Tetrahedron 70 (2014) 3683–3690

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

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

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ARTICLE INFO

Article history:
Received 6 February 2014
Received in revised form 23 March 2014
Accepted 7 April 2014
Available online 13 April 2014

Keywords:
Ruthenium
Oxidation
Amide
Alcohol

ABSTRACT

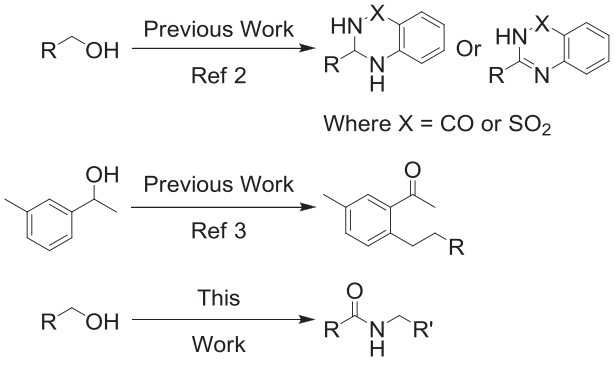
A wider investigation into the synthesis of secondary amides from primary alcohols using a hydrogen acceptor using commercially available $[Ru(p\text{-cymene})Cl_2]_2$ with bis(diphenylphosphino)butane (dppb) as the catalyst. The report looks at over 50 examples with varying functionality and steric 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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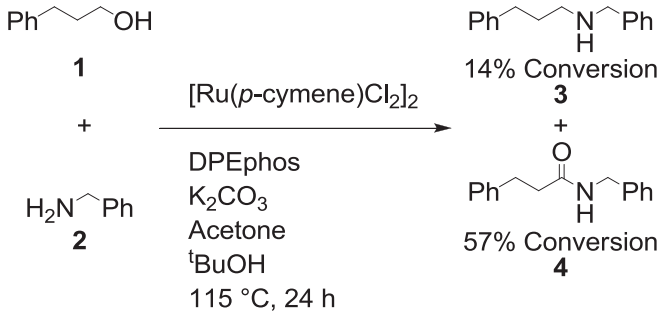
0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.04.017

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.

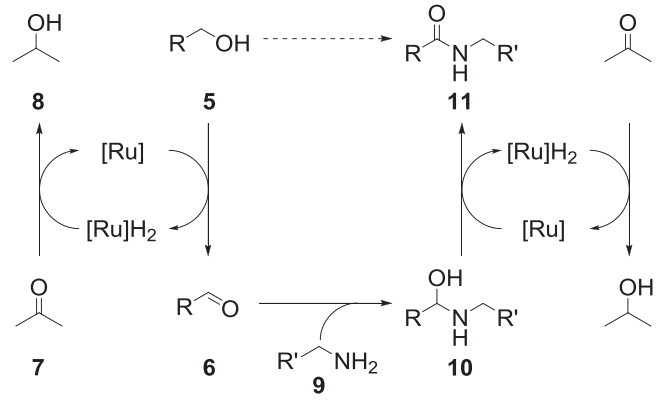
2. Results/discussion

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