

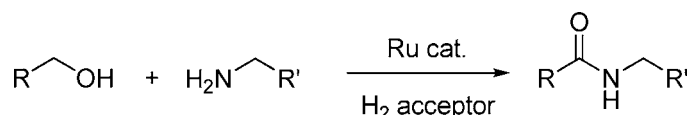
Ruthenium-Catalyzed Oxidation of
Alcohols into AmidesAndrew J. A. Watson,[†] Aoife C. Maxwell,[‡] and Jonathan M. J. Williams^{*,†}

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ABSTRACT



The synthesis of secondary amides from primary alcohols and amines has been developed using commercially available $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ with bis(diphenylphosphino)butane (dppb) as the catalyst.

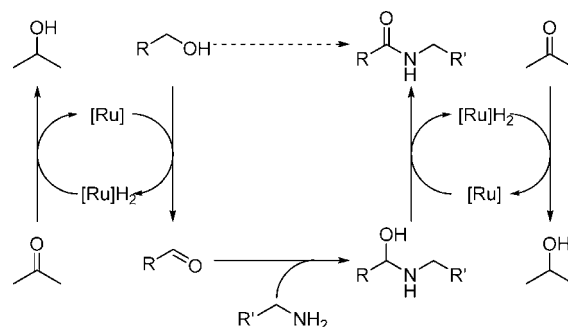
The synthesis of secondary amides has traditionally relied on the use of carboxylic acids and amines requiring stoichiometric amounts of coupling reagents such as HOAt.¹ These systems use reagents where the oxidation state of the materials is already at the required level for the product, and while giving good results, they lack atom efficiency. More recent approaches have considered the use of oxidative couplings from aldehydes,² and while the results are good, long-term storage and use of aldehydes can be troublesome due to their inherent reactivity.

Recently, several groups³ have reported catalytic amide formation from alcohols, using transition metal catalysts to oxidize the alcohol to the aldehyde in situ and then further oxidize the hemiaminal to the desired amide via the loss of 2 equiv of H_2 . Alcohols have also been used as starting materials in catalytic oxidative reactions leading to nitriles,⁴ acetals,⁵ esters,⁶ lactams,⁷ and benzazoles.⁸

We wish to report that our own research into this area has led to the oxidative coupling of an alcohol with an amine

to form amides using a commercially available ruthenium-based catalyst with a ketone as the oxidant (Scheme 1).

Scheme 1. Oxidative Coupling of Alcohols and Amines Using Hydrogen Transfer Catalysis



During our recent work on the use of alcohols as alkylating agents for amines using borrowing hydrogen methodology,^{9,10} we noticed that the formation of amides was observed in specific cases, sometimes as a significant

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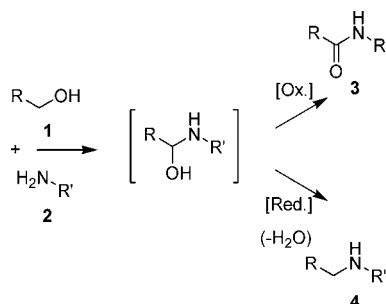
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byproduct (as much as 30%).¹¹ The coupling of an alcohol **1** with an amine **2** is expected to proceed via oxidation of the alcohol to an aldehyde and formation of an intermediate hemiaminal. Further oxidation of the hemiaminal would lead to the amide **3**, while elimination of water and return of hydrogen would provide amine **4** (Scheme 2). The balance

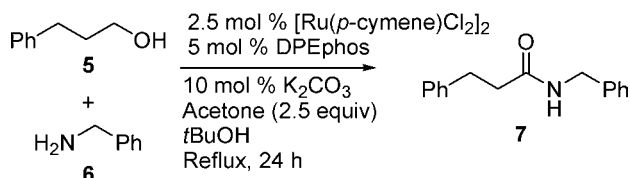
Scheme 2. Amine/Alcohol Coupling Pathways to Either the Amide or Amine Product



between these pathways may be expected to favor amide formation in the presence of an oxidant or when the hemiaminal is stabilized. Generally, hemiaminals have low stability, either reverting to carbonyl compound and amine or undergoing dehydration. However, there are examples of isolated hemiaminals.^{12,13}

We chose to examine the coupling of 3-phenylpropan-1-ol **5** with benzylamine **6** as a model reaction (Scheme 3). In an

Scheme 3. Model Reaction for Oxidative Amide Formation



initial attempt using acetone as the hydrogen acceptor with *t*BuOH as the solvent, the desired amide **7** was formed with 57% conversion. The combination of [Ru(*p*-cymene)Cl₂]₂ with bis(2-diphenylphosphinophenyl)ether (DPEphos) was chosen since it is known to be a competent catalyst for nonoxidative alcohol and amine coupling.¹¹

The choice of base was chosen as a starting point for the optimization, since base activates ruthenium chloride complexes to the catalytically active dihydride species.¹⁴ Replacement of K₂CO₃ with KHCO₃, KOH, or KO*t*Bu led to

Table 1. Optimization of Ligand, Hydrogen Acceptor, and Solvent for the Formation of Amide **7**^a

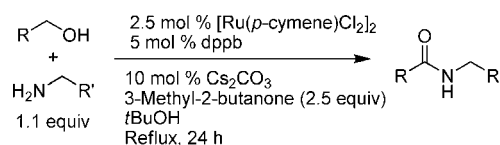
entry	ligand	ketone	solvent	convn (%) ^b	amide (%) ^b
1	dppb	MeCOMe	<i>t</i> BuOH	90	80
2	dppb	EtCOMe	<i>t</i> BuOH	89	82
3	dppb	<i>t</i> BuCOMe	<i>t</i> BuOH	78	68
4	dppb	<i>i</i> PrCOMe	<i>t</i> BuOH	91	85
5	dppb	<i>c</i> -hexanone	<i>t</i> BuOH	88	79
6	dppb	PhCOMe	<i>t</i> BuOH	95	90
7	dppb	PhCOMe ^c	<i>t</i> BuOH	93	80
8	dppb	PhCOMe	DME	92	89
9	dppb	PhCOMe	2-MeTHF	95	80
10	dppb	PhCOMe	dioxane	91	85
11	dppb	PhCOMe	toluene	77	25
12	dppb	none ^d	<i>t</i> BuOH	72	69
13	2 × PPh ₃	PhCOMe	<i>t</i> BuOH	85	75
14	DPEphos	PhCOMe	<i>t</i> BuOH	88	78
15	Xantphos	PhCOMe	<i>t</i> BuOH	41	36
16	dppm	PhCOMe	<i>t</i> BuOH	56	41
17	dppe	PhCOMe	<i>t</i> BuOH	88	57
18	dppp	PhCOMe	<i>t</i> BuOH	95	86
19	dppb	PhCOMe	<i>t</i> BuOH	95	90
20	dpppe	PhCOMe	<i>t</i> BuOH	91	86
21	dppf	PhCOMe	<i>t</i> BuOH	91	82
22	(<i>S,S</i>)-DIOP	PhCOMe	<i>t</i> BuOH	98	95

^a Conditions: 3-phenyl-1-propanol (1.0 mmol), benzylamine (1.1 mmol), oxidant (2.5 mmol), [Ru(*p*-cymene)Cl₂]₂ (2.5 mol %), phosphine (5 mol %), Cs₂CO₃ (10 mol %), solvent (1 mL); reflux; 24 h. ^b Conversions determined by ¹H NMR; formation of Ph(CH₂)₃NHCH₂Ph as a byproduct accounts for the difference in conversion vs amide formation. ^c 20 mol % water added. ^d The reaction was performed with a steady stream of N₂ over the reaction mixture.

lower conversions, as did the use of Na₂CO₃. However, the use of Cs₂CO₃ led to 67% amide **7**, and this base was selected for further optimization reactions. In the absence of base, no conversion into the amide was observed. Similarly, the use of triethylamine as base also led to no conversion. Preliminary screening reactions established that bis(diphenylphosphino)butane (dppb) was an effective ligand, providing 80% amide formation under these conditions.

The choice of hydrogen acceptor was then examined. The use of a ketone as the hydrogen acceptor also leads to the potential complication of reaction with the substrate amine to form an imine. We believe that under these reaction conditions, although some ketimine formation was observed at early stages in the reaction, this process is reversible due to the relative lack of stability of ketimines.¹⁵ We did not detect any isopropylamine derivatives which could have arisen through reduction of ketimine derived from acetone

Scheme 4. Conditions Used for the Formation of Amides



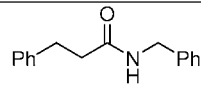


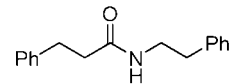

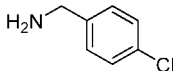
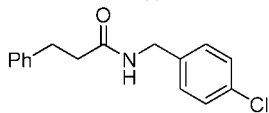

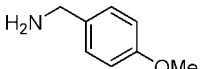
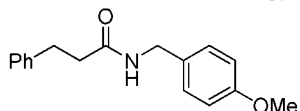
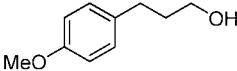

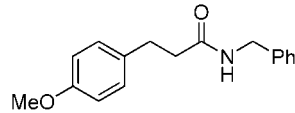
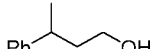

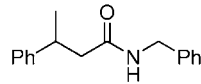
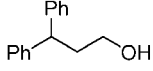

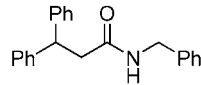
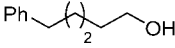

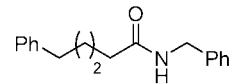
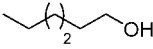

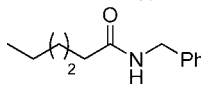
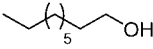

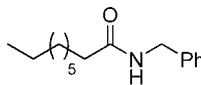
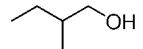

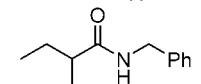
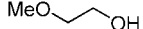

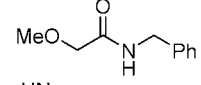
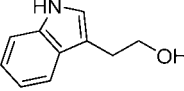

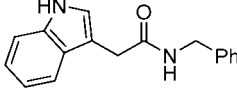


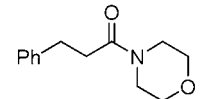


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Table 2. Oxidative Coupling of Alcohols with Amines to Give Amides^a

entry	alcohol	amine	amide	yield (%) ^b
1				68
2				67
3				51
4				66
5				72
6				62
7				72
8				67
9				70
10				71
11				65
12				73
13				36
14				31

^a Conditions: alcohol (3.0 mmol), amine (3.3 mmol), 3-methyl-2-butanone (7.5 mmol), [Ru(*p*-cymene)Cl₂]₂ (2.5 mol %), dppe (5 mol %), Cs₂CO₃ (10 mol %), *t*BuOH (3 mL); reflux; 24 h. ^b Isolated yields after column chromatography and/or recrystallization.

and benzylamine. Simple alkenes, including dodec-1-ene, styrene, and cyclohexene, did not act as hydrogen acceptors for this reaction, nor did hex-1-yne.

Replacement of acetone with alternative ketones was found to be successful, as shown in Table 1. 2-Butanone (entry 2) and cyclohexanone (entry 5) gave very similar results, while pinacolone (entry 3) gave a reduced conversion, presumably for steric reasons. The use of 3-methylbutan-2-one (entry 4) or acetophenone (entry 6) gave improvements in both

conversion and selectivity toward amide over amine, with only 6% and 5% secondary amine byproduct. The addition of water to the reaction mixture, which was hoped may help to disfavor elimination from the intermediate hemiaminal, led to a lower conversion and more amine byproduct (entry 7). The use of nonhydroxylic polar solvents afforded comparable results (entries 8–10), although the use of toluene (entry 11) led to the formation of secondary amine Ph(CH₂)₃NHCH₂Ph as the major product, with only a modest

formation of amide. Interestingly, oxidation to give amide was reasonably successful even in the absence of an oxidant; a flow of nitrogen was employed to remove any hydrogen gas which was formed (entry 12).

An investigation into the use of other ligands demonstrated that other phosphines were also effective in providing a catalytic system. Even triphenylphosphine generated a reasonably effective catalyst (entry 13). 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (entry 15) was found to be significantly less effective than DPEphos (entry 14), despite their structural similarity. The use of a series of simple bidentate phosphines, $\text{Ph}_2\text{P}(\text{CH}_2)_n\text{PPh}_2$ ($n = 1-5$, entries 16–20) confirmed that bis(diphenylphosphino)butane (dppb) was a good ligand in this process. In fact, the use of (*S,S*)-DIOP {(4*S*,5*S*)-(+)-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane} (entry 22), with the same tether length as dppb, was found to be even more effective.

Although DIOP performed better than dppb, we chose to use the latter as a simple, cheap, and effective ligand for the process. In addition, even though acetophenone was found to be a particularly good hydrogen acceptor in these reactions, we anticipated potential problems for the isolation of amides from any unreacted acetophenone and its reduction product 1-phenylethanol. We therefore selected 3-methyl-2-butanone as the hydrogen acceptor. Although it is not quite as effective as acetophenone, it is volatile (bp. 95 °C) as is the alcohol derived from it (bp. 112 °C).

With the catalytic system chosen (Scheme 4), the reaction was applied to the synthesis of a range of amides (Table 2) with good isolated yields. We were interested to note that introduction of a methoxy group into the molecule (entries 4, 5, and 12) reduced the formation of secondary amine significantly, and in most cases the byproduct was negligible only accounting for approximately 1% of the starting alcohol.

The use of the indole-containing substrate (entry 13) gave a lower yield than anticipated. Secondary amines are poor substrates in this reaction, showing very little product

formation. In the case of morpholine (entry 14), a moderate yield of the tertiary amide product was obtained.

In summary, we have identified a new catalytic system for the conversion of primary alcohols into amides in good yields. The process uses a commercially available catalyst and is operationally straightforward.¹⁶

Acknowledgment. We thank the EPSRC and Glaxo-SmithKline for providing funding for a studentship (to A. J. A. W.) through the collaborative EPSRC-Pharma Synthesis Programme.

Supporting Information Available: Details of experimental procedures and characterization data are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) **Procedure for the formation of amides from alcohols.** To an oven-dried, nitrogen-purged Schlenk tube containing $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ (46.9 mg, 0.075 mmol), dppb (64.0 mg, 0.15 mmol), and Cs_2CO_3 (97.7 mg, 0.30 mmol) was added alcohol (3 mmol), amine (3.33 mmol), 3-methyl-2-butanone (0.8 mL, 7.5 mmol), and *t*BuOH (3 mL), and the reaction was heated at reflux for 24 h. On completion, the reaction was allowed to cool to room temperature before the solvent was removed in vacuo. The crude product was purified by column chromatography (Et_2O /petroleum ether as eluent) before recrystallization (from dichloromethane/hexane), to afford the corresponding amide in good yield.