruthenium-catalysed oxidation of alcohols to their corresponding carbonyl compounds is well reported in the literature.[1] The applications of this methodology in tandem processes have led to a wide variety of different oxidation reactions of alcohols for the synthesis of esters,[2] amides,[3] functionalised alkenes,[4] heterocycles,[5] C-H activation[6] and acetals.[7]

Our previous experience in this area (Scheme 1) has been successful and we wanted to continue to expand the variety of reactions available. As such, we wanted to use alcohols in the synthesis of 2,3-dihydroquinazolinones‡ due to their use in pharmaceuticals (Scheme 2).

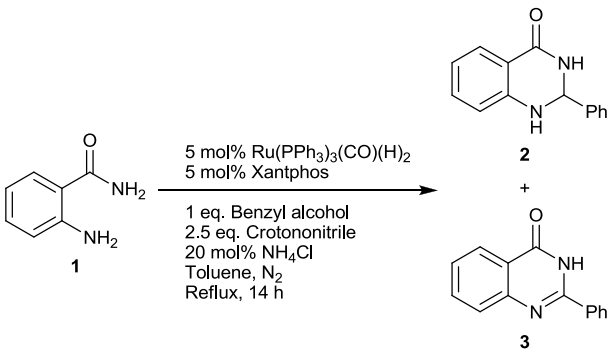


Scheme 1 Examples of ruthenium-catalysed tandem oxidative reactions of alcohols.

Our initial conditions (Scheme 3) were based on our successful conversion of alcohols into methyl esters,[2d] while the addition of a salt has proven to be important in previous work.[4a,8] A review of current syntheses of 2,3-dihydroquinazolines highlighted the



Scheme 2 Pharmaceuticals containing 2,3-dihydroquinazolines



Scheme 3 Initial reaction conditions

use of ammonium chloride[9] as a useful reagent in increasing the rate of formation, therefore it was included over other previously used salts such as piperidinium acetate. Initial results illustrated that as well as forming the desired 2,3-dihydroquinazoline, over oxidation to the quinazolinone was also occurring (Scheme 3), and optimisation of the reaction conditions would be required (Table 1).

Varying the amount of NH_4Cl below 20 mol% (Entries 2-4, Table 1) led to a decrease in conversion and selectivity for **2** over **3**. Swapping the NH_4Cl for *p*-toluenesulfonic acid (Entry 6, Table 1) led to reduced selectivity (2:1 rather than 10:1). Whilst extended heating in the absence of an additive (Entry 5, Table 1) led to 8:1 selectivity for **3** over **2**, allowing access to both 2,3-dihydroquinazolines and quinazolines. Reducing the amount of oxidant from 2.5 equivalents to 1.5 (Entries 7-8, Table 1) again led to reduced conversions and interestingly, reduced selectivity. The exact role of the ammonium chloride is unclear, however,

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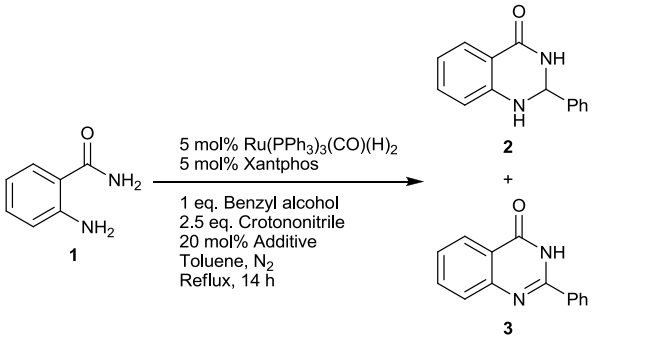
† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

Table 1 Optimisation of reaction conditions[a]



Entry	Ligand	Additive	Conversion[b] 1	2	3
1	Xantphos	NH_4Cl	0	91	9
2	Xantphos	NH_4Cl[c]	15	50	35
3	Xantphos	NH_4Cl[d]	32	17	51
4	Xantphos	-	23	15	62
5[e]	Xantphos	-	12	10	78
6	Xantphos	PTSA[d]	0	66	34
7[f]	Xantphos	NH_4Cl	0	78	22
8[g]	Xantphos	NH_4Cl	9	72	19
9	dppm	NH_4Cl	100	0	0
10	dppe	NH_4Cl	98	2	0
11	dppp	NH_4Cl	98	2	0
12	dppb	NH_4Cl	95	5	0
13	(+/-)-BINAP	NH_4Cl	0	92	8
14	DPEphos	NH_4Cl	17	79	4

[a] Reaction conditions: 2-aminobenzamide (1 mmol), benzyl alcohol (1 mmol), crotononitrile (2.5 mmol), $Ru(PPh_3)_3(CO)(H)_2$ (5 mol%), ligand (5 mol%), additive (20 mol%), toluene (1 mL), 115 °C, 14 h. [b] Conversion determined by ^1H NMR. [c] 10 mol% additive. [d] 5 mol% additive. [e] Reaction run for 24 h. [f] 2.0 eq. of crotononitrile. [g] 1.5 eq. of crotononitrile.

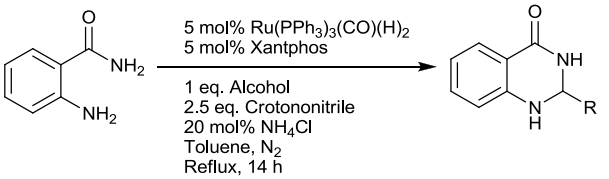
further investigations are ongoing. Finally, a screen of ligands (Entries 9-14, Table 1) highlighted that (±)-BINAP (Entry 13, Table 1) was a marginally better ligand, however, due to the increased cost, Xantphos was chosen as the ligand for further work.

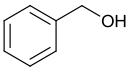
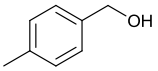
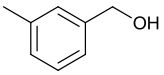
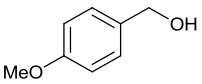
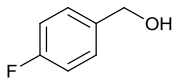
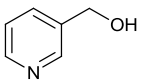
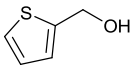
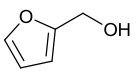
A series of benzyl alcohols was then submitted to the reaction conditions and the products isolated (Table 2). We were pleased to see that the results were generally good (60-80% isolated yields) except for furfuryl alcohol (Entry 8, Table 1). Both electron rich (Entries 2-4, Table 2) and electron poor (Entry 5, Table 2) gave good yields. The reaction also tolerated both pyridyl (Entry 6, Table 2) and thienyl (Entry 7, Table 2) with no difficulty.

When aliphatic alcohols were submitted to the reaction conditions no 2,3-dihydroquinazoline was formed, instead only the quinazoline was detected. As mentioned above, quinazolines had been previously observed; however, their formation was disfavoured under the reaction conditions chosen. This result prompted us to reconsider the role of the ammonium chloride. It was assumed that the over oxidation of the 2,3-dihydroquinazoline was disfavoured due to steric reasons, the increased bulk blocking the catalyst. In order to learn more, we ran two competition experiments to compare the over oxidation reaction with and without the ammonium chloride (Scheme 4).

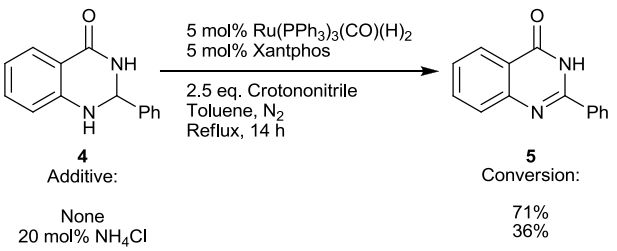
The results showed that when the ammonium chloride was present, the oxidation of **4** to **5** went to 36% conversion after 14 hours, whilst the reaction without ammonium chloride went to

Table 2 2,3-Dihydroquinazoline results[a]



Entry	Alcohol	Isolated Yield (%)
1		78
2		69
3		72
4		71
5		69
6		63
7		62
8		43[b]

[a] Reaction conditions: 2-aminobenzamide (1 mmol), alcohol (1 mmol), crotononitrile (2.5 mmol), $Ru(PPh_3)_3(CO)(H)_2$ (5 mol%), Xantphos (5 mol%), NH_4Cl (20 mol%), toluene (1 mL), 115 °C, 14 h. [b] Conversion determined by ^1H NMR.

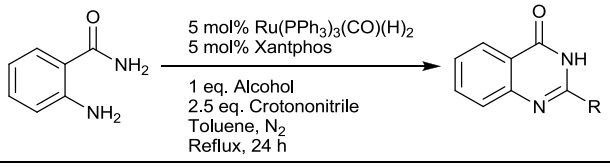


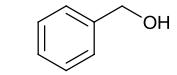
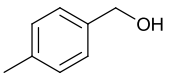
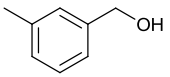
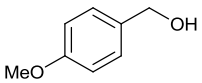
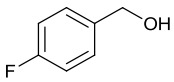
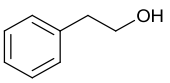
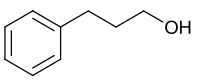
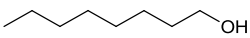
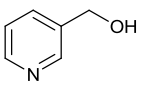
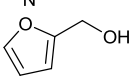
Scheme 4 Oxidation contest

71% conversion, a two fold increase in rate. This shows that the ammonium chloride has an important role in retarding the second oxidation of **4** to **5** but does not hinder the formation of the aldehyde necessary for the formation of **4**. Considering that the formation of quinazolines was indeed possible, and that it was faster without the presence of ammonium chloride, we chose to screen a series of alcohols under a new set of conditions to favour quinazoline formation (Table 3). We were also pleased to see that the products could be purified by recrystallization from the reaction mixture with no need for column chromatography.

The results were generally good (55-85% isolated yields) except for furfuryl alcohol (Entry 10, Table 3). The range of benzylic alcohols with both electron donating (Entries 3-4, Table 3) and

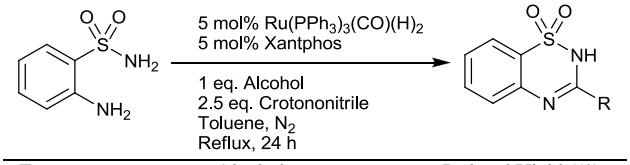
Table 3 Quinazoline results[a]

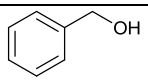
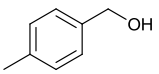
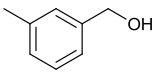
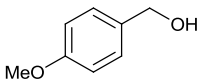
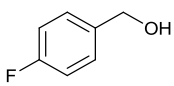
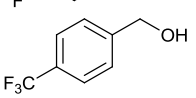
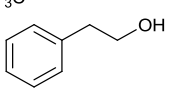
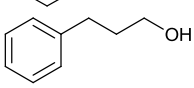
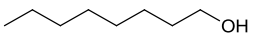
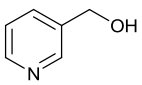
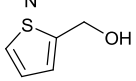


Entry	Alcohol	Isolated Yield (%)
1		72
2		47
3		72
4		70
5		67
6		85
7		83
8		82
9		56
10		40[b]

[a] Reaction conditions: 2-aminobenzamide (1 mmol), alcohol (1 mmol), crotononitrile (2.5 mmol), toluene (1 mL), $Ru(PPh_3)_3(CO)(H)_2$ (5 mol%), Xantphos (5 mol%), 115 °C, 24 h. [b] Conversion determined by ^1H NMR.

Table 4 2*H*-1,2,4-Benzothiadiazine-1,1-dioxide results[a]



Entry	Alcohol	Isolated Yield (%)
1		81
2		78
3		82
4		87
5		65
6		69
7		72
8		79
9		84
10		52
11		35

[a] Reaction conditions: 2-aminobenzenesulfonamide (1 mmol), alcohol (1 mmol), crotononitrile (2.5 mmol), toluene (1 mL), $Ru(PPh_3)_3(CO)(H)_2$ (5 mol%), Xantphos (5 mol%), 115 °C, 24 h.

electron withdrawing groups (Entry 5, Table 3) gave good results, except for 4-methylbenzyl alcohol (Entry 2, Table 3). In this case the alcohol was completely consumed and it is believed the poor solubility of the 2,3-dihydroquinazoline intermediate is responsible for the poor result. Both phenethyl (Entry 6, Table 3) and aliphatic alcohols (Entries 6-9, Table 3) were tolerated well returning excellent yields of 82-85%. Finally, the pyridyl (Entry 9, Table 3) structure was also successful in reasonable yield.

Having seen success with these heterocyclic scaffolds, we wished to expand the scope of this reaction further. Our group has been successful at *N*-alkylation of sulfonamides using Borrowing Hydrogen methodology[10] both thermally[11] and under solvent free microwave conditions.[12] This led us to conclude that sulfonamides may be tolerated under our reactions conditions allowing access to 2H-1,2,4-benzothiadiazine-1,1-dioxide structures. Indeed, by replacing the 2-aminobenzamide with 2-aminobenzenesulfonamide we were able to isolate these heterocycles in good yield (Table 4) without an increase in temperature.

Once again a range of benzylic alcohols was tolerated with both electron donating (Entries 2-4, Table 4) and electron withdrawing (Entries 5-6, Table 4) returning good yields. Phenethyl (Entry 7, Table 4) and aliphatic (Entries 8-9, Table 4) again gave good results. Heterocycles were also tolerated with the pyridyl (Entry 10, Table 4) and thienyl (Entry 11, Table 4) returning 52% and 35% respectively. The latter result was disappointing, however, when compared with the previous results of furfuryl alcohol (Entry 9, Table 2 and Entry 10, Table 3) it can be seen that the reaction is not as good with electron rich heteroaromatic structures.

To conclude, we have developed a ruthenium-catalysed synthesis of three different heterocyclic scaffolds from alcohols using similar conditions. Furthermore, no chromatography is required to access the products in good yields.

Notes and references

We thank GlaxoSmithKline, Pfizer, AstraZeneca, Novartis and the EPSRC for providing a studentship (to A. J. A. W.) through the collaborative EPSRC-Pharma-Synthesis Programme.

‡ During the preparation of this manuscript Zhou and Fang published a related iridium-catalysed synthesis of quinazolines.[13]

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