

Understanding Gold Nanoparticle Catalysis in the Oxidative Amidation of Aldehydes and Amines

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Declaration of Originality

I declare that all the work in this thesis is my own and that all other research has been appropriately referenced.

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Abstract

The amide bond is ubiquitous in nature and frequently encountered in many areas of industrial and pharmaceutical chemistry. However, industrial scale synthesis of amide bonds relies on the activation of carboxylic acids, a process which typically employs hazardous or toxic reagents and results in the formation of a stoichiometric amount of waste. Activation is required due to the prohibitively high energy cost of direct amide bond formation; a feature which can be circumvented by approaching amide synthesis via the oxidative reaction of amines with either alcohols or aldehydes.

This thesis describes work undertaken to understand and optimise the Au-catalysed oxidative amidation of aldehydes utilising O_2 as the terminal oxidant, producing water as the only by-product. Oxidative amide synthesis from alcohols and aldehydes employing O_2 as the terminal oxidant is almost unique to AuNP catalysis.

Herein, conditions applicable for many potential supported AuNP catalysts are described, with particular attention paid to the role of additives and mass transfer in the reaction outcome. The preparation and characterisation of a suitable Au/ γ - Al_2O_3 catalyst is presented, with further discussion on thermal pre-treatment and the subsequent physical changes to the catalyst surface. Attempts to elucidate the mechanism of AuNP catalysed oxidative amidation from aldehydes are made using additives. An unexpected result was further investigated and evidences the multiple roles of reactive oxygen species on the catalyst surface and subsequently a revised catalytic cycle is proposed.

The results obtained throughout this work are used in a concerted manner to develop a proof-of-concept slurry bubble column reactor. Which is used to perform the first reported example of a continuous catalytic oxidative amidation from aldehydes using O_2 as the terminal oxidant.

Abbreviations

AAB	Activated alumina ball
ABNO	9-Azabicyclo[3.3.1] nonane N-Oxyl
AgNP	Silver nanoparticle
AIBN	Azobisisobutyronitrile
AIT	Autoignition temperature
API	Active pharmaceutical ingredient
Aq.	Aqueous
Ar	Aromatic
AuNP	Gold nanoparticle
BET	Brunauer-Emmett-Teller
bs	Broad singlet
Bu ₂ O	Dibutyl ether
CDI	Carbodiimidazole
CSTR	Continuously stirred tank reactor
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIC	Diisopropylcarbodiimide
DMPO	5,5-Dimethyl-1-pyrroline-N-oxide
DNA	Deoxyribonucleic acid
dppb	Diphosphine 1,4- <i>bis</i> (diphenylphosphino)butane
EPR	Electron paramagnetic resonance
eqn	Equation
GSCR	Glass slurry column reactor
HATU	Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	Hydroxybenzotriazole
ICP-AES	Ion Coupled Plasma - Atomic Emission Spectroscopy
IR	Infra-red
KIE	Kinetic isotope effect
LA	Lewis acid
LG	Leaving group
MS	Molecular sieves
MSI	Metal-support interactions
N.D.	Not detected
NHC	N-heterocyclic carbenes
NHS	N-Hydroxy succinimide
NMO	N-Methylmorpholine N-oxide
NMR	Nuclear magnetic resonance

NP	Nanoparticle
NS-TiO ₂	Nanostructured sulfated titania
[O]	Generic oxidant
PBN	N-tert-Butyl- α -phenylnitrone
PFR	Plug flow reactor
PhMe	Toluene
PI-AuNP	Polymer-incarcerated gold nanoparticles
PtNP	Platinum nanoparticle
PVA	Poly(vinyl acetate)
PVP	Polyvinylpyrrolidone
PZC	Point of zero charge
R	Generic organic side chain
RuNP	Ruthenium nanoparticle
SBCR	Slurry bubble column reactor
SET	Single electron transfer
SSC	Stagnant separating chamber
S-WOx	Sulfated tungsten oxide
T3P	Propanephosphonic acid anhydride
TBME	<i>tert</i> -Butyl methyl ether
TBPH	<i>tert</i> -Butyl hydroperoxide
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TEM	Transmission Electron Microscopy
TGA-DSC	Thermogravimetric analysis - differential scanning calorimetry
TGA-MS	Thermogravimetric analysis - mass spectrometry
UV	Ultra-violet
Vis	Visible
wt%	Weight percentage
XRD	X-Ray Diffraction
σ_p	Hammett parameter (<i>para</i>)

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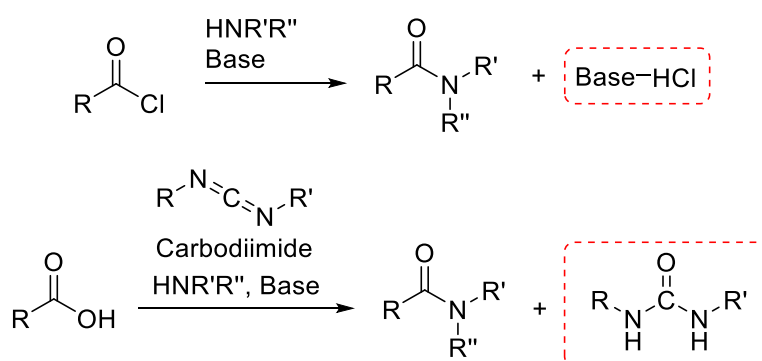
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1 Introduction

1.1 Introduction to Amide Synthesis

Amides are one of the most frequently occurring functional groups and are abundant in nature and industrial products. Amide bonds form the linkages between amino acids in proteins and are frequently found in natural products and mimicked in the production of pharmaceuticals and polymers (polyamides). A recent analysis of publications published by pharmaceutical companies found that amide bond formation features in ~50% of all reported synthetic routes and is the most frequently used reaction at both the medicinal chemistry and process scales.¹

The most common approaches to amide synthesis require the use of stoichiometric reagents. A review published in 2016 by an industrial process chemistry team identified acid chloride formation and carbodiimides (Scheme 1-1) as the most popular routes for large-scale (>100 mmol) synthesis.² Both methods produce hazardous by-products that incur additional processing costs in their removal from the product stream.



Scheme 1-1 Amide formation via the use of carbodiimides or acyl chlorides, and the by-products associated with their use

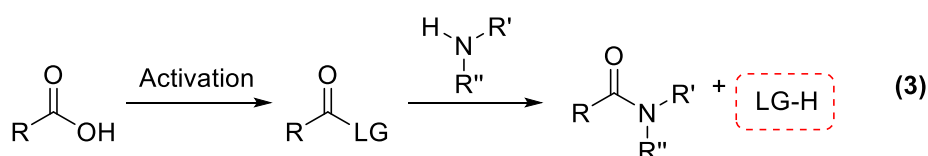
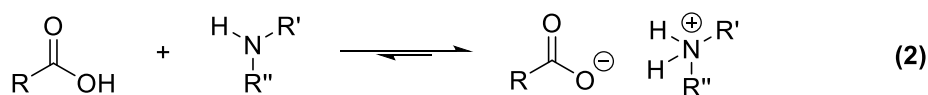
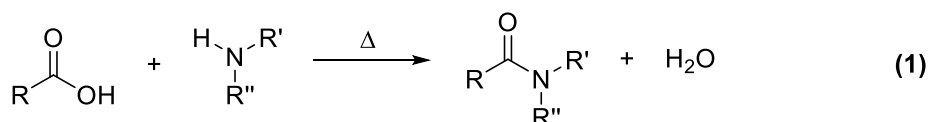
A consortium of representatives from major pharmaceutical companies unanimously selected ‘amide formation avoiding poor atom economy reagents’ as an area they would most like to see an improvement.³ This is almost certainly a consequence of many pharmaceutical molecules containing amide bonds and the lack of (catalytic) methods suitable for multi-kilogram processing.

In this chapter, a review of the most common-utilised amidation methodologies will be presented, addressing the most common approaches to amide bond formation from carboxylic acids and amines. Firstly, using stoichiometric coupling reagents (section 1.2) and then the various catalytic approaches (section 1.3). The catalytic amidation of carboxylic acids and amines is presented as three sub-sections, evaluating the most popular organocatalysts, biocatalysis and, finally, transition metal catalysts.

The introduction to catalytic oxidative amidation methods (Section 1.4) is presented in two sub-sections, based on the approach to oxidation, either by the removal of H₂ (dehydrogenative) or the addition of an external oxidant (oxidative). The last section evaluates the catalytic oxidative amidation utilising AuNP catalyst and O₂ as the terminal oxidant and a more detailed discussion of the conditions employed in these systems.

1.2 Classical Amide Formation

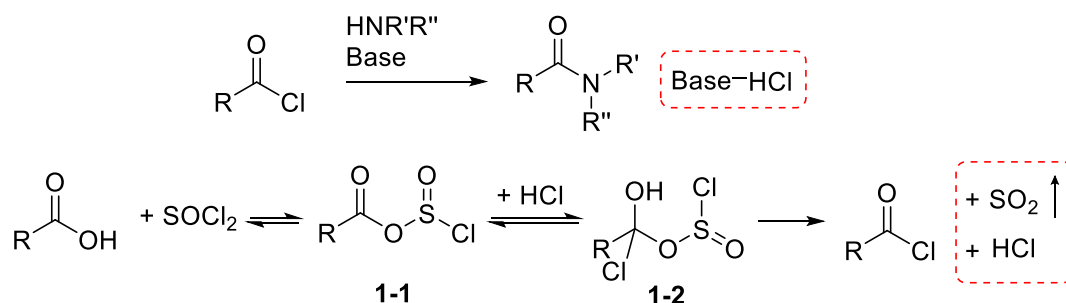
Direct amide bond formation could feasibly be achieved by the condensation reaction between a carboxylic acid and amine, producing water as the only by-product (Scheme 1-2, eqn 1).⁴ However, the direct reaction of carboxylic acid and amines does not occur spontaneously at ambient temperatures. Due to the pK_a difference of carboxylic acids and amines (approximately 5 and 11, respectively), salt formation is kinetically much more facile and essentially irreversible (Scheme 2, eqn 2). Hence, amide formation usually requires the use of a 'coupling' reagent that can activate the carboxylic acid towards nucleophilic attack by the amine (Scheme 1-2, eqn 3).



Scheme 1-2. General approaches to amide synthesis via the activation of a carboxylic acid

1.2.1 Acyl Chlorides

Activation of the carboxylic acid group by chlorination is the first example of this activation approach, the reactions of acyl chlorides with N- and O- nucleophiles were reported independently by Schotten (1884)⁵ and Baumann (1886),⁶ for amide and ester synthesis respectively.

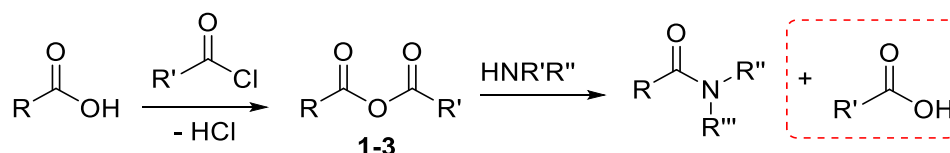


Scheme 1-3. Amidation of an acyl chloride and the preparation of an acyl chloride via the reaction of a carboxylic acid with thionyl chloride

Chlorination is most commonly achieved at process scale by the reaction of carboxylic acids with a chlorinating reagent, the most commonly used being thionyl chloride (SOCl₂) (Scheme 1-3) or oxalyl chloride (COCl)₂. Both of these chlorination reagents are cheap and have reasonably low boiling points, facilitating their removal from the product mixture by evaporation. However, the usage of either reagent has the potential to form carcinogenic or toxic by-products. Amide synthesis via chlorination inherently produces a stoichiometric amount of acidic waste which can reduce the functional group tolerance or limit the scope of the methodology.

1.2.2 Mixed Anhydrides

Amide formation via the formation of mixed anhydrides (Scheme 1-4) is frequently used on a process scale for coupling carboxylic acids and amines. Mixed anhydrides were first reported independently by three different research groups in 1951: Wieland and Bernhard,⁷ Boissonnas,⁸ and Vaughan and Osato.⁹ The activation of the carboxylic acid groups is achieved by the reaction of a carboxylic acid with an acyl chloride; forming a mixed anhydride (**1-3**) that is susceptible to nucleophilic attack by an amine to afford the desired amide.



Scheme 1-4. Amide formation via the formation of a mixed anhydride

A drawback to amidation via the formation of a mixed anhydride is that the intermediate **1-3** contains two electrophilic carbonyl groups. Controlling the selectivity of the amine attack at these reactive

centres is crucial to the success of reaction. Vaughan and Osato's reported that the best yields are achieved when the acyl chloride was both electron-rich and sterically encumbered; the added steric bulk increases selectivity for the desired amide but at the expense of the reaction's atom economy.⁹

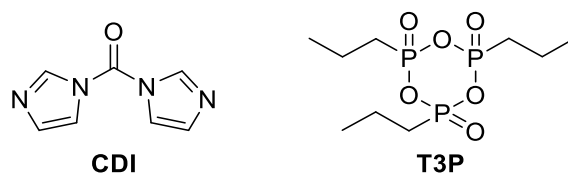
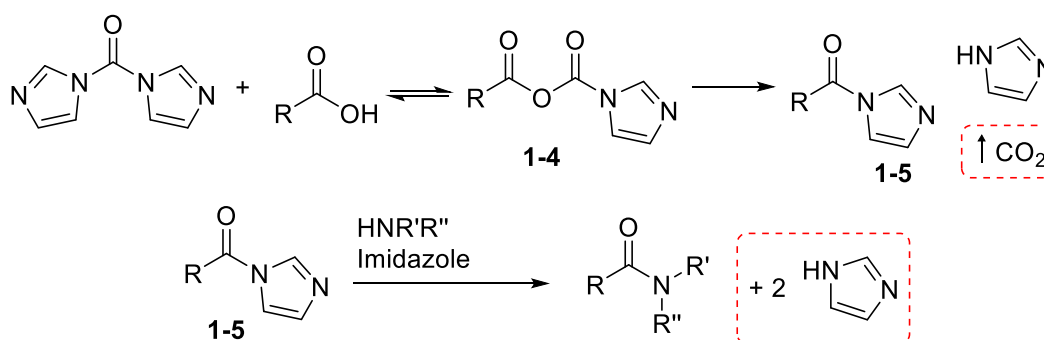


Figure 1-1. Common amide coupling reagents

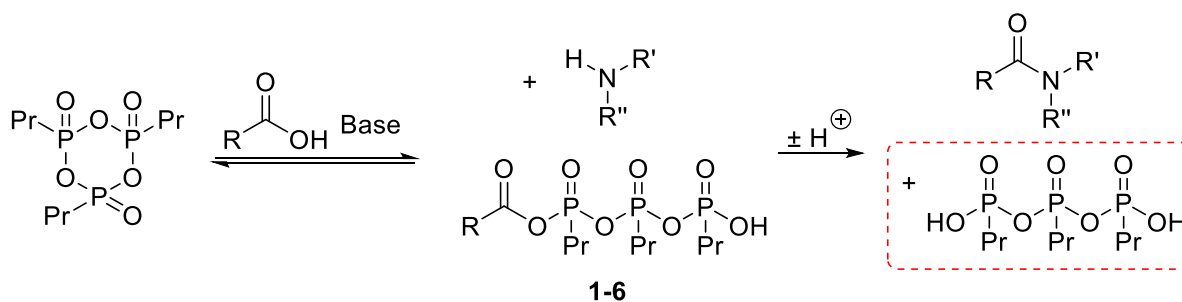
Carbodiimidazoles (CDI) and propanephosphonic acid anhydride (T3P) are the most common reagents used in mixed anhydride type couplings (Figure 1-1), which can circumvent the selectivity issue associated with using mixed anhydrides. CDI and T3P are somewhat attractive in large-scale synthesis, as both reagents are easy to handle and possess low toxicity.

CDI is cheap and available as a crystalline solid, but CDI is sensitive to atmospheric moisture and can degrade rapidly in high humidity.¹⁰ CDI reacts with the carboxylic acid to form the mixed anhydride **1-4**, which reacts with an equivalent of imidazole to yield amide **1-5** (Scheme 5). The desired amide product is formed via a *trans*-amidation reaction, assisted by the imidazole formed in the previous step.



Scheme 1-5. Amide formation using CDI via the formation of an imidazolyl amide

T3P is typically the reagent of choice for peptide bond formation and facilitates the coupling of chiral amino acids in excellent enantioselectivities. In this case, the carboxylic acid is activated by the formation of the propylphosphonate ester **1-6**. However, T3P is more expensive than CDI, and there are concerns on how to process the phosphonate by-products from an environmental perspective (Scheme 1-6).²



Scheme 1-6. Amide formation using T3P via the formation of a propylphosphonic anhydride.

1.2.3 Coupling Reagents

Carbodiimide coupling reagents are commonly employed in the modern synthesis of amides (Figure 1-2).² While they tend to be expensive and produce large amounts of waste, the reaction requires only mild reaction temperatures, tolerant of many common functional groups, and typically results in excellent yields.

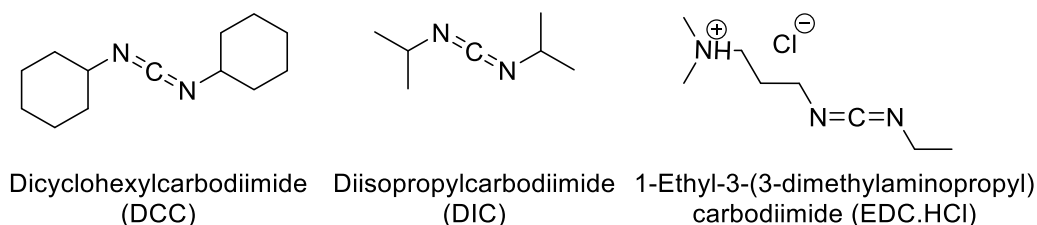
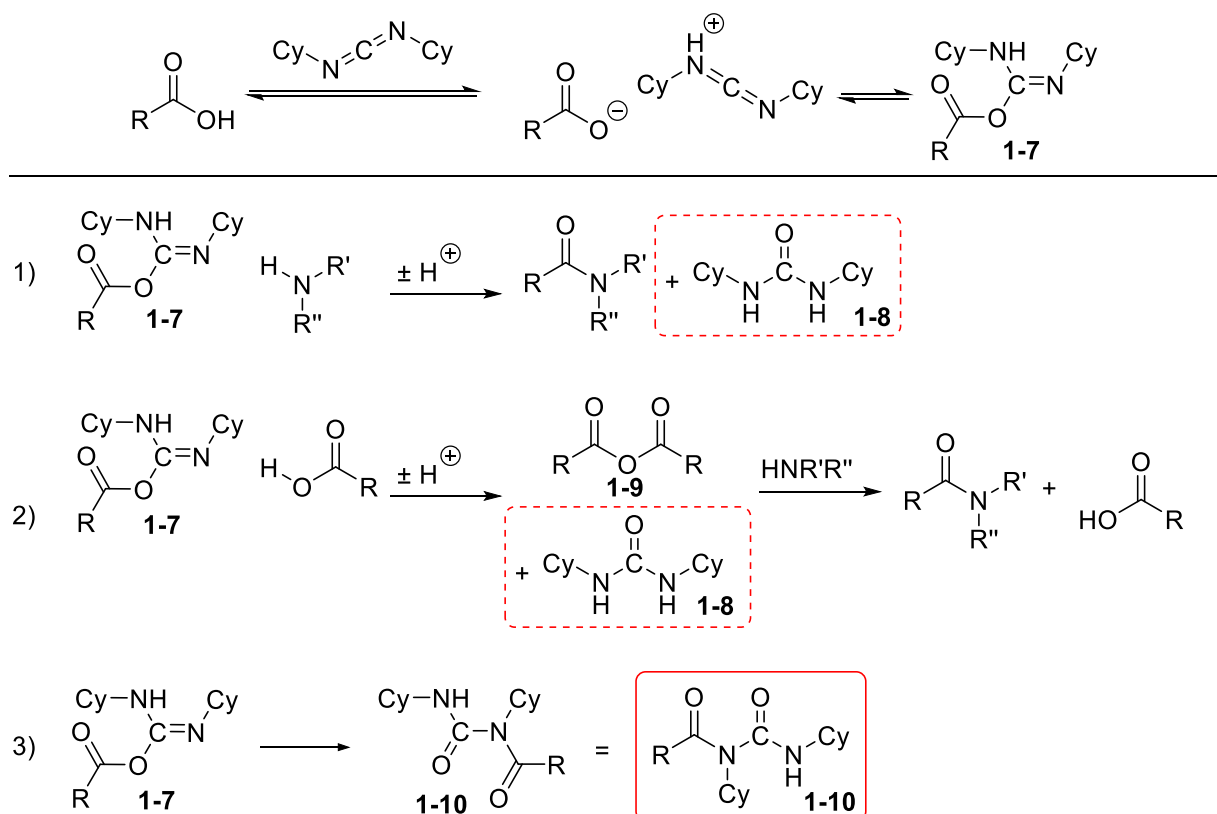


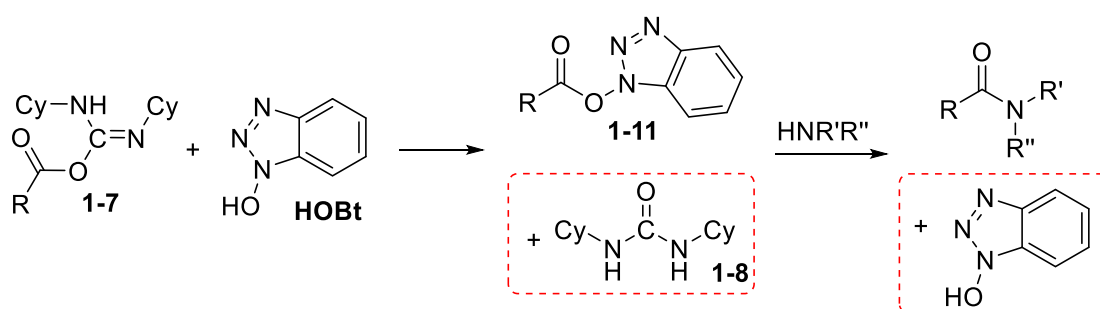
Figure 1-2. Common carbodiimide coupling reagents used for amide formation

Dicyclohexylcarbodiimide (DCC) was first reported for amide formation by Sheehan and Hess in 1955, for the synthesis of dipeptides in good yields at room temperature.¹¹ Carbodiimides facilitate amide formation in two ways (Scheme 1-7): firstly by activating the carboxylic acid toward nucleophilic attack by the formation of the intermediate **1-7**, and secondly by the formation of a stable urea by-product **1-8** that acts as a thermodynamic sink (Scheme 1-7, eqns **1** and **2**). Other carbodiimides such as DIC and EDC (Figure 1-2) are also frequently employed, the difference mainly being how the urea by-product is removed from the product stream. EDC is the most frequently encountered reagent in large-scale reactions,² as the urea by-product is water-soluble and can therefore be removed by an aqueous workup.



Scheme 1-7. Proposed reaction pathways for amide formation using carbodiimides and the formation of the N-acyl urea side product

However, in certain cases, the reactive intermediate **1-7** can undergo a competitive intramolecular rearrangement to form an N-acylated urea, **1-10** (Scheme 1-7, eqn **3**). The formation of side-product **1-10** can be avoided by the addition of HOBT, which protonates and subsequently displaces the urea, preventing the rearrangement (Scheme 1-8).



Scheme 1-8. Amide formation using DCC with additive HOBT

Uronium salts (Figure 1-3), which are derived from HOBT and HOAt, are particularly effective for coupling reactions involving sterically bulky acids and amines.¹²

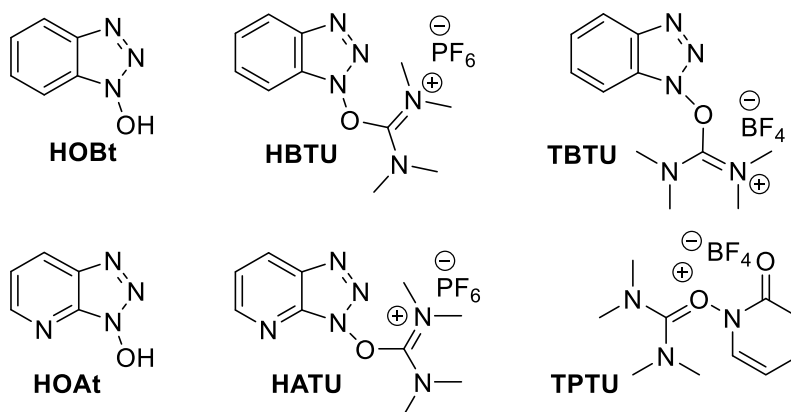
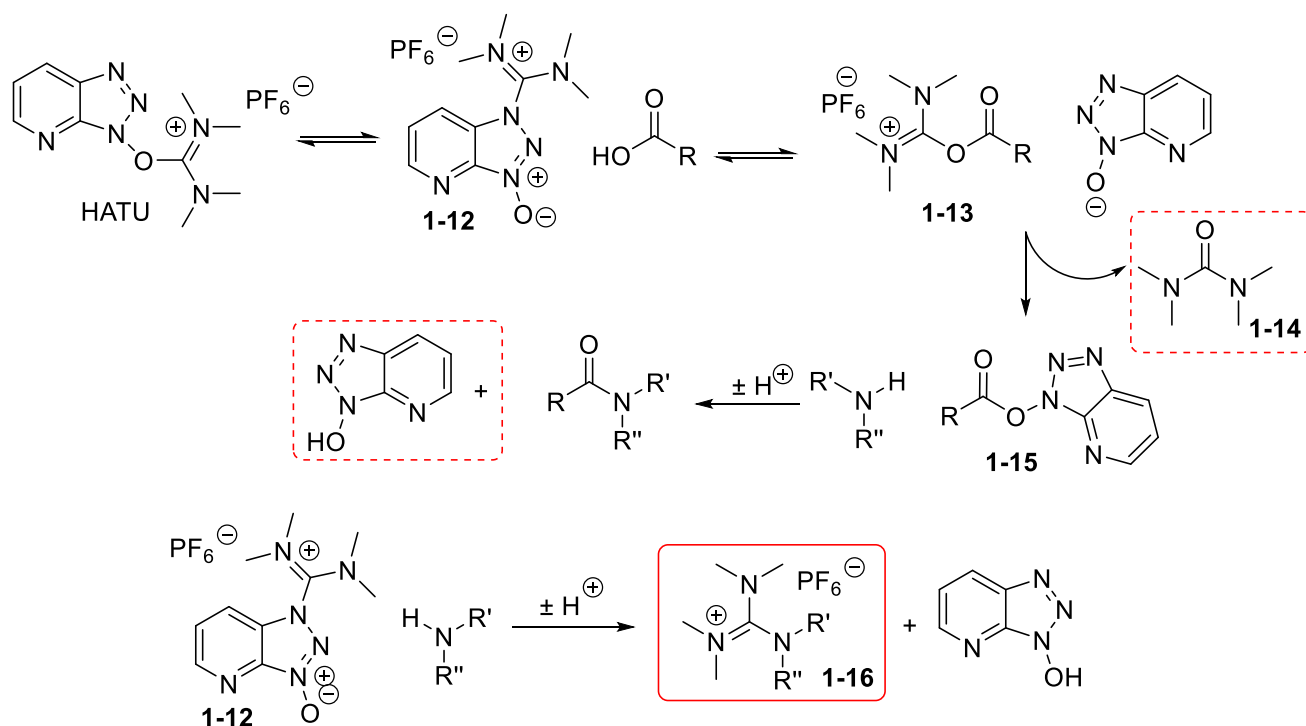


Figure 1-3. HATU and other uronium salts used in the coupling of carboxylic acids and amines

Amide formation using these reagents usually progresses rapidly, although timing the addition of the amine coupling partner is key to avoid the formation of a possible guanidinium derived side products (**1-16**) (Scheme 1-9). Uronium salts, such as HATU, are typically more expensive than other coupling reagents and their derivatives are potentially explosive, which limits their use on a process scale.¹³



Scheme 1-9. Reaction pathway for amide formation using HATU, and the formation of the guanidinium salt side product

1.2.4 Summary

Only the most commonly employed amide formation methods and reagents are presented here. While they are all capable of synthesising amides in high yields, they all share a similar limitation: They all produce stoichiometric by-products that must be removed from the product stream. Thus, their

usage requires separation procedures which incur significant operational, financial, and environmental costs.

1.3 Catalytic Amide Synthesis

The demand for amide-containing pharmaceuticals and materials is increasing. With higher demand for environmentally-friendly manufacturing processes, catalytic methodologies for amide formation with good atom-economy have become increasingly sought after. The ideal catalytic amidation reaction would proceed at low temperature using a benign solvent and would produce the minimal amount of waste.

This section will cover the developments in catalytic amide synthesis from carboxylic acids and amines. Sub-sections on organocatalysis, biocatalysis, and metal catalysis are arranged to present the key advances in each field, providing examples of both homogeneous and heterogeneous catalytic systems. The reaction of carboxylic acids and amines is presented in detail, as it is the most fundamental disconnection of the amide bond, and to highlight why this approach needs to be revised.

1.3.1 Homogeneous and Heterogeneous Catalysis

Homogeneous catalytic reactions are typically performed in the liquid phase. The structure of homogeneous catalysts is usually discreet and well-defined. The reaction pathways of homogeneously catalysed reactions can be investigated spectroscopically by employing *in situ* analytical techniques, such as NMR and IR spectroscopy, for example. In turn, this information can be used to optimise the catalytic system. The behaviour of a homogeneous catalyst can be controlled by changing its electronic and steric characteristics. A high degree of control can be further achieved by careful design/selection of additives and reaction conditions.

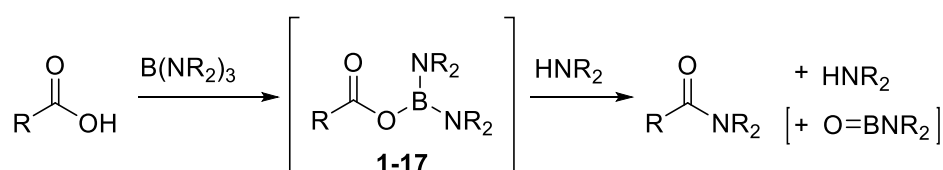
Conversely, in heterogeneous catalysis, the catalyst is often a solid material, with the reagents in either the liquid or vapour phase. The main advantage of heterogeneous catalytic processes is the ease of separation and recovery of the catalytic material, which ensures the production of high purity products and reduces costs, both in downstream processes and purchasing of catalytic materials.

Both homogeneous and heterogeneous catalysts are widely adopted in the chemical industry.¹⁴ However, heterogeneous catalysts are generally preferable to their homogeneous counterparts, particularly in large-scale production. One of the most important factors governing industrial applications is the stability of a catalyst, i.e. resistance towards deactivation and (for the heterogeneous catalyst) leaching.^{15–17}

1.3.2 Organocatalysts – Boron and Nitrogen Based Catalysts

Boronic Acids

Aryl boronic acids are among the most prominent discoveries in catalytic amidation reactions. Reported by Nelson and Pelter in 1965, the first boron catalysed amidation reaction utilised the addition of a *tris*(dialkylamino)borane species to a carboxylic acid affording the proposed boronic ester intermediate **1-17** (Scheme 1-10) with a considerable exotherm. Subsequent substitution of the boronic ester with an amine yields an amide and a stoichiometric amount of an unidentified boron-containing by-product.¹⁸



Scheme 1-10. Proposed pathway for amidation of carboxylic acids using aminoboranes

More than 30 years after the initial report, Yamamoto and co-workers reported the use of substituted aryl boronic acids as catalysts for direct amidation between carboxylic acids and amines.¹⁹ At 1 mol% loading, (3,4,5-trifluorophenyl)boronic acid (**1-18**) catalysed the direct amidation reaction of aryl, allyl, and aliphatic carboxylic acids with primary and secondary amines in refluxing hydrocarbon solvents to form acyclic and cyclic amides (Figure 1-4).

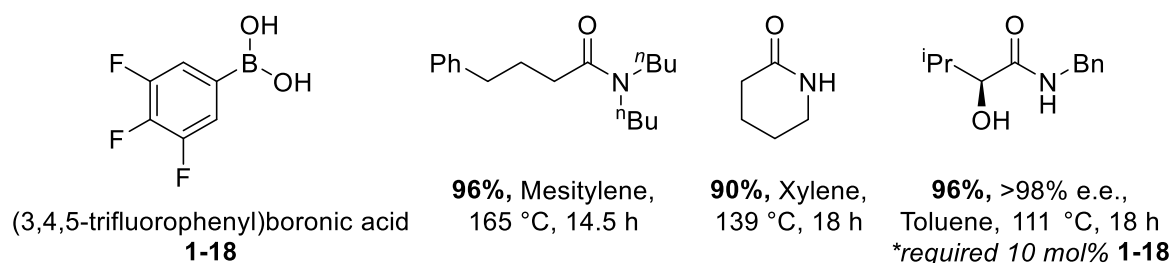
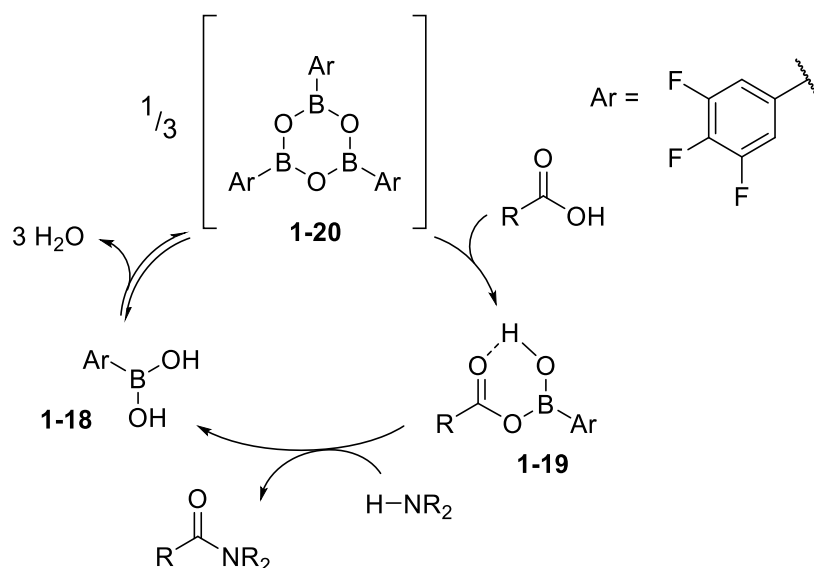


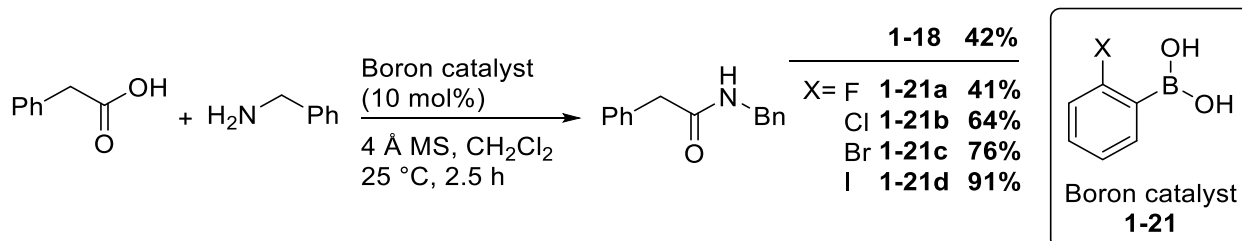
Figure 1-4. (3,4,5-Trifluorophenyl) boronic acid amidation catalyst and selected product examples

The authors proposed that the amidation reaction proceeded *via* boronic ester **1-19**, formed by the reaction of the carboxylic acid with a boronic acid trimer **1-20** (Scheme 1-11). The highly electron-deficient aryl ring of **1-18** favours the formation of trimer **1-20**, while the steric bulk provided by the aryl rings shield the intermediate ester **1-19** from nucleophilic attack, facilitating the nucleophilic attack of the carbonyl by an amine, thus regenerating the boronic acid **1-18**.²⁰



Scheme 1-11. Catalytic cycle for boron catalysed amide formation

Further developments led to the discovery that *ortho*-substituted aryl boronic acids **1-21a-d** are better catalysts, capable of effecting reactions at 25 °C (Scheme 1-12),²¹ as opposed to temperatures of >100 °C required when employing **1-18**.



Scheme 1-12. Improvement of the boronic catalysed direct amidation with *ortho*-substituted boronic acids

Greater steric influence around the boron centre was found to reduce the likelihood of the undesired substitution of the boronic ester, which results in catalyst deactivation. The introduction of an *ortho*-halide, in particular, greatly influenced reactivity; with the *ortho*-iodo compound **1-21d** being the most effective catalyst (Figure 1-5). The removal of water from the reaction (using molecular sieves) is required to achieve high conversions to the amide, by preventing the deactivation of the boron-based amidation catalyst.

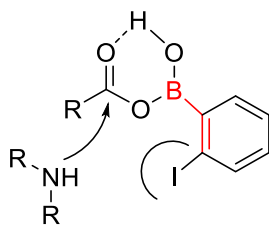
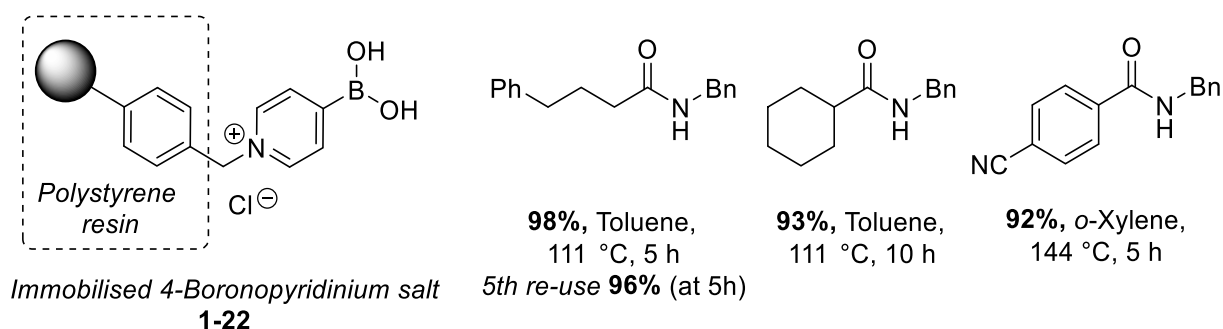


Figure 1-5. Steric bulk of ortho-substituted aryl halides influencing selectivity of boronic acid catalysed amide formation

In 2005, Yamamoto and co-workers reported a heterogeneous variant of the boron-catalysed amidation reaction (Scheme 1-13), where polystyrene-immobilised 4-boronopyridinium salts **1-22** were shown to catalyse the direct amidation of aliphatic and aryl carboxylic acids with benzylamine under azeotropic reflux. The polymer-supported boronic salts were thermally stable and could be recovered by filtration and reused at least five times without loss of activity.²² However, the need for removal of water necessitated the use of hydrocarbon solvents at elevated temperatures (>100 °C).



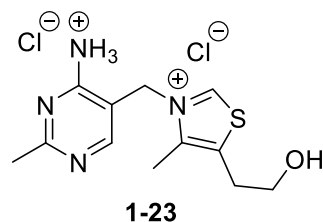
Scheme 1-13. Selected results for the polystyrene-immobilised 4-boronopyridinium salt catalysed amidation of carboxylic acids and amines under azeotropic reflux

From a process chemistry perspective, the most significant drawback to the use of boronic acid catalysts is the removal of water. On a laboratory scale, this is achieved this by azeotropic reflux (utilising a Dean-Stark apparatus) or by the addition of molecular sieves; neither can be implemented effectively in scale-up. Studies into the toxicology of boron-containing compounds have also raised concern over their safety, which has implications on their applications for pharmaceutical processes.²³⁻²⁵

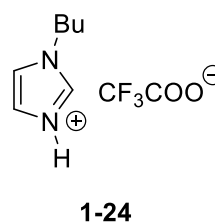
Nitrogen Based Organocatalysts

Metal-free catalytic methods of amide synthesis from carboxylic acids that are non-boron based are rarer. Methods for the formylation of amines using protonated amine heterocyclic catalysts (Figure 1-6) have been developed by Lei et al.²⁶ and Majumdar et al.²⁷, in 2010 and 2013, respectively. Reactions were performed using formic acid as the solvent at elevated temperatures (70 to 80 °C). Both reaction systems were applicable to primary and secondary amines, and good yields (>80%) were

obtained for both aryl and aliphatic amines. The process catalysed by the protic ionic liquid **1-24** required higher catalyst loadings and extended reactions times, compared to the reaction catalysed by thiamine (vitamin B₁) **1-23**.



Lei et al. (2010)
Thiamine.HCl (Vitamin B₁)
80 °C, 10 - 40 mins, 2 mol%

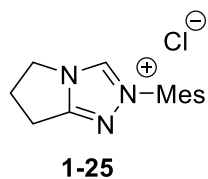


Majumdar et al. (2013)
Protic ionic liquid
70 °C, 1 - 3 h, 5 mol%

Good yields **>80%** reported in both examples for aryl and aliphatic, and 1° and 2° amines

Figure 1-6. Catalysts employed in the direct formylation of amines

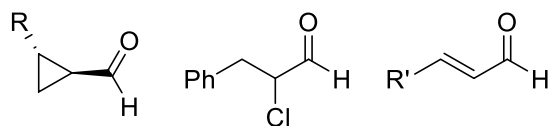
N-Heterocyclic carbene (NHC) compounds (**1-25** and **1-26**) were reported independently in 2007, by Bode and co-workers^{28,29} and by Vora and Rovis³⁰ to be active catalysts for amide formation from aldehydes and amines (Figure 1-7). These α -reducible aldehydes are considered to be 'masked' carboxylic acids. Both catalytic systems share many similarities: each system requires the addition of a base and co-catalyst to generate the active NHC, and reactions proceed under mild conditions in reasonable times. The use of these catalysts is limited to aldehydes with reducible functionalities at the α -carbonyl position, such as alkenes or carbon-halogen bonds. Nevertheless, good yields (>70%) were obtained using various amine coupling partners, except electron-poor and sterically encumbered amines, which resulted in poorer yields (40 to 60%) or required extended reaction times (12 to 15 hours).



Bode and co-workers (2007, 2009)

Standard conditions
1-25 (5 mol%)
 DBU (20 mol%)
 1.1 eq. Imidazole
 40 °C, 3 - 15 h

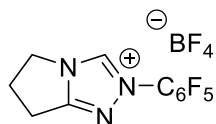
Examples of α -reducible aldehydes



R = EtO₂C, Bz, NO₂

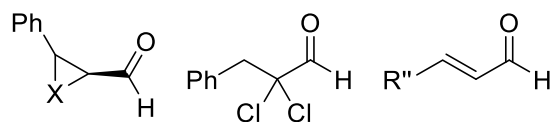
R' = Aryl or aliphatic

Yields **47 - 99%** for aryl, aliphatic, and 1° and 2° amines



Vora and Rovis (2007)

Standard conditions
1-26 (5 mol%)
 HOAt (20 mol%)
 25 °C, 6 h



X = O, NTs

R'' = Ph, CO₂Et

Yields **72 - 89%** for aryl, aliphatic, and 1° and 2° amines

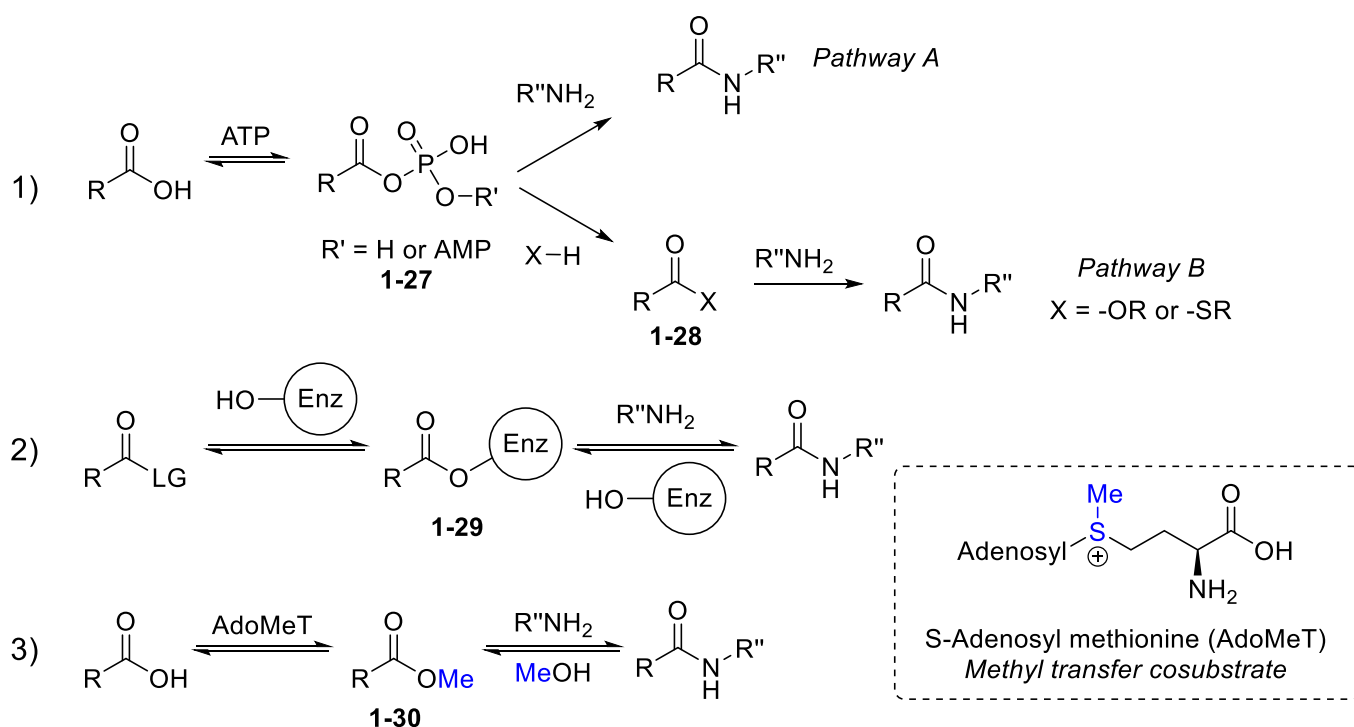
Figure 1-7. Examples of NHC catalysts for the amidation of α -reducible aldehydes and amines

1.3.3 Biocatalytic Approaches

Nature uses enzymes to catalyse the formation of amide bonds in the construction of proteins, such as collagen, antibodies, and other enzymes. Enzymes can facilitate the coupling of carboxylic acids and amines in water, at mild temperatures and producing minimal waste, making them highly desirable catalysts for 'greener' reactions.³¹

Fundamentally, biocatalytic amide bond formation proceeds in an analogous manner to the amide bond forming reactions discussed previously (section 1.2): via the activation of the carboxylic acid functionality followed by a nucleophilic attack at the activated carbonyl by an amine. A review published by Goswami and Van Lanen³² classified enzymatic amide bond formation into three general mechanisms:

- 1) Addition of sacrificial adenosine triphosphate (ATP) molecule to form an activated acyl phosphate intermediate **1-27**, followed by subsequent aminolysis (Scheme 1-14, eqn **1**, pathway A). Most acyl adenylate-forming enzymes are also known to catalyse the formation of an intermediate ester or thioester **1-28** that undergoes aminolysis (Scheme 1-14, eqn **1**, pathway B);
- 2) The reaction of the carboxylic acid with the enzyme active site to generate an acyl-enzyme complex **1-29**, followed by subsequent aminolysis (Scheme 14, eqn **2**); and
- 3) A transacylation strategy, where the carboxylic acid group is activated by S-adenosyl methionine (AdoMeT) to form a methyl ester **1-30**, which can undergo aminolysis (Scheme 14 eqn **3**).



Scheme 1-14. Summary of biocatalytic amide formation pathways

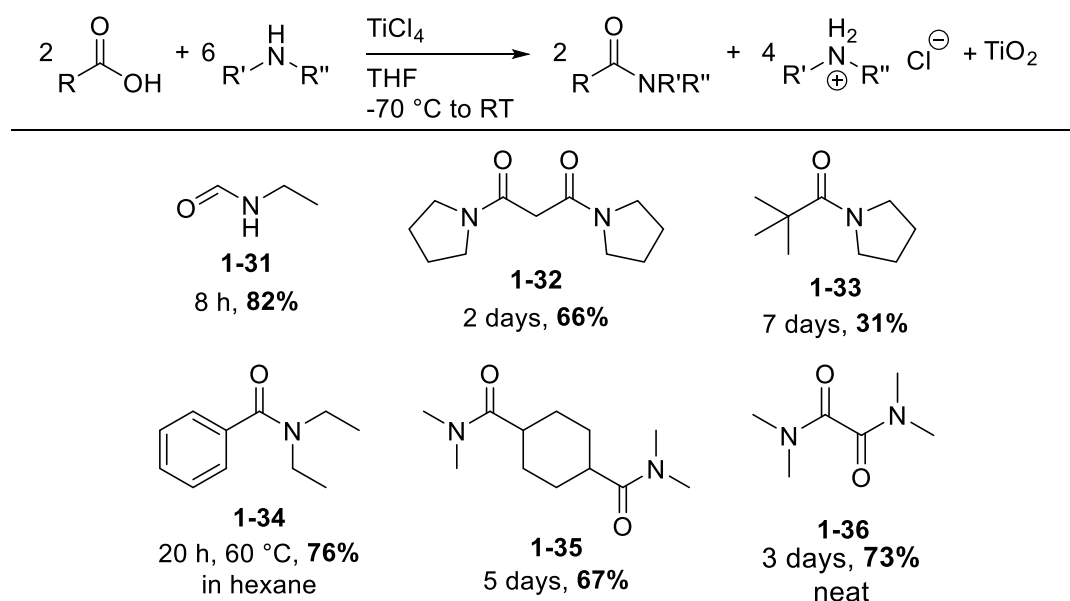
Driven by the potential for clean, energy-efficient methods for amide bond formation, biocatalysis using either wild-type (naturally occurring) enzymes or those synthesised by ‘directed evolution’ are becoming increasingly popular. Biocatalytic transformations are becoming more accessible to synthetic chemists and enzymes are increasingly being introduced in industrial processes for a variety of redox and synthetic chemical reactions.³³ Iterative ‘directed evolution’ of enzymes can be used to rationally or randomly optimise a biocatalyst for the desired chemical process.^{34,35}

However, enzymes in nature typically fulfil a specialist role, which can restrict their synthetic application. Additionally, while the mild temperatures and aqueous conditions that enzymes typically operate under are highly desirable, optimal performance of enzymes can only be achieved in a very narrow range of reaction conditions. The restrictive conditions that enzymes operate under can make the scale-up of enzymatic reactions challenging, and their intolerance to many organic solvents may eventually limit their industrial application.^{36,37}

1.3.4 Metal Catalysis

The development of metal-catalysed amide formation reactions has been surprisingly slow, perhaps due to the ubiquity of coupling reagents and the development of relatively cheap boron- and nitrogen-based catalysts.

In 1970, Wilson and Weingarten reported that stoichiometric TiCl_4 was able to affect the direct coupling of formic acid and ethylamine to form ethyl formamide **1-31** in 82% yield.³⁸ The catalytic methodology was employed for the synthesis of a handful of simple amides (**1-31** to **1-36**) but excludes the use of sterically hindered carboxylic acids or poorly nucleophilic amines, such as anilines.

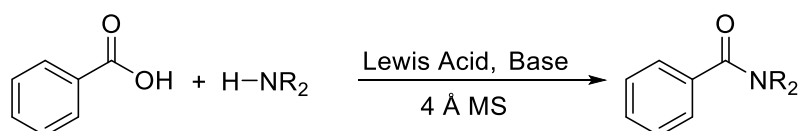


Scheme 1-15. Scope of Wilson and Weingarten's amidation with stoichiometric TiCl_4

The use of TiCl_4 requires moisture- and oxygen-free atmosphere and slow addition of the catalyst at -70°C . Despite these restrictive conditions, this result demonstrated that transition metals could be employed as catalysts for the coupling of carboxylic acids and amines.

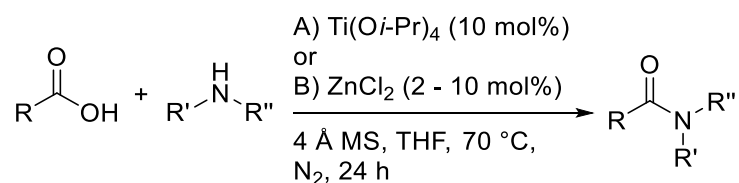
Homogeneous Metal Catalysis

Nordahl and Carson demonstrated the principle of employing Lewis acid (LA) transition metal catalyst in combination with molecular sieves for water removal. In this work, several LA's (BF_3 , TiCl_4 , AlCl_3) catalyse the formation of benzamides using 4 Å molecular sieves to drive the reaction toward completion (Scheme 1-16), though catalyst deactivation by water was not observed in the absence of the desiccant.³⁹



Scheme 1-16. Amide bond formation using a Lewis acidic metal.

After 1990, the use of transition metals for catalytic amide formation appears to have been largely overlooked by the academic community. Nevertheless, several research groups continued to demonstrate the application of early, electron rich LA metals for the amidation of carboxylic acids. Molecular sieves were often used in combination with complexes of group IV metals Ti ⁴⁰ and Zr ^{41,42} (Scheme 1-17), which were shown to have comparable activity (Table 1-1). Examples with other metal salts (Fe , Al , In , Zr , Co , Ni , Zn)⁴³ Sb ⁴⁴ have also been reported for similar oxidative amidation reactions.



Scheme 1-17. Direct amidation of carboxylic acids catalysed by either Ti or Zn

Table 1-1. Comparing the yields obtained in the direct amidation of carboxylic acids and amines catalysed by either A) Ti or B) Zn

Compound	Catalyst A Yield ^a (%)	Catalyst B Yield ^b (%)	Compound	Catalyst A Yield ^a (%)	Catalyst B Yield ^b (%)
	91	99 (2)		78 ^c	73 (10)
	81	95 (5)		X = O 96 S 97	X = O 95 (2) S 93 (5)
	75	>99 (5)		69 ^{c,d}	83 (10)
	88	>99 (2)		79	94 (5)

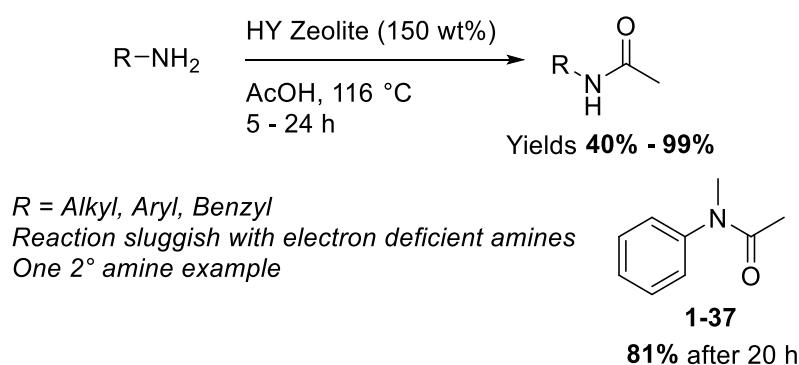
^aIsolated yield. Reaction conditions for **catalyst A**: 10 mol% Ti(Oi-Pr)₄, carboxylic acid (1.2 mmol), amine (1.0 mmol), 4 Å MS (0.5 g), THF (2.5 mL), ^bIsolated yield. Reaction conditions for **catalyst B**: ZnCl₂ (number in parenthesis is catalyst loading mol%), carboxylic acid (1.0 mmol) amine (1.2 mmol), 4 Å MS (0.5 g), THF (2.5 mL), ^c1.5 equivalents of carboxylic acid and 20 mol% Ti(Oi-Pr)₄ ^dReaction heated to 100 °C. All reactions performed in sealed reaction tubes under N₂

A recyclable metal-oxide catalyst in an ionic liquid was reported by de Oliveira and co-workers⁴⁵ using CdO or SnCl₂. The recycling of the catalytic system is achieved by extracting the product from the metal/ionic liquid using ethyl acetate or hexane, and the catalytic ionic liquid suspension was recharged with the desired reactants.

The homogeneous metal catalysed amidation reaction between carboxylic acids and amines is inherently hindered by the same problems that prevent the thermal coupling – the addition of amines to carboxylic acids typically results in the formation of a thermodynamically favourable salt, a reaction that is further facilitated by polar solvents. While metal catalysts facilitate a lower energy pathway for the formation of amide, salt formation remains a kinetically-facile process. The removal of water also remains a significant hurdle.^{39–43}

Heterogeneous Metal Catalysis

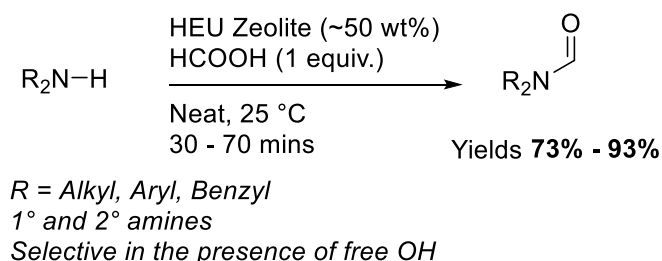
Zeolites are porous aluminosilicates with well-defined meso- and macro-pore structures known for their catalytic applications.⁴⁶ The first example of catalytic amidation using zeolites was reported by Raghavan and co-workers in 2000, where the acylation of amines was achieved in refluxing acetic acid by using zeolite HY (Scheme 1-18).⁴⁷ Despite the elevated temperatures (116 °C) and acidic conditions, the method can be applied to the acetylation of several amine substrates and was tolerant to the presence of ester groups. However, employing electron-poor amines required extended reaction times (>20 hours) and resulted in poorer amide yields (<60%).



Scheme 1-18. Catalytic acylation of amines by HY zeolite in acetic acid

Following this initial report, several groups have published further work exploiting the versatile porous aluminosilicate structure. Dopant metals inserted into the aluminosilicate structure have been shown to enhance the acylation of both alcohols and amines⁴⁸ and controlling the mesoporous structure,⁴⁹ allowing access to a greater scope of carboxylic acid coupling partners.

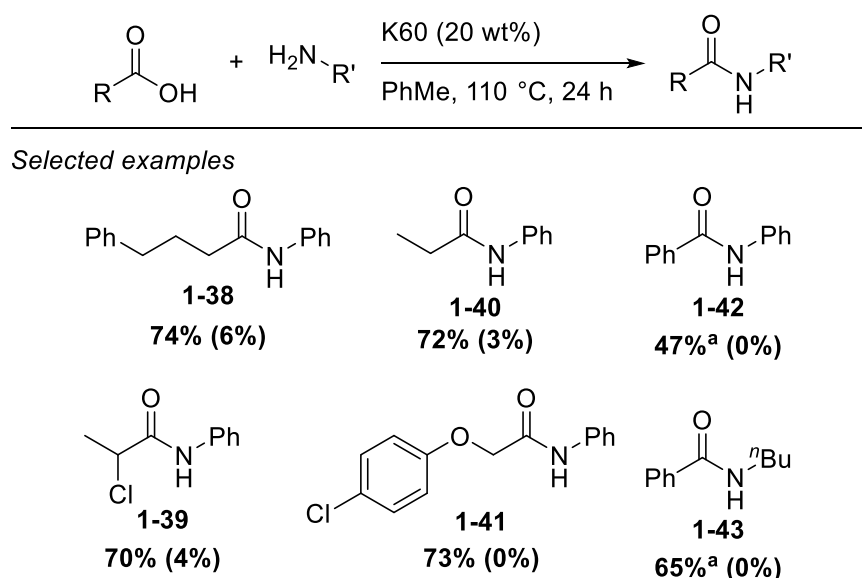
A structured HEU zeolite, with controlled pore sizes of 3.05 Å, 1.34 Å, and 3.67 Å⁵⁰ was shown to affect the selective formylation of various amines at room temperature in formic acid (Scheme 1-19).⁵¹ This increased activity of the HEU zeolite at milder conditions is remarkable, considering the HY and HEU zeolites are both silicate materials and are essentially structural isomers.



Scheme 1-19. Formylation of amines using structured HEU zeolite

Given the catalytic activity of zeolites in direct amidation reactions, it is perhaps unsurprising that the reaction can also be catalysed by silica, a substance that is readily accessible to most organic chemists.

In 2009, Comerford et al. reported the direct amidation of carboxylic acids, in refluxing toluene, catalysed by flash silica gel (Scheme 1-20).⁵² Thermal treatment of the silica is necessary to activate the surface; the authors proposed that structural changes allow the weakly acidic surface to activate the carboxylic acid without protonating the amine.



(The number in parentheses denotes the yield of the uncatalysed reaction)

Scheme 1-20. Direct amidation of carboxylic acids catalysed by silica gel

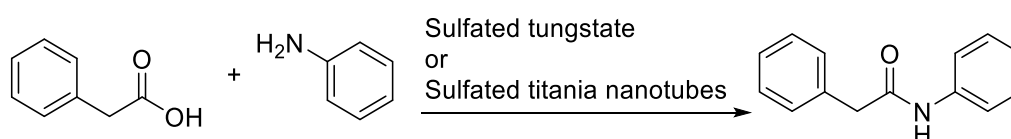
The addition of silica gel accelerated many challenging amidation reactions that do not proceed thermally at 110 °C (**1-41** to **1-43**), such as the reaction of the poorly nucleophilic aniline with 4-chlorophenoxyacetic acid **1-41**, and benzoic acid **1-42**. Further investigations demonstrated that the catalyst was tolerant of moisture. Removal of water, by molecular sieves or Dean-Stark apparatus, did not accelerate the reaction.

The silica-catalysed amidation system is a significant improvement in both scope and catalyst efficiency compared to zeolite systems; essentially facilitated by the thermal pre-treatment and structural change of the silica surface. However, the activation and regeneration of the catalyst at 700 °C is a significant energy cost that should be considered alongside its favourable E-factor (1.1) and atom economy (typically >90%). Each catalytic material: HY, HEU, and silica are different forms of silicon oxide; the variety of reaction conditions and scope of the amidation reaction with these different types of silica highlights the importance of the porous structure and surface of solid catalytic materials.

A similar thermal activation effect was reported later by Ghosh et al., investigating the direct amidation of carboxylic acids using 'activated alumina balls' (AABs).⁵³ The most significant

improvement in the AAB system over silica is that similar activities could be achieved by thermal activation at 400 °C. However, AAB-catalysed amidation was performed without solvents at 140 °C, at which point the background thermal reaction is likely to be a significant contributor.⁵⁴

Enhancing the catalytic properties of a metal oxide by controlling the composition or porous structure is not a trait unique to zeolites. Sulfated tungsten oxide (S-WOx) (Chaudhari et al., 2010)⁵⁵ and nanostructured sulfated titania (NS-TiO₂) (Nagarajan et al. 2012)⁵⁶ structures have both been shown to accelerate the amidation of carboxylic acids and amines (Scheme 1-21, Table 1-2).



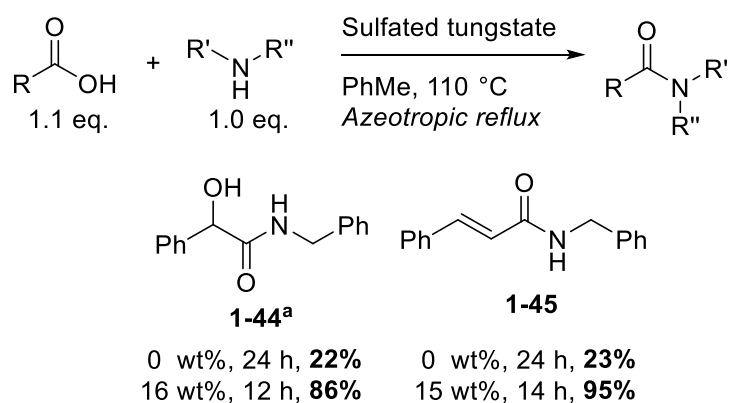
Scheme 1-21. Direct amidation of phenylacetic acid and aniline catalysed by either sulfated tungstate or sulfated titania nanotubes

Table 1-2. Comparison of the reported yields obtained for the catalysed and thermal background amidation and catalysed amidation of phenylacetic acid and aniline

Entry	Catalyst (loading wt%) and reaction conditions	Scale ^a (mmol)	Yield ^b (%)	Uncatalysed reaction ^c (%)
1	Sulfated tungstate (15 wt%) 12 h, PhMe, 110 °C	Not reported ^d	96	24 ^e
2	Sulfated titania nanotubes (24 wt%) 30 mins, neat, 110 °C	1.4	77	45

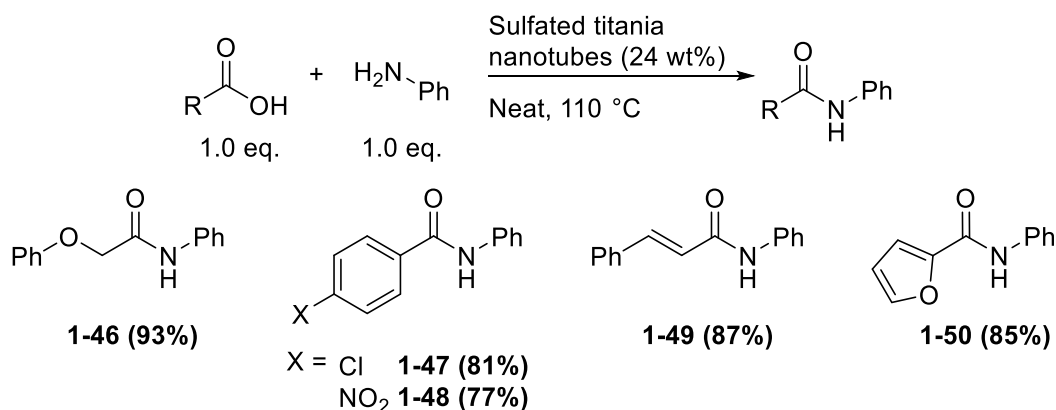
^ammol of aniline added ^bReported isolated yield ^cReported (uncatalyzed) thermal amidation ^dScale for the amidation reaction of phenylacetic acid and aniline was not reported; however, the general procedure reports a scale of 14.9 mmol ^eUncatalysed amide formation after 24 h

The reported scope for S-WOx catalysed amidation is limited to aryl and aliphatic acids and amines that lack functional group diversity, except for a free hydroxyl group **1-44** and an olefin **1-45** (Scheme 1-22).



Scheme 1-22. Functionalised substrates reported in the direct amidation reaction catalysed by S-WOx
^aReaction was performed under azeotropic reflux in xylene at 140 °C

The substrate scope for NS-TiO₂ is also restricted; the authors report the use of aniline, para-toluidine, and meta-toluidine as the only amine coupling partners (Scheme 1-22). Although there is a more diverse pool of functional groups including ethers **1-46**, substituted aryls **1-47** and **1-48**, and an olefin **1-49**, present in the carboxylic acid substrate. The poor functional diversity reported for both catalytic systems could be a result of either the harsh reaction temperatures.



Scheme 1-23. Functionalised substrates reported in the direct amidation reaction catalysed by NS-TiO₂

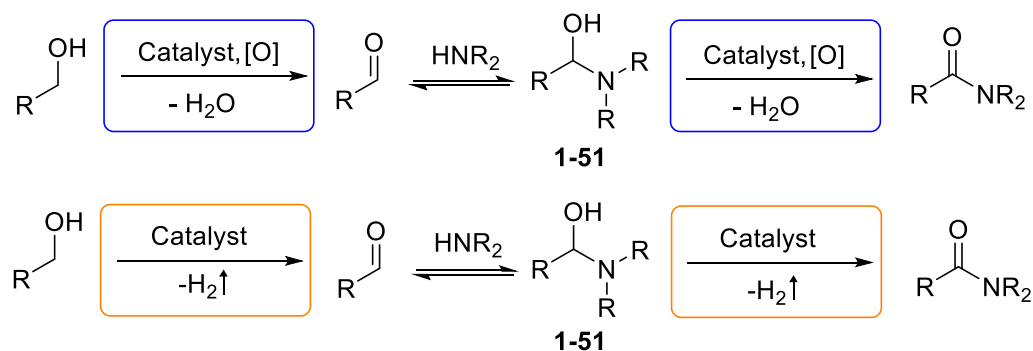
Both S-WOx and NS-TiO₂ are described as ‘sulfated’, but Chaudhari et al. proposed that the enhanced activity of the S-WOx material is due to a reduction in the Brønsted acidity of the catalyst surface.⁵⁵ Controlling the surface pH of the sulfated material facilitates the activation of the carboxylic acid without protonating the amine, that would prevent the nucleophilic attack. Nagarajan et al., on the other hand, attributed the enhanced activity of NS-TiO₂ to an increased surface area.⁵⁶ The enhancement of the catalytic activity is likely to be a combination of factors (surface area and acidity changes), but these examples reiterate the difficulty in quantifying the relative contributing factors in heterogeneous catalysis.

The underlying principle of effective heterogeneous catalysts for direct amide formation from carboxylic acids and amines is the same as the homogeneously catalysed process, i.e. hard, oxyphilic transition metal oxides and elevated temperatures are needed to activate the carbonyl towards direct amine substitution. Heterogeneous-catalysed amidation systems suffer the same pitfalls as their homogeneous counterparts, in that the reaction must overcome the high enthalpic barrier of salt formation that requires the use of excessive temperatures. While not addressed in most reports, the removal of water would also be of concern, especially for scale-up. The desiccant properties of metal oxides are well established,⁵⁷ and reuse of the catalyst would require thermal treatments to dehydrate the surface.

1.4 Catalytic Oxidative Amidation

One of the most straightforward ways to overcome the limitation of carboxylic acid-amine salt formation is to avoid the direct use of carboxylic acids as a precursor. The oxidative amidation of alcohols or aldehydes is a desirable alternative that is highly atom-efficient.

Oxidative amidation from alcohols requires two formal oxidations: Firstly, the oxidation of an alcohol to an aldehyde, followed by the oxidation of a hemiaminal type intermediate **1-51** to yield an amide (Scheme 1-24).

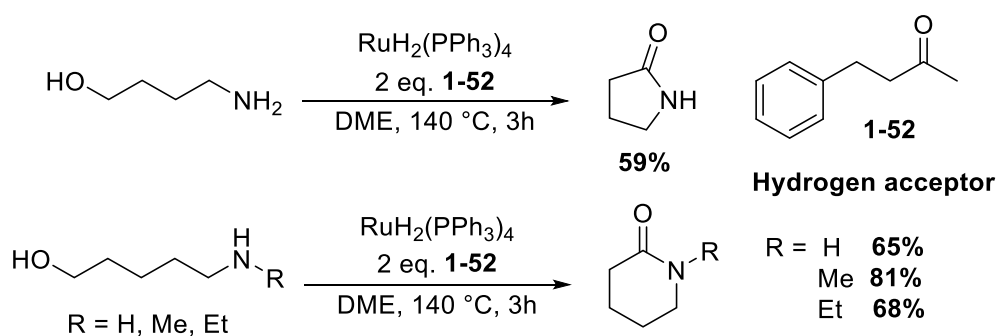


Scheme 1-24. Possible approaches to oxidative amide bond formation

The challenge of this approach is how to achieve the oxidation(s) in a selective and atom-economical way, either by using a H-acceptor (oxidative) or by the liberation of H₂ (dehydrogenative) - both pathways are desirable for the catalytic amidation of both alcohols and aldehydes.

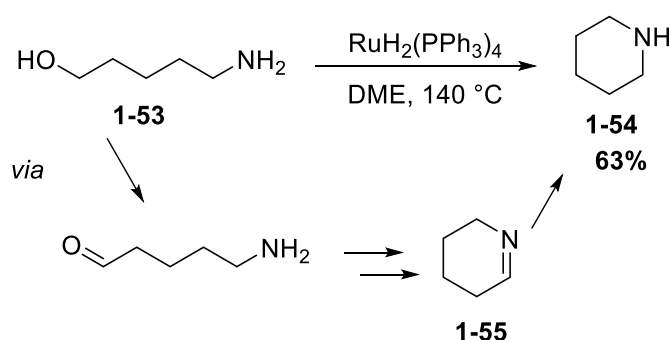
1.4.1 Dehydrogenative Amidation

The first catalytic oxidative amidation reaction between an alcohol and an amine was reported by Naota and Murahashi in 1991 using $[\text{RuH}_2(\text{PPh}_3)_4]$ to catalyse the intramolecular oxidative amidation of linear amino alcohols to lactams at elevated temperatures (Scheme 1-25).⁵⁸ Two equivalents of the ketone **1-52** were used as a hydrogen-acceptor in the cyclisation of four amino alcohols to the corresponding 5- and 6-membered lactams with moderate yields of between 59 – 81%.



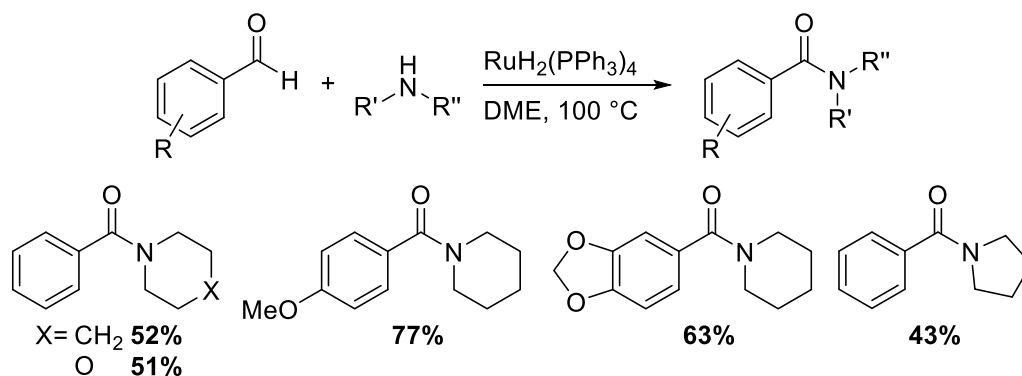
*Scheme 1-25. First examples of Ru catalysed amide formation by dehydrogenation using a hydrogen acceptor **1-52***

The authors proposed that the role of **1-52** is to accelerate the regeneration of the Ru catalyst and prevent the formation of the amine. In the absence of hydrogen acceptor, the Ru-catalysed oxidation of 5-aminopentan-1-ol **1-53** led exclusively to the formation of piperidine **1-54** (Scheme 1-26), which is formed via the hydrogenation of the corresponding cyclic imine **1-55**. Based on this, it was proposed that the reaction proceeds through a dehydrogenative pathway, by the loss of 2 equivalents of H_2 .



*Scheme 1-26. Ru catalysed cyclisation of **1-53** without the addition of a hydrogen acceptor*

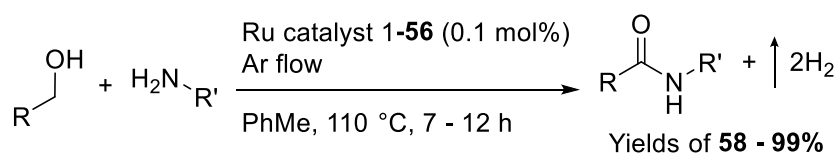
Using the same $\text{RuH}_2(\text{PPh}_3)_4$ catalyst, five examples of amide formation from benzylic aldehydes were also reported. In the absence of a H-acceptor, the reaction of secondary cyclic amines afforded the corresponding tertiary amides in moderate yields of 43 – 77% (Scheme 1-27).



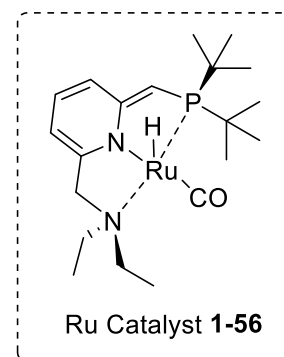
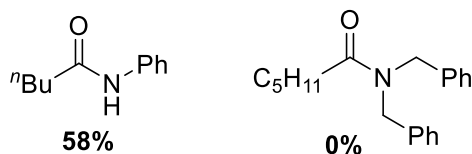
Scheme 1-27. Ru catalysed dehydrogenative amide synthesis without employing a hydrogen acceptor

The first intermolecular example of the dehydrogenative amidation reaction from alcohols and amines was reported in 2007 by Milstein and co-workers.⁵⁹ The authors reported a Ru catalyst containing pincer ligand **1-56** (Scheme 1-28) that facilitated the oxidation of both alcohols **1-57** and hemiaminals **1-58**. It was proposed that the addition and oxidation of carbinol species (**1-57/1-58**) lead to the formation of Ru dihydride complex **1-59**, and the catalyst regenerated by the elimination of H₂ (Scheme 1-29).

Milstein and co-workers (2007)

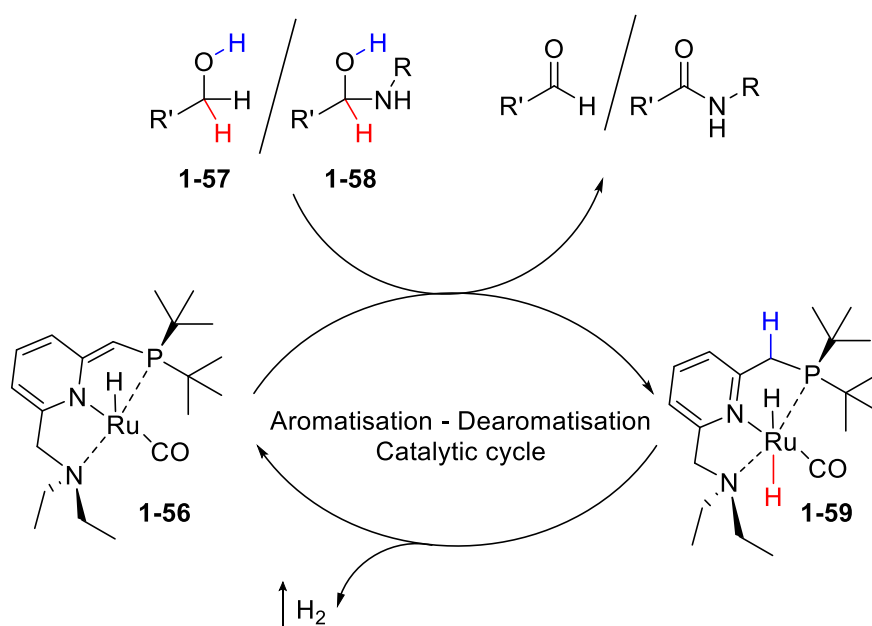


*Limited scope - restricted to linear aliphatic alcohols.
Only 1° amines reported, and poor yield obtained with aniline*



Scheme 1-28. Dehydrogenative amidation of alcohols catalysed by a Ru catalyst containing a pincer ligand

In an earlier publication on the esterification of primary alcohols,⁶⁰ Milstein and co-workers demonstrated the aromatisation/dearomatisation catalytic cycle using NMR experiments. Addition of excess H₂ to a solution Ru complex **1-56** yielded the aromatic Ru complex **1-59**, and upon standing at ambient conditions, the aromatic complex **1-59** slowly eliminated H₂ to regenerate the dearomatised Ru complex **1-56**. Based on this, a similar dehydrogenative pathway was proposed for the catalytic amidation reactions (Scheme 1-29).



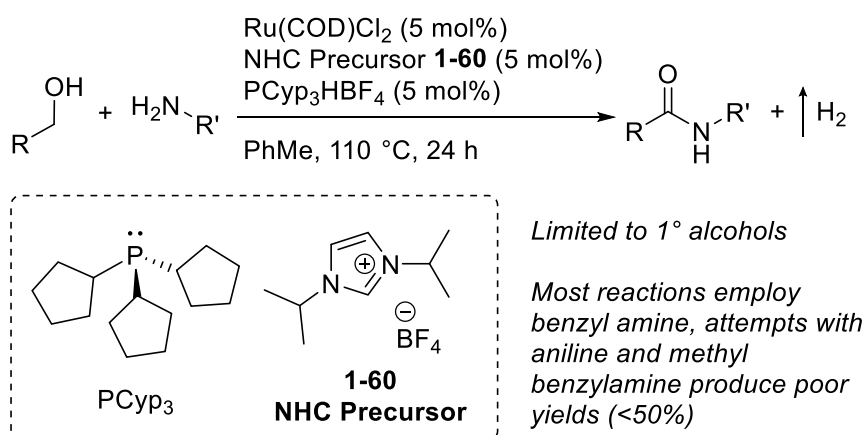
Scheme 1-29. Dehydrogenative mechanism for the Ru-pincer complex catalysed amide formation from alcohols

Due to the sterically hindered nature of the Ru pincer complex, the dehydrogenative amidation reaction was only effective with primary amines, while poorer yields were obtained with electron-deficient amines, such as aniline. For the same reasons, the methodology is also limited to linear aliphatic alcohols

In subsequent years since Milstein's report, several reports have emerged of different Ru catalytic systems with expanded substrate scope. Madsen and co-workers published an alternative Ru catalyst **1-60** containing N-heterocyclic carbene (NHC) and phosphine PCyp₃ ligands (Scheme 1-30).⁶¹ The isopropyl-substituted NHC **1-60** was selected as the top-performing ligand from eight candidates containing different N-substituents.⁶²

There is little improvement in the reaction conditions compared to the previous report of Ru catalysts: similar reaction temperatures, longer reaction times and a comparatively high catalyst loading (5 mol%, compared to 0.1 mol% reported by Milstein) were needed. Nevertheless, an expanded scope of the alcohol substrate is reported; notably, including a terminal alkene that is reduced during the reaction. However, all reported examples are still limited to primary amines, apart from a single attempt employing methyl benzylamine, that produced a modest yield of 40% at elevated reaction temperature (163 °C).

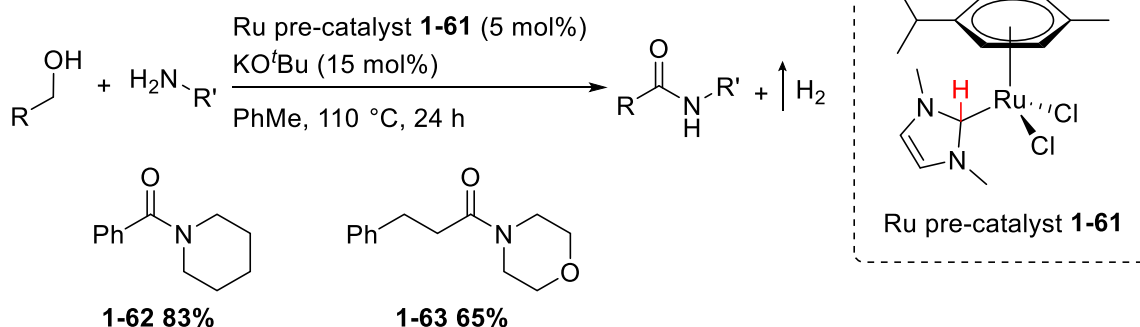
Madsen and co-workers (2008)



Scheme 1-30. Dehydrogenative amidation of alcohols catalysed by a Ru-NHC-phosphine catalyst

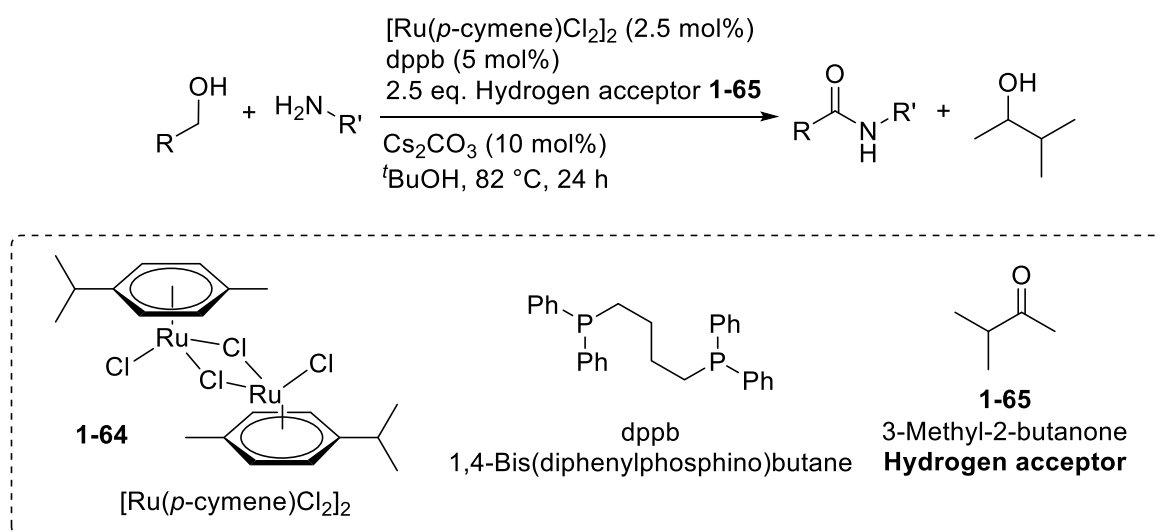
A similar attempt to optimise an NHC-Ru complex for dehydrogenative amidation reactions was reported by Hong and co-workers, using a Ru-NHC pre-catalyst **1-61** that is deprotonated to form the active complex in solution (Scheme 1-31). This system can be used to prepare amides from secondary cyclic amines **1-62** and **1-63** in reasonable yields but still requires a high catalyst loading.⁶³

Hong and co-workers (2010)



Scheme 1-31. Dehydrogenative amidation of alcohols catalysed by a Ru-NHC catalyst

In 2011, Williams and co-workers reported another variant of the Ru catalysed dehydrogenative amidation using a commercially available complex, $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ **1-64**, and diphosphine 1,4-bis(diphenylphosphino)butane (dppb) as a ligand (Scheme 1-32).⁶⁴ The use of sacrificial 3-methyl-2-butanone **1-65** as a hydrogen acceptor facilitated higher yields of amides at reduced reaction temperatures of 82 °C. However, the system does not enhance reactions utilising hindered amines, and requires 5 mol% catalyst loading.

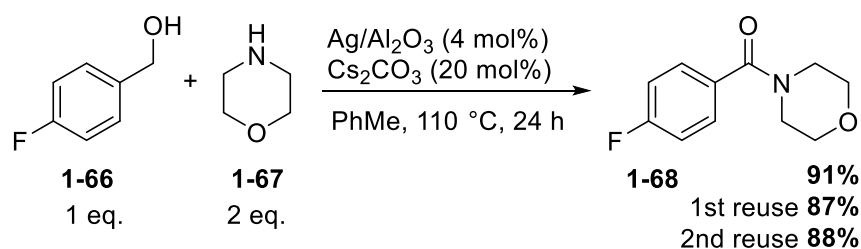


Scheme 1-32. Dehydrogenative amidation of alcohols catalysed by a Ru catalyst with a chelating diphosphine ligand

Further examples of dehydrogenative amide synthesis have reported by several groups using different ligand systems,⁶⁵ and different catalytic metal centres, such as Re,⁶⁶ Fe,⁶⁷ and Mn.⁶⁸ However, to date, there have been no reports of homogeneous dehydrogenative catalyst systems for amide formation that significantly enhance the scope or reduce the reaction temperature without the addition of a sacrificial hydrogen acceptor.

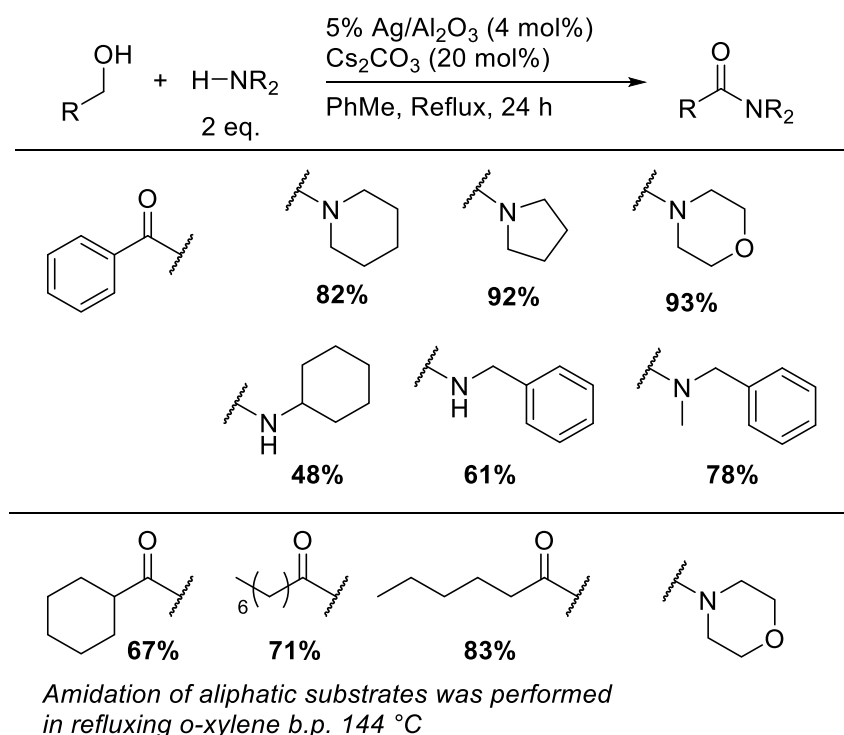
To date, there has been only one reported example of a heterogeneous Ru catalyst for the dehydrogenative amidation reaction, which is surprising, given that immobilised Ru pincer complexes have been reported for esterification.⁶⁹ In the example, RuNPs supported on either carbon or alumina were employed for the dehydrogenative amidation reaction of 2-phenylethanol and benzylamine, but poor yields of 19% and 15% respectively were obtained for each catalyst.⁷⁰

In 2009, Satsuma and co-workers investigated the use of several transition metal nanoparticles as heterogeneous catalysts for dehydrogenative amidation of alcohols.⁷¹ Initial catalyst screening found Ag/Al₂O₃ to be the most effective for the oxidative coupling between para-fluorobenzyl alcohol **1-66** and morpholine **1-67** (Scheme 1-33).



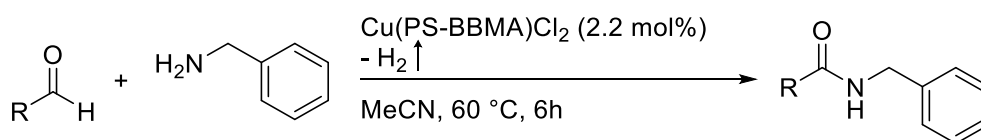
*Scheme 1-33. Ag/Al₂O₃ catalysed dehydrogenative amidation between para-fluorobenzyl alcohol **1-66** and morpholine **1-67***

The authors reported that the reaction proceeds with a stoichiometric production of H₂ gas, which was quantified using a GC equipped with a thermal conductivity detector (TCD). Removal of the Ag catalyst midway through the reaction prevented further amide formation, establishing that there was no leaching of active Ag species into the liquid phase. Good to excellent amide yields were obtained for the coupling of both benzylic and aliphatic alcohols with benzylic and aliphatic amines (Scheme 1-34), including secondary amines, which are challenging substrates for the homogeneous Ru catalysts. The supported silver catalyst could be easily recovered by filtration and reused at least twice without loss of activity.



Scheme 1-34. Heterogeneously catalysed dehydrogenative amide formation from alcohols

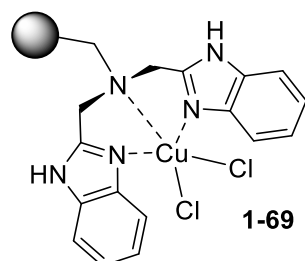
Polymer-supported Cu complex **1-69** was reported to catalyse the dehydrogenative amidation of aliphatic aldehydes, and both electron-rich and electron-poor benzylic aldehydes. However, only benzylamine was employed as the amine substrate (Scheme 1-34).⁷²



R = Aryl and aliphatic

Performs equally well with electron rich and electron poor aldehydes

Reported examples are all couplings with benzylamine



Cu(PS-BBMA)Cl₂

2.3 wt% Cu

Prepared in 2 steps
using CuCl₂·2H₂O

 Polystyrene bead

Scheme 1-35. Polymer support Cu-catalysed dehydrogenative formation of amides from aldehydes

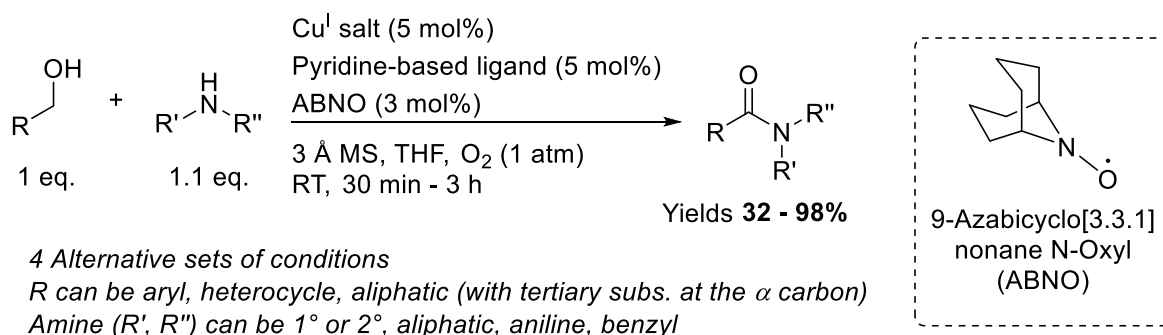
The authors excluded the leaching of catalytically active Cu species by a hot filtration test. It was proposed that the reaction proceeded via a dehydrogenative mechanism on the basis that the addition of *tert*-butyl hydroperoxide (TBHP) did not lead to any improvement.

The formation of amides from alcohols via the extrusion of H₂ is an exciting area of research, due to its near-perfect atom efficiency. However, most reports of metal-catalysed dehydrogenative amide synthesis suffer similar limitations. Notably, the amidation of secondary amines remains a significant challenge; and yields obtained with benzyl alcohols are typically lower than aliphatic alcohols, presumably due to the competitive oxidation to benzoic acid derivatives. Most authors reported that the catalysed dehydrogenative amidation required long reaction times (>24 hours) and elevated temperatures (> 80 °C), due to the thermodynamic challenge of cleaving C-H bonds.

In contrast, the heterogeneous catalyst systems were reported to proceed under similar reaction conditions, with the added benefit of catalyst recovery and reuse. However, despite the broader scope in amine substrates, a lower selectivity was obtained employing heterogeneous catalysts compared to homogeneous Ru systems.

1.4.2 Oxidative Amidation using Stoichiometric Oxidants

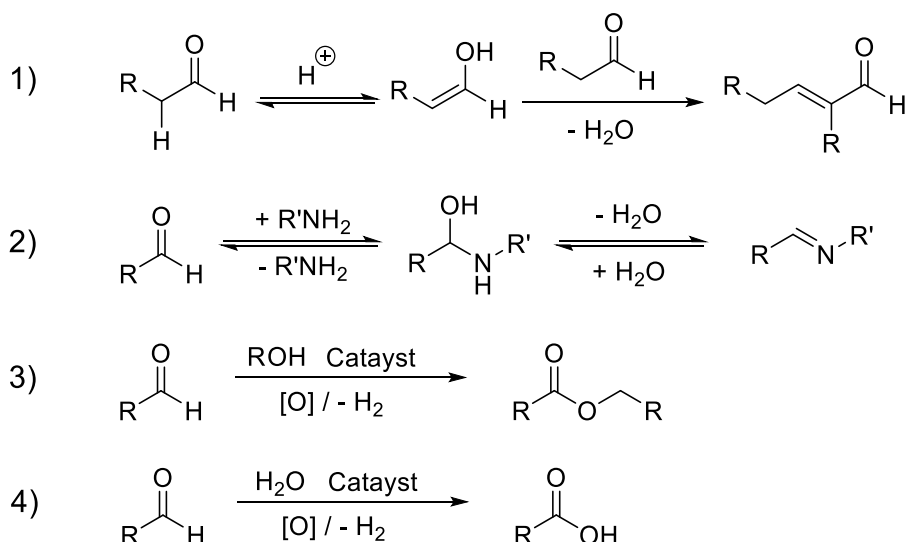
Despite the prevalence of catalysed dehydrogenative amidation methods for alcohols and amines, to the best of our knowledge, there is a single report for the equivalent reaction utilising a terminal oxidant. Stahl and co-workers reported a Cu-catalysed system utilising O₂ as the terminal oxidant (Scheme 1-36).⁷³ The system employs ABNO as a co-catalyst. The role of ABNO was described in a previous publication by the same group,⁷⁴ who proposed that the stable free radical facilitates the formation of active Cu^{II}-OH species from the Cu^I salt.



Scheme 1-36. Cu^I/ABNO catalysed oxidative amidation of alcohols and amines using O₂ as the terminal oxidant

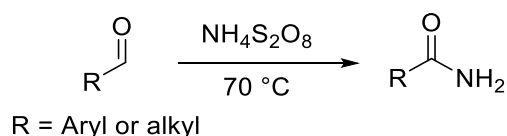
The authors reported four sets of reaction conditions for the Cu-catalysed oxidative amidation reaction, which exhibited an excellent substrate scope without the steric limitations that tend to persist in the dehydrogenative methods discussed previously. Aryl, allyl, and aliphatic alcohols are all tolerated, and the system is compatible with both primary and secondary amines, and good yields (>70%) were obtained even when electron-poor anilines are employed. However, the addition of 3 Å molecular sieves is required to remove water from the system.

Despite the limited number of reports for the oxidative amidation reaction of alcohols utilising stoichiometric oxidants, there are many reports for the oxidative amidation of aldehydes and amines. The oxidative addition of amines to alcohols necessitates the formation of an aldehyde intermediate. Yet, aldehydes are notoriously reactive species, and many of the systems reported for the oxidative amidation of alcohols rely on a low steady-state concentration of aldehyde to prevent competitive side reactions, such as aldol condensations (Scheme 1-37, eqn **1**), imine formation (eqn **2**), and the oxidative formation of esters (eqn **3**) and acids (eqn **4**). Hence, the direct formation of amides from aldehydes presents unique chemoselectivity problems.



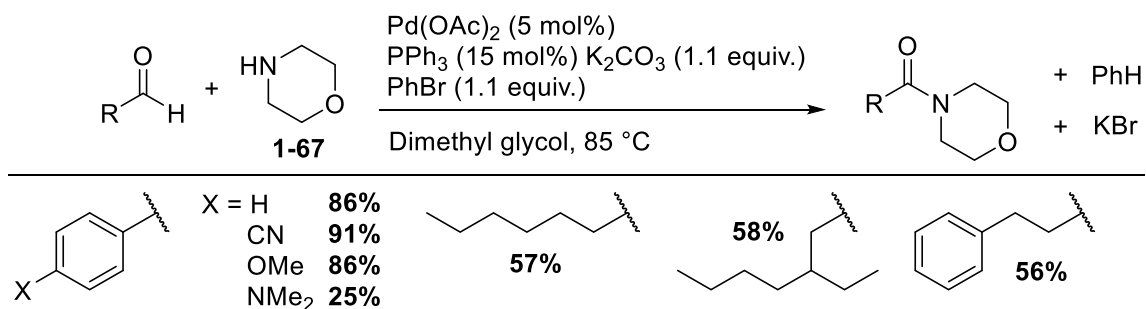
Scheme 1-37. Possible side reactions in the oxidative amidation of aldehydes

The oxidative addition of ammonia to aliphatic and benzylic aldehydes without a catalyst was reported as early as 1901, using $\text{NH}_4\text{S}_2\text{O}_8$ as a stoichiometric oxidant (Scheme 1-38).⁷⁵ The reaction required rigorous temperature control to avoid a ‘violent’ side reaction, highlighting the hazardous nature of using the highly reactive oxidant.



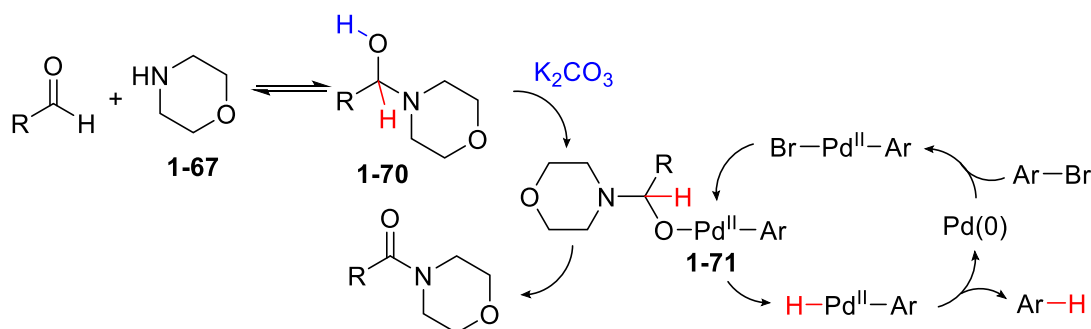
Scheme 1-38. Oxidative synthesis of primary amides from aldehydes and $\text{NH}_4\text{S}_2\text{O}_8$

The first catalytic example of oxidative amidation of aldehydes, avoiding the use of highly energetic oxidants, was reported by Yoshida and co-workers in 1983, where a palladium catalyst was employed in the presence of a sacrificial aryl bromide.⁷⁶ The catalytic system required elevated temperatures and prolonged (24 h) reaction times. A reasonable scope in aldehydes was demonstrated, but only morpholine **1-67** was utilised as a coupling partner (Scheme 1-39).



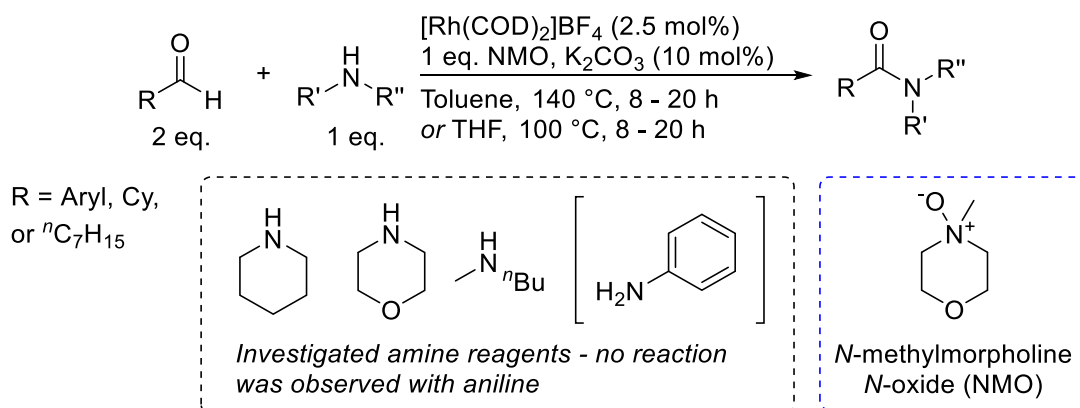
Scheme 1-39. Palladium catalysed oxidative amidation of aldehydes using a sacrificial aryl bromide

The authors proposed that the reaction proceeds via the reversible formation of a hemiaminal **1-70** that is subsequently oxidised via a β -hydride elimination of the Pd(II) intermediate **1-71** (Scheme 1-40). The reduced yield obtained for the amidation of *para*-dimethylaminobenzaldehyde is attributed to the sluggish formation of the hemiaminal intermediate **1-70** due to the increased negative charge around the aldehyde carbon.



Scheme 1-40. Proposed catalytic cycle for the palladium catalysed oxidative amidation of aldehydes

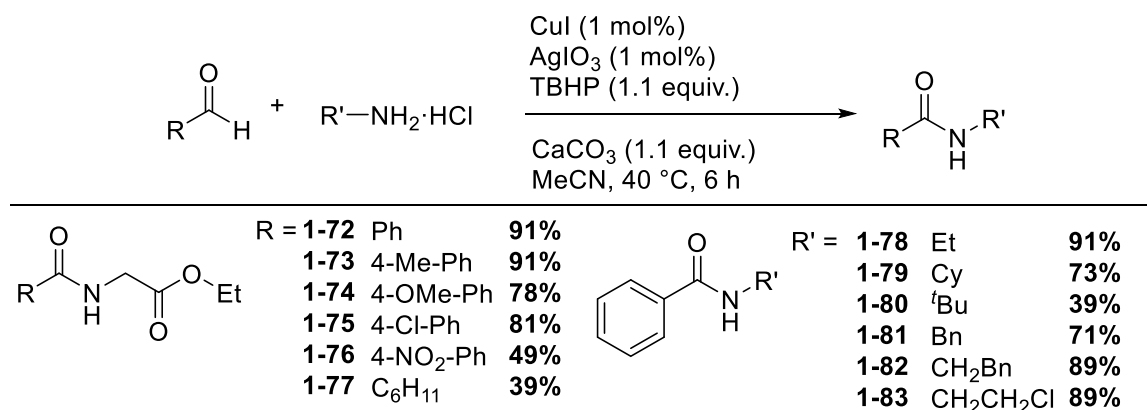
In 2001, Beller and co-workers reported a Rh-catalysed oxidative amidation using *N*-methylmorpholine *N*-oxide (NMO) as the terminal oxidant (Scheme 1-41).⁷⁷ The authors demonstrated an expanded scope of both aldehyde and amine compared to the Pd-catalysed amidation. Notably, compared to the Ru catalysed oxidative amidation of alcohols, the oxidative amidation of aldehydes tend to favour secondary amine substrates, likely due to the competing imine formation that can occur between primary amines and aldehydes.



Scheme 1-41. Rh catalysed oxidative amidation of aldehydes using NMO as the terminal oxidant

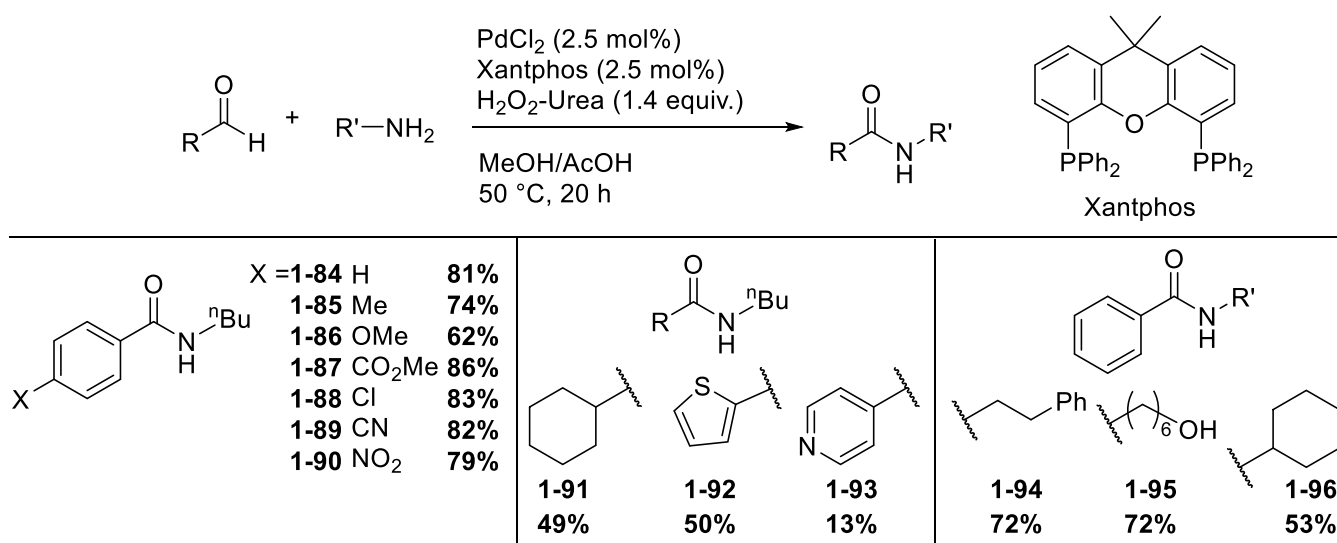
Subsequently, Yoo and Li reported a bimetallic Cu/Ag catalytic system that employed TBHP as the terminal oxidant (Scheme 1-42).⁷⁸ The reaction was performed using amine hydrochloride salts, thus requiring the addition of a stoichiometric base. Reactions of many benzylic aldehydes **1-72** to **1-75** proceeded with good yields, but electron-poor substrates **1-76** and **1-77** performed poorly. Increasing steric encumbrance of the amine reagent **1-78** to **1-80** also reduced the yield of the amide. Notably,

the system worked well for the oxidative amidation of benzaldehyde and benzylamine **1-81**, despite the potential for the formation of a stabilised imine. The improved scope and lower catalytic loading using cheaper metals is a notable improvement over Pd and Ru systems, although the system has limited application to aliphatic aldehydes or bulky amines.



Scheme 1-42. Cu/Ag catalysed oxidative amidation of aldehydes using TBHP

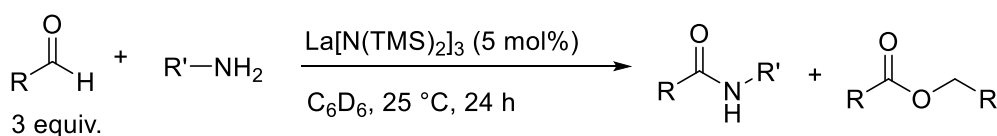
Torisawa and co-workers reported the oxidative amidation reactions of aryl aldehydes and cyclohexylcarboxaldehyde using PdCl₂, Xantphos and a stoichiometric amount of H₂O₂-urea; achieving good yields for benzylic aldehyde substrates (Scheme 1-43).⁷⁹ The catalytic system produced marginal improvements in the amidation of aliphatic and electron-poor aldehydes (**1-88** to **1-93**) compared to the Cu/Ag amidation system above. Employing aliphatic amines (**1-94** to **1-96**) resulted in average yields. On the other hand, the reaction of an amino alcohol (**1-95**), demonstrated preference for the amidation reaction over the competing esterification. However, no examples were demonstrated using aniline substrates.



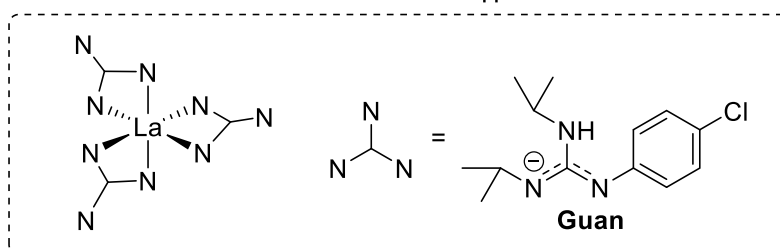
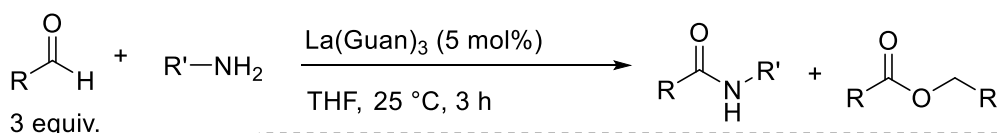
Scheme 1-43. Pd catalysed oxidative amidation of aldehydes using H₂O₂-Urea

Lanthanide-amido complex capable of affecting the direct amidation of aldehydes have been reported by Seo and Marks⁸⁰ and Qian et al.⁸¹ Both La-catalysed reactions proceeded at ambient temperatures and the catalysts were highly air- and moisture-sensitive. However, both systems utilise aldehyde as a hydrogen acceptor, limiting their potential applications for fine chemical production, where the aldehyde component may be costly. Furthermore, this also produces the equivalent alcohol as a by-product, which can lead to the competitive formation of ester side-products.

Seo and Marks (2007)



Qian et al. (2009)

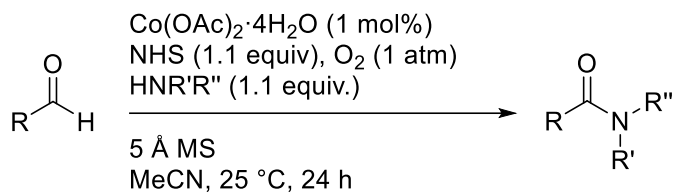


Scheme 1-44. La complex catalysed oxidative amidation of aldehydes employing excess aldehyde as a stoichiometric hydrogen acceptor

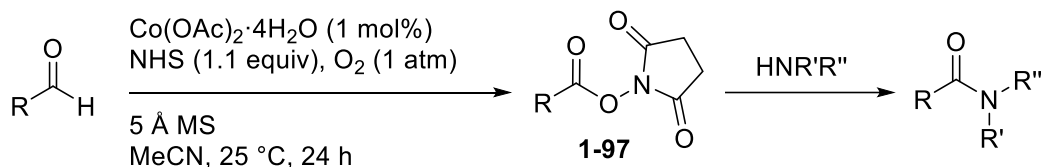
Two further reports that are particularly relevant to this work are the catalytic oxidative amidation of aldehydes via an *N*-hydroxy succinimide adduct (NHS), published by Yao and Yamamoto,⁸² and Pilo et al.⁸³ The former reported a $\text{Co}(\text{OAc})_2$ catalysed system with an excellent reaction scope, if only moderate yields, for aryl and aliphatic aldehydes, that utilised an O_2 atmosphere as the terminal oxidant (Scheme 1-45). In comparison, Pilo et al. reported a $\text{Cu}(\text{OAc})_2$ catalysed system with an equally impressive scope but utilised stoichiometric TBHP as the terminal oxidant (Scheme 1-46). In both reports, NHS is proposed to first react with the carbonyl group to generate activated NHS esters **1-97** and **1-98** (Scheme 1-45, Scheme 1-47).

Yao and Yamamoto (2012)

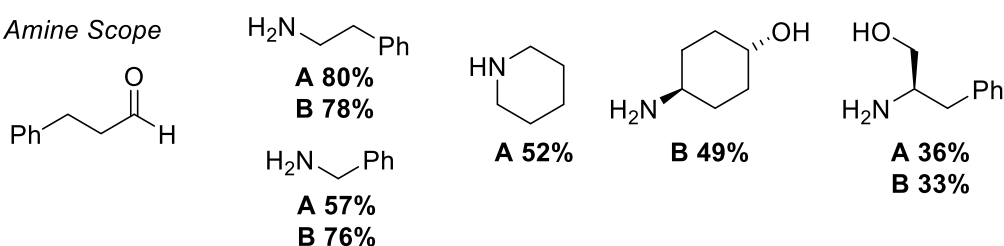
A) One-step method



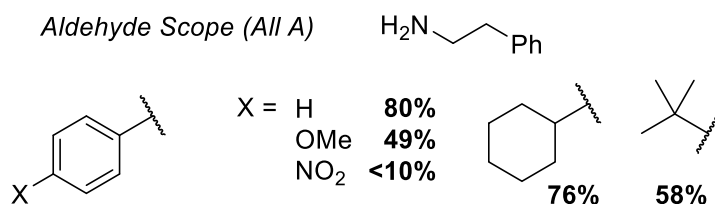
B) Two-step method



Amine Scope

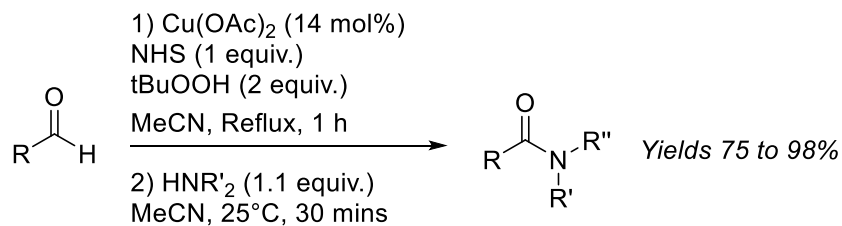


Aldehyde Scope (All A)



Scheme 1-45. Yao and Yamamoto's Co(OAc)_2 catalysed amidation of aldehydes via the formation of an intermediate NHS-ester

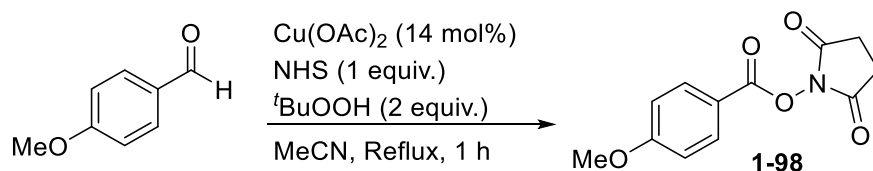
Pilo et al. (2013)



Aldehyde can be aliphatic, aryl, heterocycle

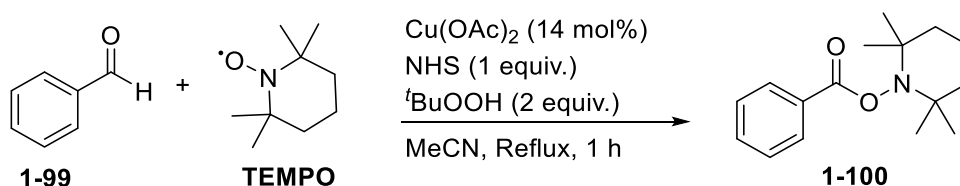
Amine can be 1° or 2°, aliphatic, aniline, benzylamine, or methylated hydroxylamine for Weinreb amide synthesis

Scheme 1-46. Cu(OAc)_2 catalysed oxidative amidation of aldehydes via the formation of an intermediate NHS-ester



*Scheme 1-47. $\text{Cu}(\text{OAc})_2$ catalysed oxidation formation of NHS-ester **1-98***

Pilo et al. proposed that the observed reactivity could result from the formation of N-oxy radicals. The addition of TEMPO to a solution of benzaldehyde **1-99** containing the Cu catalyst, NHS and $t\text{BuOOH}$, led to the formation of stable TEMPO ester **1-100** (Scheme 1-48), which was isolated in excellent yield via an aqueous work-up and purification on silica gel. The formation of the TEMPO ester **1-100** suggests that either acyl or acetal radicals may be present, but further mechanistic experiments are required to confirm that the formation of the NHS-ester also proceeds via a radical mechanism.



Scheme 1-48. Radical trapping experiment with TEMPO in the $\text{Cu}(\text{OAc})_2$ catalysed oxidative amidation of aldehydes

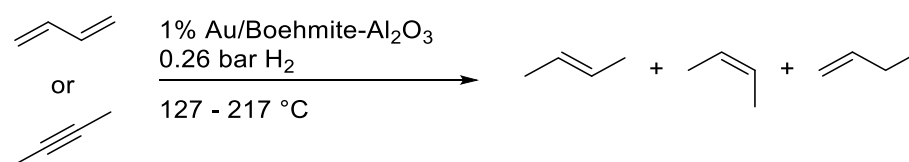
Heterogeneously-catalysed oxidative amidation from alcohols and aldehydes poses a unique problem. As in the case of homogeneous oxidative amidation reaction, there are two foreseeable chemical pathways for the oxidation of the C-H bond – a catalytic dehydrogenation pathway involving the release of H_2 ; or utilising an oxidant/hydrogen acceptor, ideally O_2 . However, examples for the heterogeneous catalytic oxidative amidation reactions utilising O_2 are rare in the literature. To the best of our knowledge, these are limited exclusively to the use of AuNP, which will be described in further detail later in this chapter.

1.5 Supported Gold Nanoparticle Catalysts

1.5.1 Background

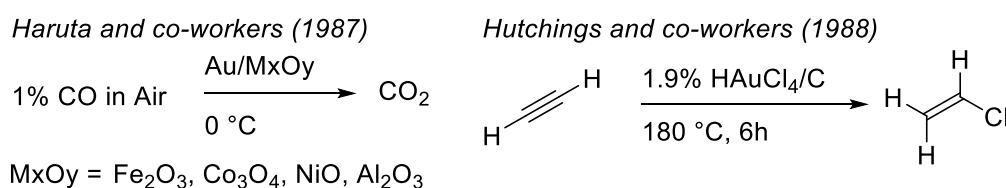
The application of AuNP as catalysts is remarkable not least because it is generally accepted that metallic gold is chemically inert. However, both ionic Au complexes and nanosized clusters of Au have been shown to be active for several synthetic transformations;⁸⁴ one of the most interesting applications is the ability of Au to facilitate selective oxidations at low temperature via the activation of molecular O₂.⁸⁵ The origin of the activity of AuNP is still not fully understood, although it has been proposed that the reactivity could result from surface plasmon resonance effects.⁸⁶

The first use of nano-sized Au for the catalytic hydrogenation of alkenes was reported in 1973 by Bond et al. (Scheme 1-49),⁸⁷ However, given the higher cost of Au compared to other metals, it is not surprising that potential chemical applications of atomic and nanoscale Au species have only been discovered relatively recently.



Scheme 1-49. Heterogeneous Au-catalysed reduction of 1,3-butadiene and 2-butyne

The field of supported Au catalysis was popularised later, through seminal work by Haruta and co-workers,⁸⁸ who demonstrated the use of Au catalysts for low temperature oxidation of carbon monoxide, and also Hutchings and co-workers,⁸⁹ who utilised Au NP's for the hydrochlorination of ethylene (Scheme 1-50). Since then, the potential catalytic applications of AuNPs has been realised for many reactions.

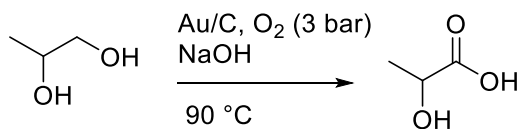


Scheme 1-50. Seminal works in supported Au catalysis published by Haruta and Hutchings on the low-temperature oxidation of CO, and the hydrochlorination of acetylene respectively

Haruta and co-workers reported the first example of selective oxidation of hydrocarbons; converting propene to propene oxide, an important intermediate in polymer synthesis, using a Au/TiO₂ catalyst (Scheme 1-51).⁹⁰ The concept was further developed by Prati and Rossi, who were the first to show the selective oxidation of diols in the liquid phase, using both Au/C and Au/Al₂O₃.⁹⁰ These reports

formed the basis for the further study of heterogeneous gold catalysts for the selective oxidations of organic molecules.

Prati and co-workers (1998)

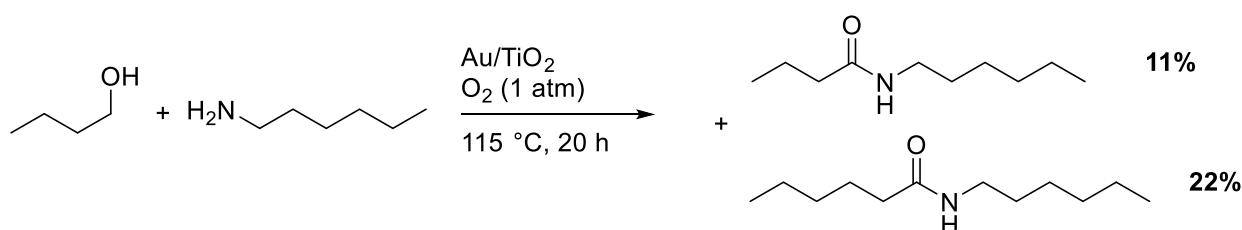


Scheme 1-51. Au-catalysed oxidation of propan-1,2-diol into lactic acid

There are multiple reviews which explore the field of Au catalysis in organic synthesis,^{84,91–93} and many heterogeneous AuNP catalysts are now available from commercial sources. Presented in this thesis are the reported examples of AuNP catalysis in the oxidative amidation of alcohols and aldehydes.

1.5.2 AuNP Catalysed Oxidative Amidation

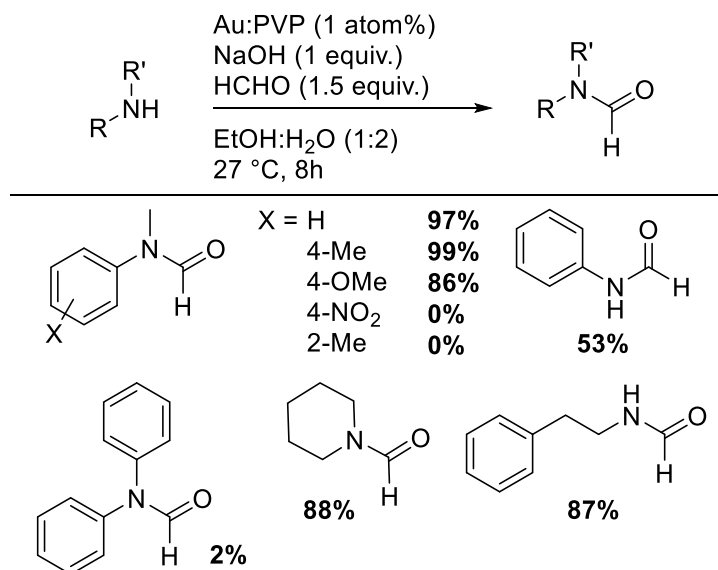
During a study on the synthesis of ϵ -caprolactam (a nylon precursor), Christensen and co-workers reported the first example of using gold nanoparticles (AuNP's) to catalyse an oxidative amidation reaction utilising O_2 as the terminal oxidant.⁹⁴ The authors found that Au/TiO₂ catalysed the oxidative amidation of butanol and hexylamine (Scheme 1-52), yet the reaction was still sluggish despite employing elevated temperatures of 115 °C. A small amount of water was found to play a key role in the activity of the catalyst; this is in direct contrast to direct amidation from carboxylic acids, where the removal of water was necessary to enhance catalyst performance. Additionally, the authors detected the presence of the N-hexyl hexanamide, which can only result from the coupling of two hexylamine molecules. Suggesting that the Au catalyst adsorbs, and is capable of oxidising an amine molecule to an imine, followed by subsequent hydrolysis or nucleophilic attack of an amine.



Scheme 1-52. Au/TiO₂ catalysed oxidative amidation of butan-1-ol and hexylamine

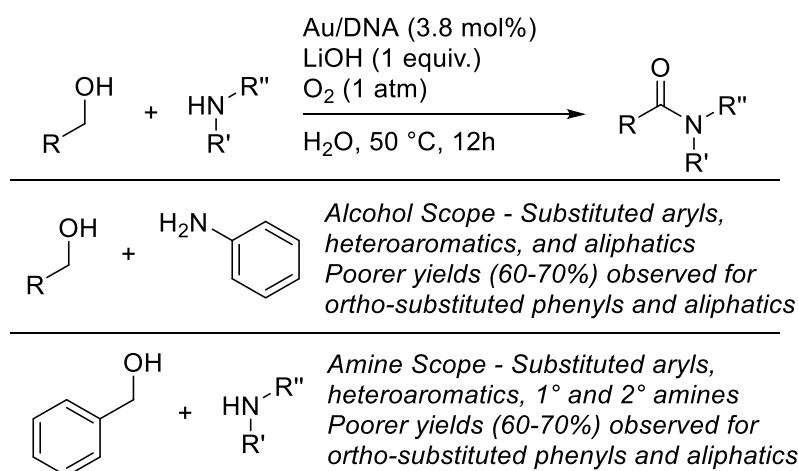
Sakurai and co-workers reported the formylation of amines using water-soluble polyvinylpyrrolidone (PVP) incarcerated Au clusters (Au/PVP), but the system was ineffective for the amidation of electron poor and sterically hindered amines (Scheme 1-53).⁹⁵ While not strictly heterogeneous, this provided the first example of a Au-catalysed aerobic amidation reaction with an expanded amine scope. The reaction occurs readily at ambient conditions in an aqueous solution of ethanol. This is a significant

improvement over the elevated reaction temperatures needed for dehydrogenative approaches using Ru complexes and Ag/Al₂O₃, described in the earlier section.



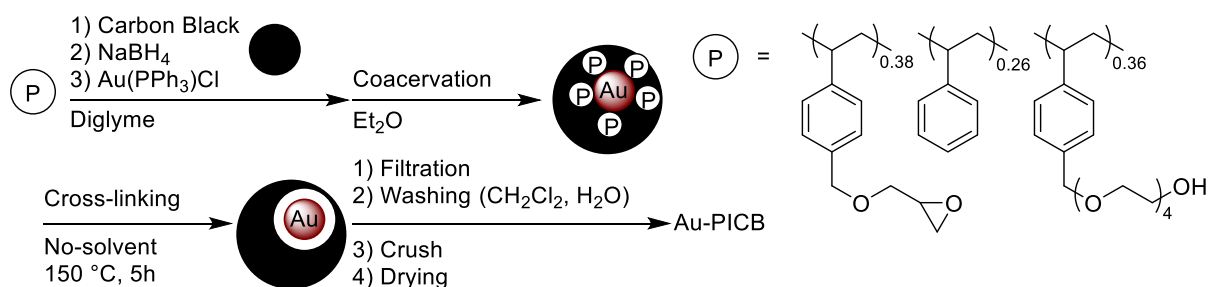
Scheme 1-53. Oxidative formylation of amines catalysed by polymer stabilised AuNPs

Wang and co-workers investigated the use of deoxyribonucleic acid (DNA) as a support for metal nanoparticles.⁹⁶ The authors found that the water-soluble Au/DNA catalyst was active for the oxidative amidation of alcohols in aqueous conditions at 50 °C, but the Au/DNA catalyst could be recovered from the reaction solution (Scheme 1-54).⁹⁷ The Au/DNA system offers a synthetically useful reaction scope, including both benzylic and aliphatic alcohols; which could be coupled with electron-poor anilines. The activity of the recovered Au/DNA catalyst, however, reduced with each subsequent reaction, which was associated with a concurrent increase in AuNP size. This observation suggests that the interaction between the AuNP and DNA support is weak, or that the AuNP may even dissociate from the support during the reaction. In both of Sakurai's and Wang's reports, the presence of a strong base is necessary, a factor that is consistent with many other AuNP catalysed selective oxidations.^{98,99}



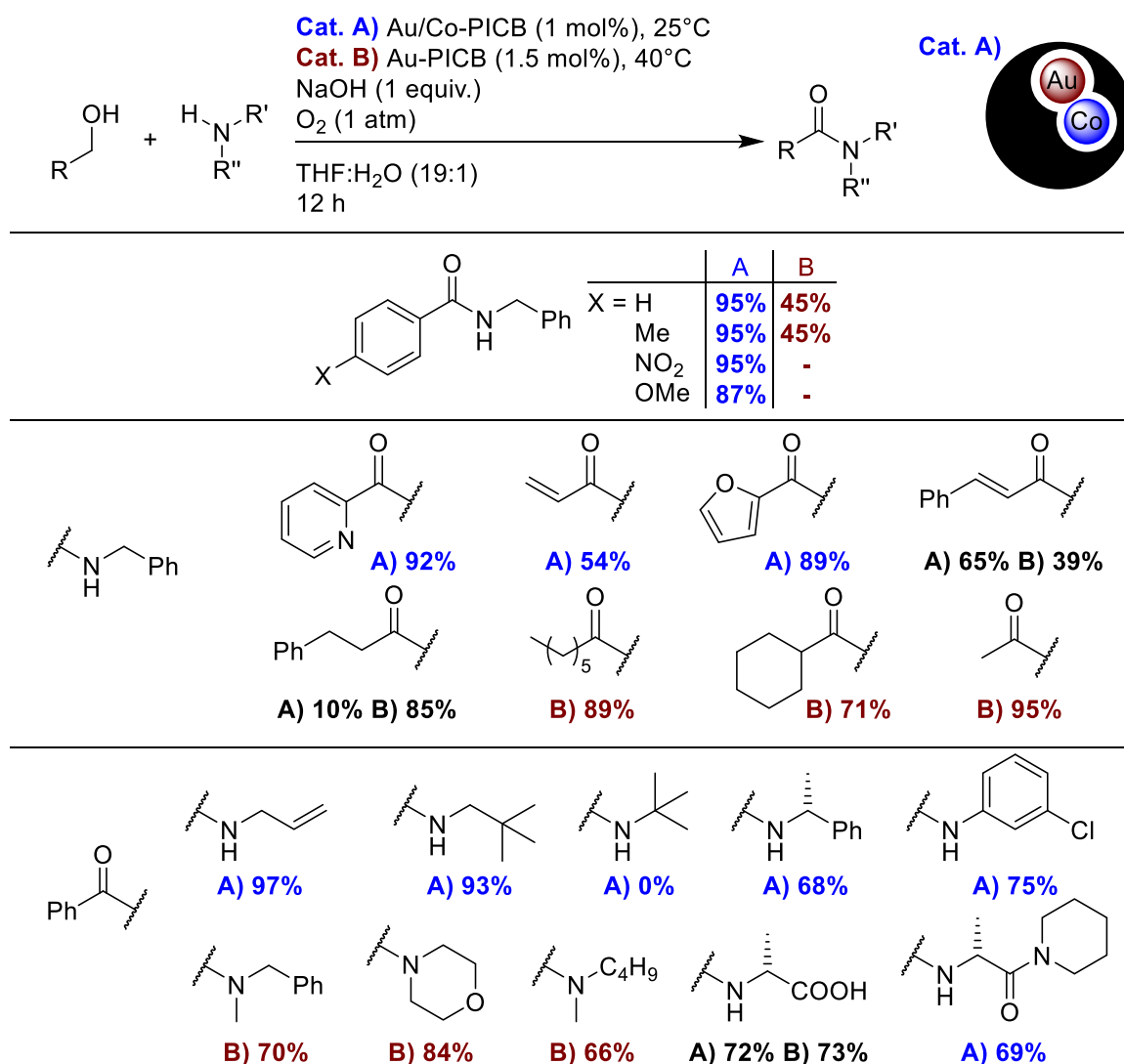
Scheme 1-54. Oxidative amidation of alcohols catalysed by water-soluble AuNP supported on DNA

In 2011, Kobayashi and co-workers published their approach to oxidative amidation of alcohols using a **Polymer Incarcerated AuNP**, supported on **Carbon Black** (Au-PICB).¹⁰⁰ The catalytic system proceeded at 40 °C in a THF-water mixed solvent system, requiring one equivalent of NaOH. The Au-PICB system is compatible with a broad scope of coupling partners, although electron-poor amines such as anilines proved challenging. The synthesis of Au-PICB catalysts (Scheme 1-55) is achieved using a custom method where the AuNP are synthesised in the presence of a polymer material to control the particle size and a carbon support to improve the dispersion of the AuNPs. The polymer incarcerating the deposited AuNP is then thermally cross-linked to improve the stability of the AuNP toward agglomeration.



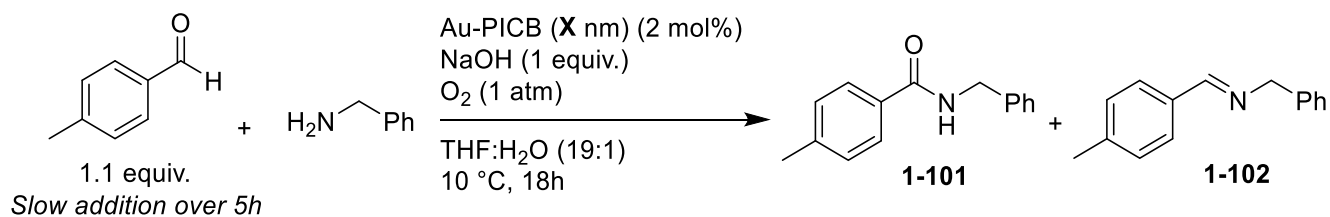
Scheme 1-55. Schematic representation of Kobayashi's synthesis of a polymer incarcerated AuNP supported on carbon black

The inclusion of dopant metals Fe, Ni, and Co was found to enhance the activity of their PICB catalysts. The metal additives likely modulate the electronic activity of the AuNP by formed discrete nanoparticles that exist in close proximity to the AuNP, but do not form metallic alloys (Scheme 1-56).



Scheme 1-56. Scope of the oxidative amidation of alcohols and amines using either Au-PICB or Au/Co-PICB (inset – schematic representation of Cat. A, a bimetallic polymer incarcerated Au/Co catalyst supported on carbon black)

However, Au-PICB was found to be ineffective at catalysing amide formation from aldehydes. Only the imine **1-102** was obtained from the reaction between 4-methyl benzaldehyde and benzylamine. This limitation was addressed in a subsequent paper by the same research group,¹⁰¹ investigating the role that the size of the nanoparticle. In this case, medium-sized AuNP (between 4.5 and 11 nm) were found to be the most selective catalyst for the coupling of para-tolualdehyde and benzylamine (Scheme 1-57, Table 1-3). Subsequently, the Au-catalysed oxidative amidation of aldehydes was achieved with the addition of stoichiometric NaOH and reduced temperatures (10 °C), compared to the amidation of alcohols using the same catalyst.



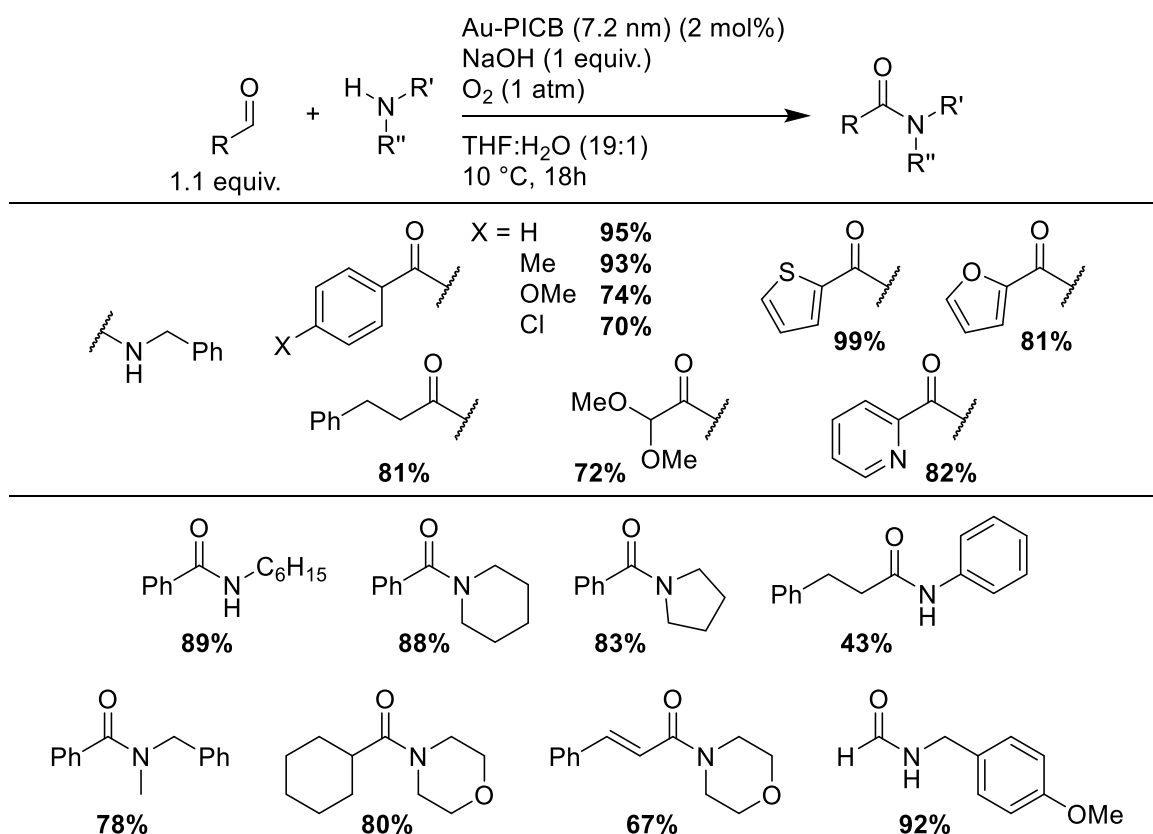
Scheme 1-57. Effect of the average NP size of a Au-PICB catalyst for the oxidative amidation of 4-tolualdehyde and benzylamine

Table 1-3. Summary of the selectivity of Au-PICB catalysts of increasing size in the oxidative amidation between benzylamine and para-tolualdehyde (Scheme 1-57)

Entry	AuNP size ^a X (nm)	Yield ^b 1-101 (%)	Yield ^b 1-102 (%)
1	2.9 ± 1.0	88	12
2	3.4 ± 1.5	86	14
3	4.5 ± 1.4	89	11
4	4.8 ± 1.9	93	7
5	5.2 ± 1.9	92	8
6	6.0 ± 3.3	90	10
7	7.2 ± 2.5	96	4
8	11 ± 4.9	92	8
9	33 ± 11	64	36

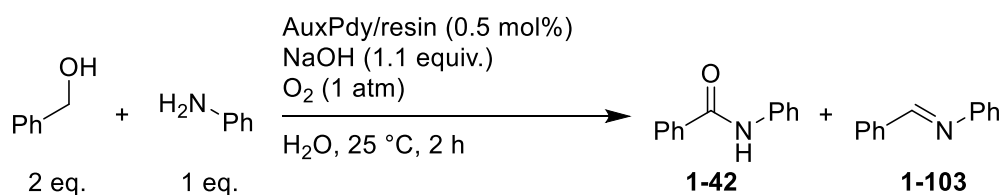
^aAuNP sizes were statistically measured by TEM ^bYields determined by ¹H NMR spectroscopy.

The scope of the Au-PICB catalysed oxidative amidation of aldehyde was similar to that previously reported for the oxidative amidation alcohols, performing poorly with electron-poor amines (Scheme 1-58). The authors proposed that ‘medium-sized’ (Table 1-3, entries **4** to **8**) AuNPs are optimal for the oxidative amidation due to a balance between the oxidative activity of smaller AuNPs and weaker adsorption of nitrogen containing molecules to the surface of larger AuNPs.^{102,103} Therefore, the effectiveness of the AuNP system in the oxidative amidation reaction is a balance between small particles that can adsorb and activate both amines and O₂, but not such that the adsorption of amine is too strong and prevents the formation of the hemiaminal intermediate. The authors reported that in both the oxidative amidation of alcohols and aldehydes, the Au-PICB catalyst remained stable under reaction conditions and could be reused multiple times without loss of activity.



Scheme 1-58. Scope of the oxidation amidation of aldehydes and amines catalysed by a Au-PICB catalyst with an average NP size of 7.2 nm

A Au-Pd bimetallic catalyst system was reported Zhang and co-workers which afforded a similar control over the selectivity of amide formation versus imine formation (Scheme 1-59, Table 1-4).¹⁰⁴ Greatest yield of amide **1-42** was achieved using a Au-Pd catalyst, where the atoms were in 6:1 ratio (entry **3**). Amide formation was only observed in bimetallic catalysts that contained more than 33% Au (entries **1** to **6**).



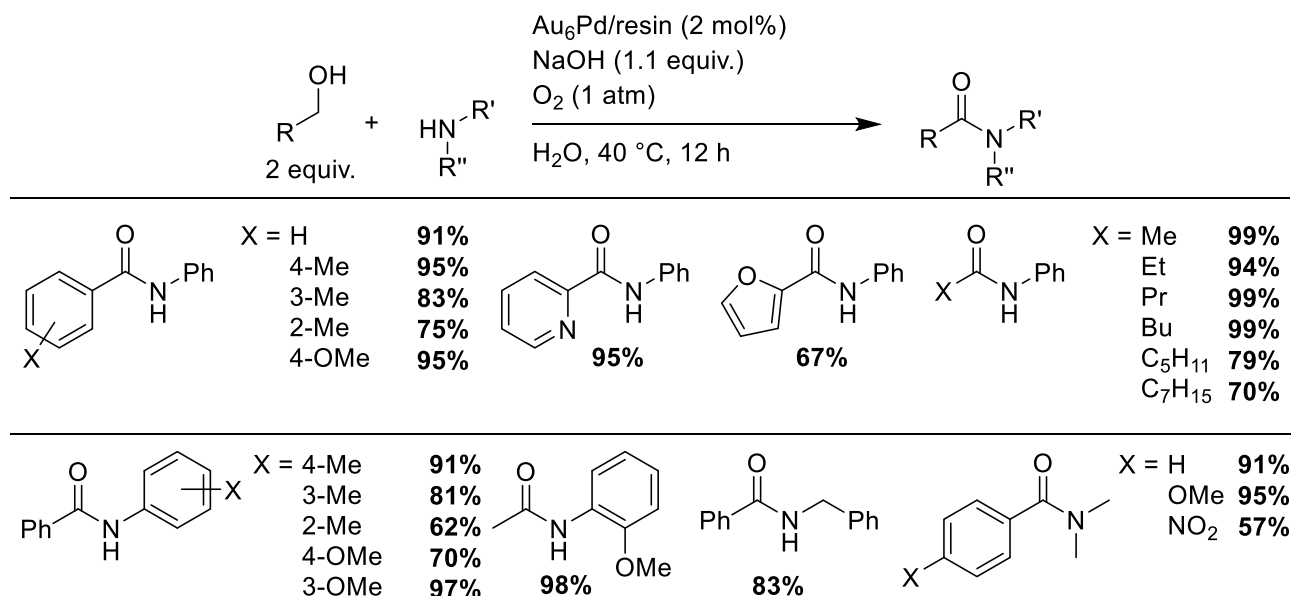
Scheme 1-59. Oxidative reaction of benzyl alcohol and aniline catalysed by a bimetallic Au-Pd catalyst supported on an anion exchange resin where the ratio of the metals controls the selectivity for amide or imine

Table 1-4. Yields of amide **1-42** and imine **1-102** in the oxidative amidation of benzyl alcohol and aniline catalysed by Au_xPd_y/resin catalyst (Scheme 1-59)

Entry	Au:Pd Ratio ^a	Yield ^b 1-42 (%)	Yield ^b 1-103 (%)
1	1:0	93	6
2	10:1	91	8
3	6:1	97	2
4	2:1	71	28
5	1:1	33	66
6	1:2	4	95
7	1:4	0	99
8	0:1	0	99

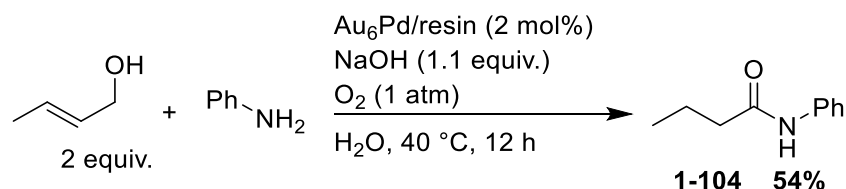
^aMolar ratio of Au:Pd ^bDetermined by GC

The enhanced activity of Au-Pd alloyed catalysts was attributed to the ability of Pd to stabilise abstracted hydride atoms, although the formation of a Pd hydride species was not directly observed. The Au-Pd bimetallic was applicable to a broad range of both aryl and aliphatic alcohols (Scheme 1-60). The bimetallic catalyst was also effective in the oxidative amidation reaction of anilines, electron deficient amine nucleophiles where Au-PICB was less effective.



Scheme 1-60. Scope of the oxidative amidation of alcohols catalysed by Au₆Pd/resin catalyst

Attempted oxidative amidation reaction of 2-buten-1-ol with aniline resulted in the formation of the butyl amide **1-104** (Scheme 1-61). The authors proposed that an intermediate Pd hydride species is formed during the reaction, which reduce the alkene.



Scheme 1-61. Oxidative amidation of 2-buten-1-ol and aniline with Au₆Pd/resin that resulted in the hydrogenation of the alkene bond expected in the amide product.

The same research group subsequently published a further example using Au/HAP (HAP – hydroxyapatite, a mixed calcium phosphate oxide) and other metal oxide supported AuNP catalysts (Au/TiO₂, Au/Fe₂O₃, Au/CeO₂, Au/ZnO) for the oxidative amidation of amines and alcohols.¹⁰⁵ However, the Au/HAP catalyst could not be recycled, due to sintering of AuNP in the recovered catalyst, suggesting either the support surface area is too small or there is a weak interaction between the AuNP and the support surface.

A dehydrogenative AuNP catalysed process was published by Deng and co-workers using Au/HT (HT – Hydrotalcite, a mixed aluminium magnesium oxide) for the oxidative amidation of alcohols.¹⁰⁶ In the presence of one equivalent of potassium *tert*-butoxide, the Au/HT system can be used in the amidation of benzylic and aliphatic alcohols but is limited to secondary cyclic amine substrates and a single example employing benzylamine. However, there is no precedent for the reactivity of AuNPs for the dehydrogenative amidation reaction and the authors do not provide evidence for the observation of H₂ formation, only the reaction does not proceed under O₂ free conditions.

Despite all these reports, the mechanism for AuNP catalysed oxidative amidation is poorly understood. The consensus is that the oxidative amidation of alcohols proceeds via sequential oxidations. The second oxidation converts the aldehyde into the product, is thought to occur at a much faster rate than the oxidation of the alcohol, thereby maintaining a low steady-state concentration of aldehyde in the reaction mixture. The reactivity of the aldehyde limits the use of amine reagents to the most nucleophilic substrates and can lead to the formation of undesired ester by-products. To date, there have been several catalyst systems that catalyse the oxidative amidation from alcohols, but there is only one example that can be used for the oxidative amidation of aldehydes.¹⁰¹

1.5.3 Water and Base in AuNP Oxidative Amidation

To date, all reported examples of the AuNP catalysed oxidative amidation of alcohols and aldehydes that utilise O₂ as the terminal oxidant require the addition of water and a stoichiometric amount of strong base (Table 1-5, entries **1** to **6**). Despite this, the role of the base is rarely discussed explicitly.

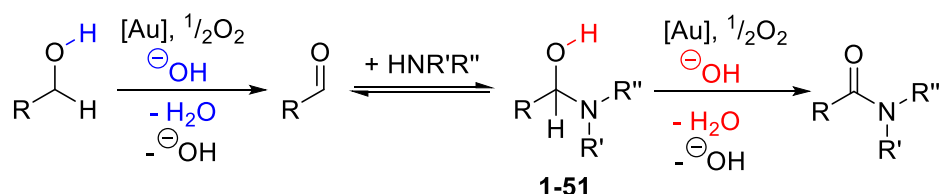
Table 1-5. Summary of the use of water and base in the AuNP catalysed oxidative amidation of alcohols and amines

Entry	Catalyst (X nm) ^a	Solvent	Base	Equiv.	Ref.
1	Au:PVP (1.30)	H ₂ O	NaOH	1	[95]
2	Au/DNA (4.03)	H ₂ O	LiOH	1.1	[97]
3	Au-PICB Au/Co-PICB (2.36)	THF: H ₂ O (19:1)	NaOH	1	[100]
4	Au-PICB (7.2) ^b	THF: H ₂ O (19:1)	NaOH	1 ^c	[101]
5	Au/Pd-resin (4.0)	H ₂ O	NaOH	1	[104]
6	Au/HAP (2.8)	H ₂ O	NaOH	1	[105]
7	Au/HT (2 to 3) ^d	<i>o</i> -Xylene	^t BuOK	1.1	[106]

^aAverage AuNP size reported ^bAu-PICB for the oxidative amidation of aldehydes range of NP sizes reported between 2 and 11 nm ^bSome examples reported using 0.25 equiv. of NaOH ^dDehydrogenative amidation of alcohols and amines, size reported as being between 2 and 3 nm

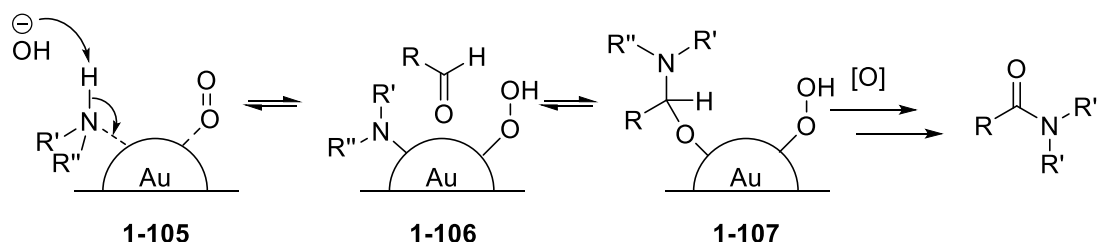
The exact role of a base in AuNP catalysed selective oxidations remains a controversial issue, with many different hypotheses. A common suggestion is that the base is involved in the deprotonation of the alcohol substrate; forming an alkoxide that subsequently adsorbs to the AuNP surface. The deprotonation of alcohols to form more reactive nucleophiles is an intuitive mechanistic step in many synthetic reactions and has been identified as a key step in other Au-catalysed selective oxidations.¹⁰⁷

In addition to the deprotonation of alcohols (Table 1-5, entry **6**),¹⁰⁵ Zhang and co-workers proposed that the base is also required in the deprotonation of a hemiaminal intermediate in the formation of the amide (Scheme 1-62).



Scheme 1-62. General scheme for the Au catalysed oxidative amidation of alcohols highlighting the two carbinol deprotonation steps

Kobayashi and co-workers¹⁰³ propose that the base is required for the deprotonation/activation of an adsorbed amine species (Scheme 1-63). The deprotonation of the adsorbed amine **1-105** leads to the formation of a surface-bound Au-amide type species **1-106** that subsequently reacts with an aldehyde to form hemiaminal **1-107**. This proposal appears to be supported by work from Friend and co-workers on the gas-phase oxidation of acetaldehyde and dimethylamine on oxygenated Au (111) surfaces, by demonstrating the low temperature (120 K) adsorption and activation of dimethylamine onto oxygenated Au (111) which was observed using X-ray photoelectron spectroscopy.^{108,109}



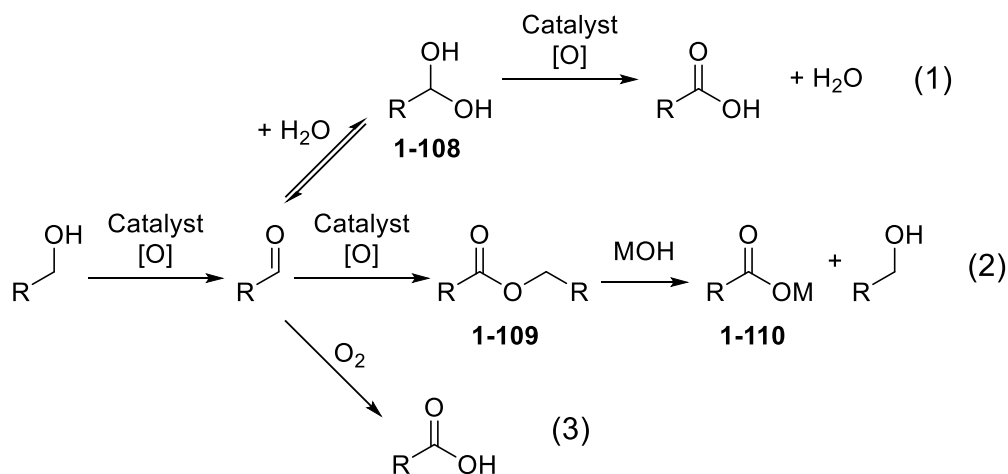
Scheme 1-63. Schematic representation of the adsorption and activation via deprotonation of amine onto a AuNP surface (omitting the important of O₂)

Other reports of Au-catalysed oxidative amidation (Table 1-5, entries **1** to **3**, **5**, **7**) do not discuss the role of the base in their systems, other than the addition of base is essential for catalytic activity. The adsorption/activation of either alcohol or amine, and the deprotonation of a hemiaminal, are all chemically intuitive mechanistic steps and probably occur to some degree on the AuNP surface. However, it is highly likely there are other overlooked effects.

The deactivation of catalyst surfaces by the presence of carboxylic acids is a known process in the alcohol oxidation reaction, for AuNP⁹⁸ and other supported metal systems.^{110,111} Adsorption of carboxylic acid to catalytic surfaces is a reversible process, the regeneration of catalyst activity can be achieved by washing with a solution of NaOH.⁹⁸ In all reports of the oxidation amidation, the formation of carboxylic acid is only acknowledged as a possible side reaction by Kobayashi and co-workers in the Au-catalysed oxidative amidation of alcohols.¹⁰⁰

The formation of carboxylic acids in the oxidation of alcohols can occur via three different pathways (Scheme 1-64):

- 1) A catalysed over-oxidation of the alcohol via the aldehyde and formation of a gem-diol **1-108** (eqn **1**), which undergoes another oxidation to the acid.
- 2) A catalysed oxidative esterification, yielding ester **1-109** followed by saponification; resulting in the formation of 1 equivalent of a carboxylic acid salt **1-110** and one equivalent of alcohol.^{112–114} (eqn **2**)
- 3) Autocatalytic radical oxidation of the intermediate aldehyde by O₂ (eqn **3**).



Scheme 1-64. Possible pathways for the formation of carboxylic acid or carboxylate in catalysed oxidative amidation of alcohols

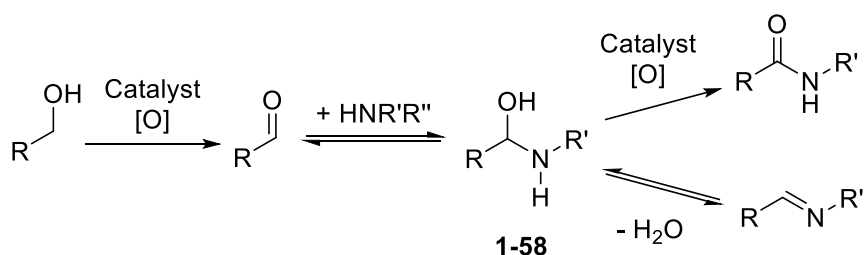
Most AuNP catalysed oxidative amidation reactions utilise an excess of the alcohol substrate (Table 1-6), with the exception being the Au-PICB catalyst systems reported by the Kobayashi group (entries **3** and **4**). The need for the excess of alcohol is not discussed in any of the reports. However, the excess reagent is likely added to account for the competitive formation of carboxylic acid. The formation of carboxylic acid would be difficult to detect as the presence of base would result in the formation of a water-soluble carboxylate salt **1-110** that is removed during aqueous work-up.

Table 1-6. Summary of the reaction stoichiometry employed in Au catalysed oxidative amidation

Entry	Catalyst (X nm) ^a	Alcohol equiv.	Amine equiv.	Ref.
1	Au/PVP (1.30)	1.5	1	[95]
2	Au/DNA (4.03)	2	1	[97]
3	Au-PICB Au/Co-PICB (2.36)	1	1	[100]
4	Au-PICB (7.2) ^b	1.1	1	[101]
5	Au/Pd-resin (4.0)	2	1	[104]
6	Au/HAP (2.8)	2 – 20	1	[105]
7	Au/HT (2 to 3) ^c	2	1	[106]

^aAverage AuNP size reported ^bAu-PICB for the oxidative amidation of aldehydes
range of NP sizes reported between 2 and 11 nm ^cDehydrogenative amidation
of alcohols and amines, size reported as being between 2 and 3 nm

Selectivity discussions on the Au catalysed oxidative amidation of alcohols typically focus on the preference between amide and imine, formed by the competing dehydration of a secondary hemiaminal intermediate **1-58**. Imine formation is acid-catalysed, usually requiring between pH 4 and pH 6 (Scheme 1-65). Therefore, the strongly alkaline conditions may impede the rate of the imine formation, although a catalysed dehydration is possible over hydrophilic supports, such as metal oxides (Table 1-6, entries **6** and **7**).



Scheme 1-65. Pathway for the formation of imine in catalysed oxidative amidation of alcohols

The effects of using H₂O as a solvent or co-solvent are also typically not discussed, particularly given the poor solubility of organic substrates under aqueous conditions. The promoting effect of H₂O adsorbed to the catalyst surface is well established in AuNP catalysis.¹¹⁵ It may be possible that H₂O is responsible for the activation of O₂ adsorbed to the AuNP surface, although the exact nature of the species on the surface are difficult to identify.^{116,117}

1.6 Summary of Catalytic Amidation Methods

In this Chapter, the main advances in catalytic amide bond formation have been discussed. Organocatalysts for amide formation based on boronic acids are promising, but their scale-up is limited by the high reaction temperatures ($>100\text{ }^{\circ}\text{C}$ in many cases) and the necessity for the continuous removal of water. Biocatalytic approaches to amide formation can provide quantitative yields at ambient conditions, but the enzymes required are highly specific and tend to be very sensitive to reaction conditions. Transition metal catalysis is a less promising area in catalytic amide formation, requiring comparatively higher catalyst loadings and elevated temperatures. But almost all metal catalysed approaches to the amidation of amines and carboxylic acids require the removal of water, which presents a significant barrier to reaction scale up.

Two main approaches were adopted for catalytic oxidative catalytic amidation reactions: the dehydrogenative coupling of alcohols and amines, and the addition of an external stoichiometric oxidant. The dehydrogenative approach is desirable for the near-perfect atom economy. However homogeneous catalysts required high temperatures and were mostly limited to non-sterically demanding amines. Homogeneously-catalysed reactions that employ oxidants has developed into a promising area. The activation of O_2 using homogeneous catalysis has been reported with the addition of hydroxylamine and other radical species, however these reactions require multiple additives and extensive work-up procedures would be required to recover the catalyst.

The final sub-section of this introduction presents the reports to date of the heterogeneous oxidative amidation of alcohols and aldehydes utilising O_2 as the terminal oxidant, a reaction that is unique to AuNP catalysis. The importance of the reaction conditions, namely the addition of base and water in Au catalysis is discussed.

1.7 Opportunities and Objectives

A significant thermodynamic hurdle restricts amide formation by the direct coupling of carboxylic acids and amines. Salt formation and the need for removal of water can be overcome by using alternate starting materials of lower oxidation states, such as alcohols and aldehydes. The synthesis of amides from either of these substrates requires both a catalyst and an oxidant. Heterogeneous catalysts have many advantages from a process perspective, and the ideal oxidant should produce no toxic or costly by-products.

This thesis outlines an investigation into the oxidative formation of amides from aldehydes using AuNP catalysts and atmospheric O₂ as the terminal oxidant. Attempts to expand the reaction scope was made by exploiting metal support interactions to fine-tune the activity of the AuNP. During this work, the roles of base and effect of radical species are explored, to provide further mechanistic detail on AuNP catalysed oxidative amidation. Finally, a bespoke reactor was designed and constructed to demonstrate a new approach to performing multiphasic aerobic amidation reactions in continuous flow.

2 Amidation of Aldehydes using Au/Al₂O₃

2.1 Introduction

It is generally accepted that the oxidative synthesis of amides from alcohols proceeds through sequential oxidations via an aldehyde intermediate. The oxidation of primary alcohols requires more forcing conditions than the oxidation of aldehyde. Hence, the oxidative synthesis of amides from aldehydes may require milder conditions than similar reactions starting from alcohol precursors, which can potentially lead to increased selectivity and reaction scope.

That said, the reactivity of aldehydes can also pose a unique challenge: The nucleophilic addition of amines to aldehydes leads to the formation of side products, such as aminals, imines, or the competitive (over)oxidation of the aldehyde to the carboxylic acid.

Currently, the only example of oxidative amidation of aldehydes using a heterogeneous catalyst under aerobic conditions (using O₂ as the terminal oxidant), was reported by Kobayashi using AuNP's dispersed on carbon and encapsulated in a styrene–glycidyl ether copolymer (Au-PICB).¹⁰¹ Kobayashi and co-workers demonstrated that 'medium-sized' AuNPs (4.5 to 11 nm) gave the greatest selectivity for amide. The selectivity was further enhanced by maintaining a low reaction temperature of 10 °C, and the controlled (slow) addition of the aldehyde. Under these conditions, poor yields were obtained with electron-poor amines, such as anilines.

This Chapter describes the use of a metal oxide-supported AuNP catalyst for the oxidative amidation of aldehydes, utilising atmospheric O₂ as the terminal oxidant. Using benzaldehyde and morpholine as model substrates, a multiphasic catalytic system was developed that can be applied to both aryl and aliphatic aldehydes, and a reasonable scope in the amine substrate.

2.2 Aims

This aim of this chapter is to identify a suitable metal oxide support for AuNP's that can be used in the oxidation amidation of aldehydes, particularly with electron-deficient amines. In this chapter, we will exploit these metal support interactions to both regulate the activity and stability of the catalyst. Included in this part of the work is the investigation of the importance of water, base, the removal of acidic by-products and the reaction conditions in AuNP catalysed oxidative amidation reactions.

2.3 Catalyst Identification

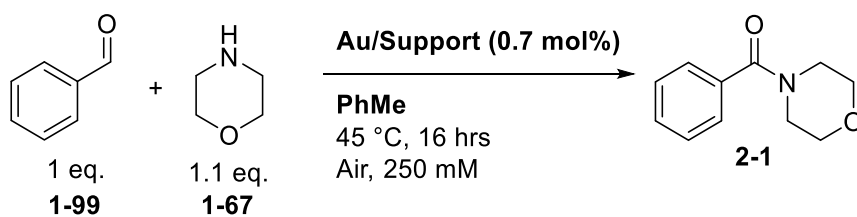
The size, morphology, and dispersion of AuNPs all influence the reactivity and stability of the catalyst in oxidation reactions.¹¹⁸ Previous reports have identified many contributing factors to the success of Au-catalysed oxidation reactions, such as the necessity of a strong base⁹⁸ and the critical role of water.^{115,119} However, the reasons for these conditions in oxidative amidation remain unclear.

The sol-immobilisation catalyst preparation method was employed in this project to achieve consistency of size distribution and morphologies of the AuNP across different supports.¹²⁰ Additionally, it is expected the sol-immobilisation method will make the most efficient use of Au, as the deposition of AuNPs happens primarily at the surface of the support.

2.3.1 Supported AuNP Catalysts

Initial experiments were performed using several AuNP catalysts available in the Hii research group, which were prepared by a previous graduate student for use in amine alkylation.¹²¹ The oxidative amidation reaction between benzaldehyde **1-99** and morpholine **1-67** was investigated using AuNP supported on different metal oxides and a carbon support. Reactions were conducted at one mmol scale in parallel, using a Radley's carousel reactor.

Table 2-1. Screening sol-immobilised catalysts in toluene without additives



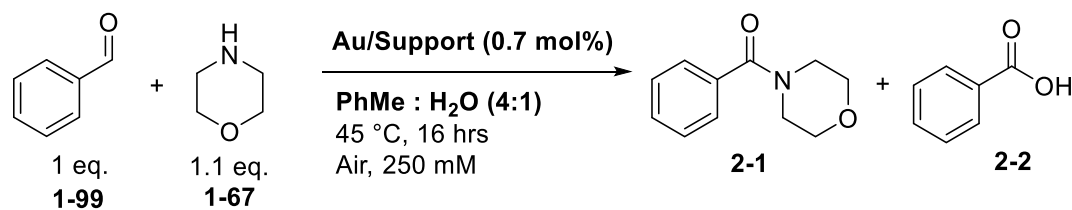
Entry	Support	Conversion 1-99 ^a (%)	Yield 2-1 ^b (%)
1	γ -Al ₂ O ₃	7	7
2	α -Al ₂ O ₃	N.D.	N.D.
3	TiO ₂	4	4
4	CeO ₂	6	Trace
5	Fe ₃ O ₄	Trace	Trace
6	C	N.D.	N.D.

^aReaction conditions: AuNP catalyst (~1 wt%, 150 mg, 0.7 mol%), benzaldehyde (1 mmol), morpholine (1.1 mmol), PhMe (4 mL) ^bConversion of aldehyde and yield of amide were determined by HPLC

Initial experiments investigating AuNP catalysts were conducted in the absence of base and water (Table 2-1). Reactions were heated at 45 °C for 16 h using air as the terminal oxidant. An aliquot of reaction mixture was diluted using a 2.2 mM biphenyl solution in MeOH and analysed by HPLC. As expected, minimal conversion of benzaldehyde **1-99** was observed in all the reaction mixtures.

The next reactions were conducted using the same catalysts but with the addition of water (Table 2-2).

Table 2-2. Screening sol-immobilised catalysts in biphasic neutral conditions



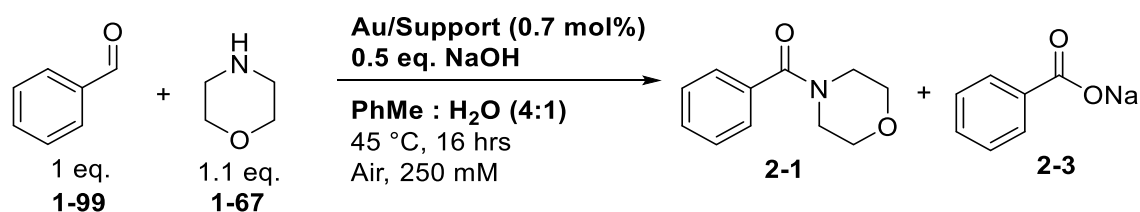
Entry	Support	Conversion 1-99 ^b (%)	Yield 2-1 ^b (%)
1	γ -Al ₂ O ₃	40	33
2	α -Al ₂ O ₃	2	7
3	TiO ₂	11	10
4	CeO ₂	5	4
5	Fe ₃ O ₄	24	27
6	C	3	7

^aReaction conditions: AuNP catalyst (~1 wt%, 150 mg, 0.7 mol%), benzaldehyde (1 mmol), morpholine (1.1 mmol), PhMe (4 mL), H₂O (1 mL) ^bConversion of aldehyde and yield of amide were determined by HPLC

The addition of water improved the observed yield of the amide with all tested sol-immobilised AuNP catalysts (Table 2-2). The best amide yield was obtained using Au/ γ -Al₂O₃ (entry 1). In comparison, the poor conversion obtained with α -Al₂O₃ (entry 2) demonstrates that the physical structure of the support is as important as the chemical composition. α -Al₂O₃ has a significantly smaller surface area (13 m²g⁻¹) compared to γ -Al₂O₃ (143 m²g⁻¹), and the different phase of the material changes the surface affecting the available acidic and basic sites.

Other support materials tested: TiO₂, CeO₂, Fe₃O₄, and C (Table 2-2, entries 3 to 6) all performed poorly compared to γ -Al₂O₃ in the absence of a base. The metal oxide supports TiO₂, CeO₂, and Fe₃O₄ have a range of surface areas (55 m²g⁻¹, 242 m²g⁻¹, and 16 m²g⁻¹, respectively) and all possess different acid/base properties. However, the poor result obtained with Au/C which possess a large surface area (689 m²g⁻¹) (entry 6) suggests that surface hydroxide species may also be a significant factor. It is proposed that both the amphoteric nature and large surface area of γ -Al₂O₃ are the key contributing factors to the catalytic activity and stability of the Au/ γ -Al₂O₃.

Table 2-3. Screening sol-immobilised catalysts in biphasic alkaline conditions



Entry	Support	Conversion 1-99 ^b (%)	Yield 2-1 ^b (%)
1	γ-Al ₂ O ₃	99	95
2	α-Al ₂ O ₃	98	89
3	TiO ₂	99	91
4	CeO ₂	20	20
5	Fe ₃ O ₄	88	79
6	C	62	67

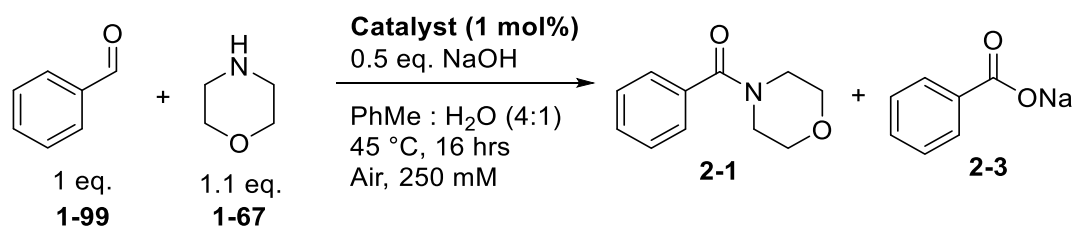
^aReaction conditions: AuNP catalyst (~1 wt%, 150 mg, 0.7 mol%), benzaldehyde (1 mmol), morpholine (1.1 mmol), PhMe (4 mL), 0.5 M NaOH (1 mL) ^bConversion of aldehyde and yield of amide were determined by HPLC

Addition of a sub-stoichiometric amount of aqueous NaOH to the amidation reaction drastically improved the catalytic activity of all supported AuNP catalysts tested (Table 2-3). Multiple mechanistic suggestions have been proposed for the role of the base; one of the most common explanations is that the base deprotonates the alcohol, to facilitate its binding to the surface (as an alkoxide).^{105,122} However, this is not applicable to the amidation of aldehydes.

2.3.2 Alternate Metal Catalyst Control Experiment

To confirm the unique activity of AuNP, additional experiments were performed with several commercially available metal catalysts available in our research lab. Additionally, controlled reactions were also performed to eliminate the possibilities of an uncatalysed or γ -Al₂O₃-catalysed reaction (Table 2-4).

Table 2-4. Screening alternate metal nanoparticles in biphasic alkaline conditions



Entry	Catalyst	Conversion 1-99 ^b (%)	Yield 2-1 ^b (%)
1	Ag/Al ₂ O ₃	27	<2%
2	Pt/Al ₂ O ₃	10	N.D.
3	Pd/Al ₂ O ₃	0	N.D.
4	Rh/Al ₂ O ₃	0	N.D.
5	Ru/Al ₂ O ₃	0	N.D.
6 ^c	Blank γ -Al ₂ O ₃	N.D.	N.D.
7 ^d	HAuCl ₄ .3H ₂ O & γ -Al ₂ O ₃	N.D.	N.D.
8	No Catalyst	N.D.	N.D.

^aReaction conditions: Catalyst (~1 mol%), benzaldehyde (1 mmol), morpholine (1.1 mmol), PhMe (4 mL), 0.5 M NaOH (1 mL) ^bConversion of aldehyde and yield of amide were determined by HPLC ^cAl₂O₃ (150 mg) added ^dHAuCl₄.3H₂O (1 mg, 1.3 mol% Au loading) and Al₂O₃ (150 mg) added

None of the other metal nanoparticle catalysts tested were found to be effective for the oxidative amidation of aldehydes (entries **1** to **5**), thus confirming the unique application of AuNPs. Of the metal catalysts tested, Ag/Al₂O₃ and Pt/Al₂O₃ (Table 2-4, entries **1** and **2**) were the only systems where conversion of the aldehyde was observed. HPLC analysis of the reaction mixtures, however, show no quantifiable yield of amide (<2%). It was assumed that the benzaldehyde **1-99** was oxidised to sodium benzoate **2-3** in these cases.

The low levels of conversion observed with the AgNP and PtNP are noteworthy. AgNPs have been reported to catalyse similar amidation chemistry via a dehydrogenative mechanism,⁷¹ while PtNPs have been shown to be active in other selective aerobic oxidation reactions.^{123,124} However, no amide

formation was observed with a PtNP catalyst under the specified reaction conditions. Due to the lack of reactivity, no additional metal NP catalysts were studied in this work.

Controlled experiments using the γ -Al₂O₃ support material (entry **6**) and with the addition of Au(III) precursor (entry **7**) confirm that AuNP species are responsible for the catalytic activity, as opposed to unreduced Au(III) adsorbed to the support surface. Similarly, no uncatalysed reaction was detected in under the specified reaction conditions (entry **8**).

Hereafter, the oxidative amidation reaction is optimised using an Au/ γ -Al₂O₃ catalyst prepared via a sol-immobilisation method.¹²⁰ The preparation, pre-treatment, and characterisation of Au/ γ -Al₂O₃ will be discussed in Chapter 3.

2.3.3 Role of O₂

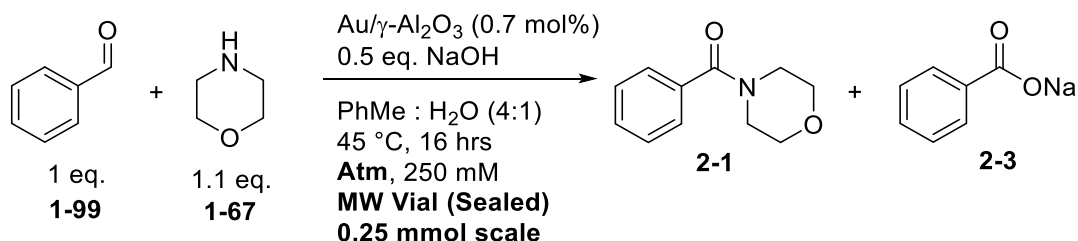
The solubility of O₂ in both toluene and water is low: Maximum concentrations of 9.26 mM and 0.45 mM respectively, have been calculated under atmospheric pressure (Table 2-5).^{125–127} The concentration of O₂ in the organic phase, 9.26 mM (entry **1**) is substantially lower than the concentration of benzaldehyde typically employed during this work (250 mM).

Table 2-5. The concentration of O₂ in toluene and water

Entry	Solvent	Mol frac. O ₂	Conc. O ₂ (mM)
1	Toluene	$(9.81 \pm 0.07) * 10^{-4}$	9.26
2	Water	$(8.07 \pm 0.05) * 10^{-6}$	0.45

Reactions were performed under controlled atmospheres to confirm molecular oxygen as the terminal oxidant in the amidation reaction catalysed by Au/ γ -Al₂O₃ (Table 2-6). Reactions were performed in sealed microwave vials loaded with Au/ γ -Al₂O₃ and aqueous NaOH, before they were purged and filled at 45 °C with the requisite gas, before the addition of the solvent and reactants: benzaldehyde **1-99** and morpholine **1-67**. The amount of O₂ available for the reaction is calculated based on the headspace of the reactor. The concentration of O₂ in the organic phase, 9.26 mM (Table 2-5, entry **1**), equates to 0.37 equivalents with respect to **1-99**.

Table 2-6. Au/ γ -Al₂O₃ catalysed oxidative amidation of benzaldehyde **1-99** and morpholine **1-67** in sealed vials under inert and oxygenated atmospheres



Entry	Atm	mmol of O ₂ ^b	Conversion 1-99 ^c (%)	Yield 2-1 ^c (%)	Max Conversion on O ₂ ^d (%)
1	N ₂	0	<1	Trace	0
2	Air	0.09	25	28	36
3	O ₂	0.43	96	79	100

^aReaction conditions: Au/ γ -Al₂O₃ (35 mg) Benzaldehyde (0.25 mmol), morpholine (0.28 mmol), PhMe (1 mL), 0.5 M NaOH (0.25 mL) ^bTotal molar volume of O₂ available from the headspace (9.75 mL) ^cConversion of aldehyde and yield of amide were determined by HPLC. ^dMaximum conversion of aldehyde based on moles of molecular O₂ available.

Under an inert atmosphere, the formation of amide was not detected under the specified conditions (Table 2-6, entry **1**). This shows that aldehyde is not acting as a sacrificial hydrogen acceptor in the reaction and rules out the formation of competitive by-products (acids and esters) via surface-catalysed disproportion (Cannizzaro) reactions.

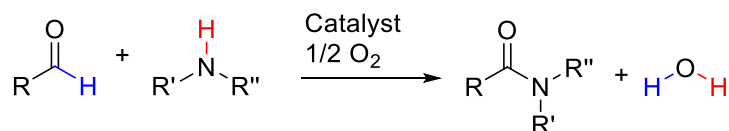
The effect of O₂ was investigated in two separate experiments; one reaction under an atmosphere of air (21% mixture of O₂ in N₂) (entry **2**) and another under an atmosphere of pure O₂ (entry **3**). As may be expected, a lower conversion of the aldehyde was obtained using air. Two important observations were made in this study:

- The reaction performed under air (entry **2**) appears to proceed with a greater selectivity to the reaction performed under a pure O₂ atmosphere (entry **3**)
- Reaction under air, 0.06 mmol benzaldehyde was consumed; while there was 0.09 mmol of O₂, therefore 0.18 mmol of O atoms were available

Greater selectivity for the amide product at lower O₂ concentrations may seem counter-intuitive initially. Lower selectivity for Au-catalysed oxidative amidation reactions at higher O₂ surface coverage has been reported for the gas-phase reaction between acetaldehyde and dimethylamine.¹⁰⁹ It was rationalised that while higher O₂ concentrations can increase the availability of the active sites towards amidation reactions, it can also accelerate the catalytic formation of the carboxylic acid by-product

and accelerate the autoxidation of the aldehyde to acid products. The use of pure O₂ as an oxidant is also undesirable on a process scale due to safety concerns.¹²⁸

The second observation on the reaction stoichiometry of O₂ allows us to infer on the behaviour of O₂ at the surface. A balanced chemical equation (Scheme 2-1) for the oxidative amidation of aldehydes requires half an equivalent of O₂. The strikingly low conversion of the aldehyde in a limited O₂ atmosphere could suggest that one equivalent of O₂ is necessary for the reaction.

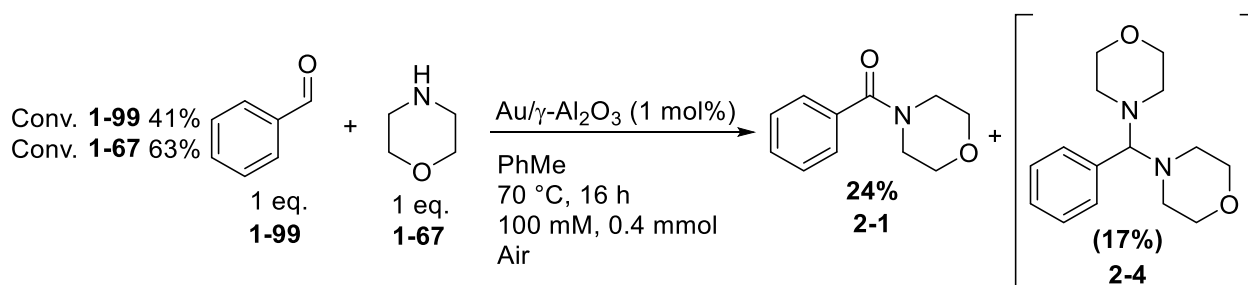


Scheme 2-1. Balanced reaction scheme for the oxidative amidation reaction

2.4 Role of Base

2.4.1 Aminal Formation

In an attempt to eliminate the necessity for the addition of base or H₂O, the oxidative amidation of benzaldehyde **1-99** was performed at higher temperatures in toluene. Reactions were conducted under air using a parallel reactor at a 0.4 mmol scale. Initially, analysis of the reaction mixture was performed by gas chromatography; it was noted that there was a significant deficit in the mass balance of both aldehyde **1-99** and amine **1-67**, roughly in a proportion of 1:2 (Scheme 2-2).



Scheme 2-2. Au/γ-Al₂O₃ catalysed oxidative amidation in toluene without additives

Additionally, the gas chromatogram (

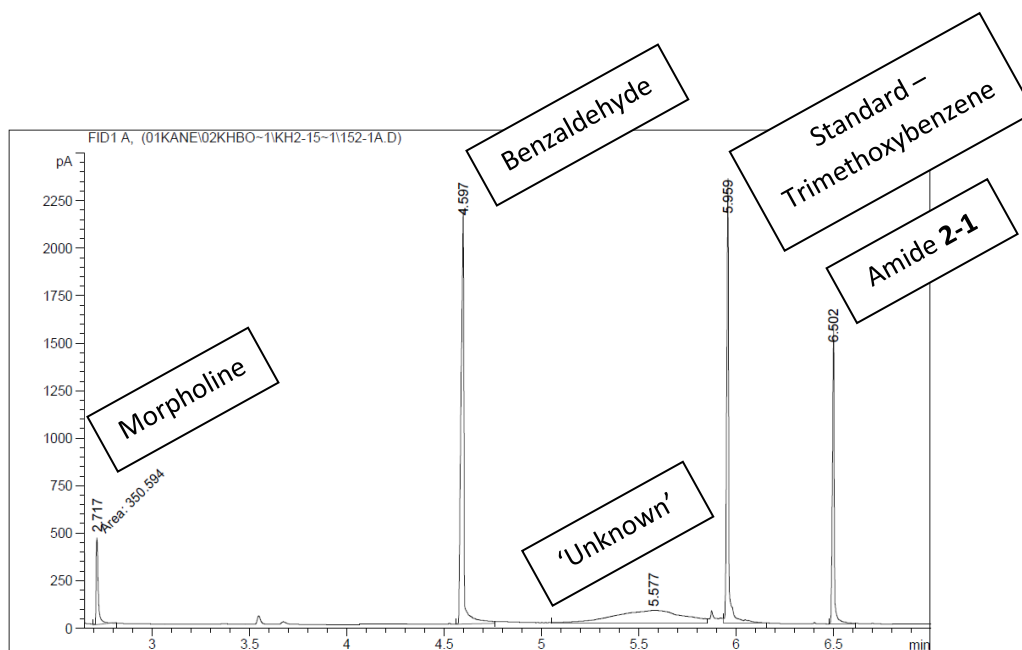


Figure 2-1) displayed a broad peak at 5.57 mins that could not be reliably integrated. These observations led us to speculate that aminal **2-4** may be formed by an undesired condensation reaction. This was verified by the independent synthesis of the aminal; subsequent GC analysis resulted in the thermal decomposition of the compound in the injection port. On the other hand, the mass deficit of benzaldehyde is not observed by HPLC analysis, as TFA and H₂O eluents hydrolyse the aminal back to benzaldehyde and morpholine. The difficulty in detecting aminals chromatographically may explain why it's formation has remained unnoticed in previous studies.

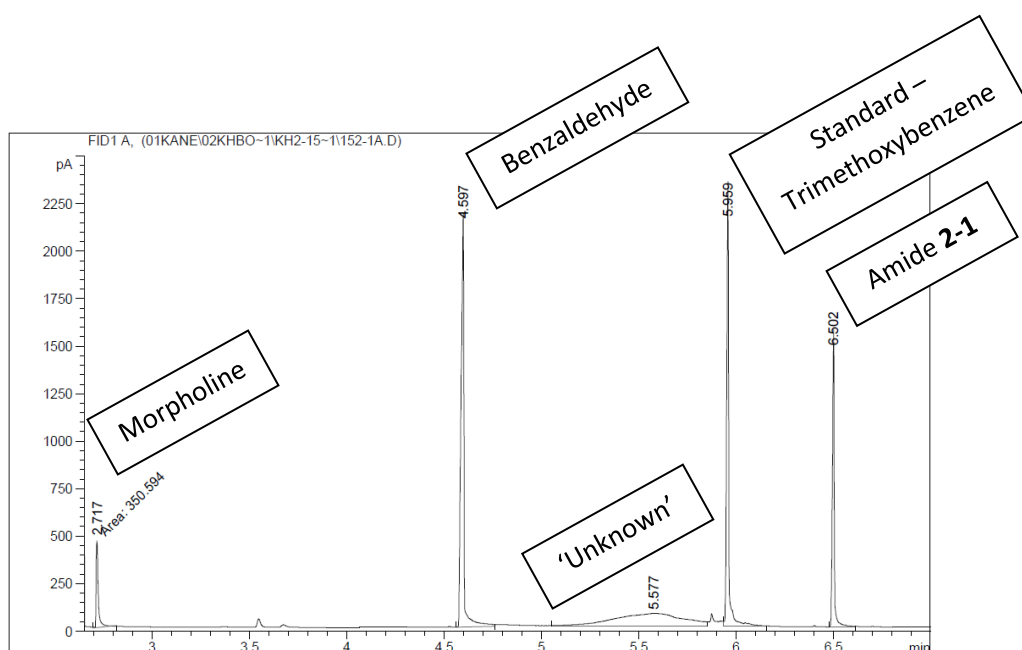
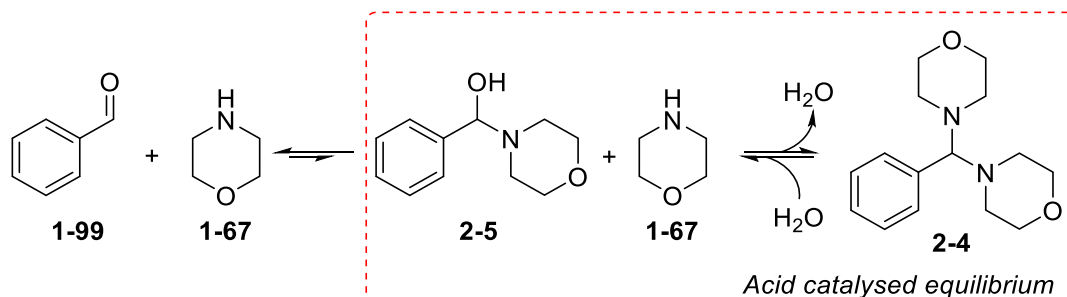


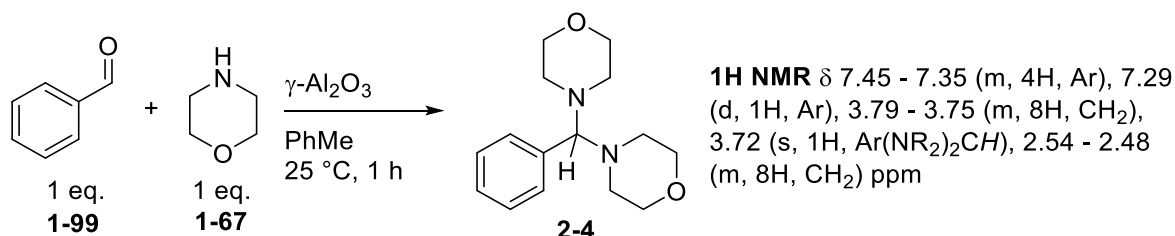
Figure 2-1. Gas chromatogram analysis of the oxidative amidation reaction between benzaldehyde **1-99** and morpholine **1-67** (Scheme 2-2). 'Unknown' broad peak likely resulting from the thermal decomposition of aminoral **2-4** during GC injection.

Alumina, and many other acidic and amphoteric metal oxides, are commonly used as supports for metal NPs in catalysis. The use of acidic materials catalyses the condensation of benzaldehyde with two equivalents of morpholine **1-67** to afford the aminoral **2-4** (Scheme 2-3).



Scheme 2-3. Reaction equilibrium between benzaldehyde and morpholine, hemiaminal, and aminoral

Alumina has been reported as acting as both an acidic catalyst and dehydrating agent for the isolation of aminorals.¹²⁹ This was verified in this work, by the addition of γ -Al₂O₃ support material into a solution of benzaldehyde **1-99** and morpholine **1-67** in toluene (Scheme 2-4). Aminoral formation was confirmed via ¹H NMR spectroscopy and differentiated from hemiaminal **2-5** by the 16:5 integral ratio of CH₂ to aromatic C-H atoms.



Scheme 2-4. Aminoral condensation of benzaldehyde **1-99** and morpholine **1-67**

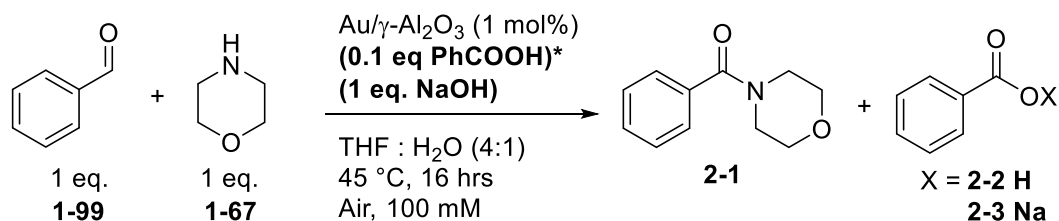
The formation of aminoral is an undesirable process as it reduces the amount of amine available for the reaction. In theory, the addition of base to the reaction system suppresses the acid-catalysed process; prohibiting the formation of both aminoral **2-4** and hemiaminal **2-5** in the bulk solution.

2.4.2 Catalyst Inhibition – Carboxylic Acids

The addition of carboxylic acids to AuNP catalysed oxidations is known to have an inhibitory effect in the oxidative esterification of benzyl alcohol with methanol, which can be restored by the addition of the base.⁹⁸ A series of experiments were performed to assess the effect of benzoic acid on the catalytic activity of Au/ γ -Al₂O₃.

In this work, Au/ γ -Al₂O₃ was used either 'as-prepared' or pre-treated with a carboxylic acid, by stirring in a 10 mM benzoic acid solution in THF. Pre-treatment of the catalyst was performed either with or without the addition of 1 mL of aqueous 1 M NaOH. The catalyst was then collected by centrifugation and gently oven-dried (80 °C) before use in the oxidative amidation reaction. Reactions were performed either with or without the addition of NaOH, to establish the relationship between carboxylic acid formation and the presence of a base (Table 2-7).

Table 2-7. Preliminary results pre-treating the catalyst using benzoic acid with and without the addition of NaOH



Entry	Catalyst pre-treatment ^b	1 eq. NaOH added to amidation reaction	Yield 2-1 ^c (%)
1	None	No	30
2	0.1 eq Benzoic acid in THF	No	7
3	0.1 eq Benzoic acid and 1 eq. NaOH in THF-H ₂ O	No	32
4	None	Yes	60
5	0.1 eq Benzoic acid in THF	Yes	52
6	0.1 eq Benzoic acid and 1 eq. NaOH in THF-H ₂ O	Yes	51

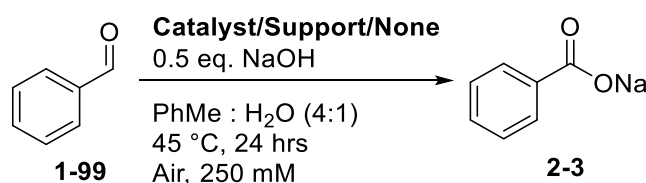
^aReaction conditions: Au/ γ -Al₂O₃ (75 mg, 1 mol%), benzaldehyde (0.4 mmol), morpholine (0.4 mmol), THF (4 mL), 1 M NaOH (1 mL) ^bAu/ γ -Al₂O₃ was stirred in 10 mM benzoic acid solution (4 mL) with or without the addition of aqueous 1 M NaOH (1 mL) ^cYield of amide was determined by GC

The catalyst pre-treated with benzoic acid in the absence aqueous NaOH is expected to perform poorly, due to inhibitory binding of benzoic acid to the catalytic sites,⁹⁸ which is confirmed by the reaction of the pre-treated catalyst in the absence of base (Table 2-7, entry **2**). The addition of sodium hydroxide during acid pre-treatment (entry **3**) prevented the binding of sodium benzoate **2-3** to the active sites, and catalyst performs comparably to the untreated catalyst (entry **1**).

The oxidative amidation reactions performed in the presence of 1 equivalent of NaOH (entries **4** to **6**) all showed comparable yields of amide **2-1**, irrespective of whether the catalyst has been pre-treated with benzoic acid. In all cases, the amide yield is higher than when the reaction performed without base (entry **1**). These results show that the addition of base not only prevents the formation of aminal, but that base can also reverse the binding of the carboxylic acid by-product to the active sites. It can also be concluded that the presence of sodium benzoate does not prevent the formation of amide.

2.4.3 Acid Formation

Aldehydes are known to react with O_2 to form carboxylic acids ('autoxidation') and is generally accepted to proceed via a radical process.^{130,131} Pure benzaldehyde **1-99** left exposed to air oxidises to benzoic acid **2-2** readily over the course of a few hours. To determine whether the addition of Au/ γ - Al_2O_3 catalyst also affects the rate of **2-2** formation, a series of experiments were performed to monitor the rate of the benzaldehyde oxidation process. In these experiments, a 250 mM solution of **1-99** in a toluene–water mixture was treated with 0.5 equivalent of NaOH in the presence of Au/ γ - Al_2O_3 (catalyst), γ - Al_2O_3 (support), or neither (blank), and the benzaldehyde consumption was monitored by HPLC (Scheme 2-5, Figure 2-2).



Scheme 2-5. Effect of Au/ γ - Al_2O_3 and γ - Al_2O_3 on the rate of **1-99** oxidation in solution

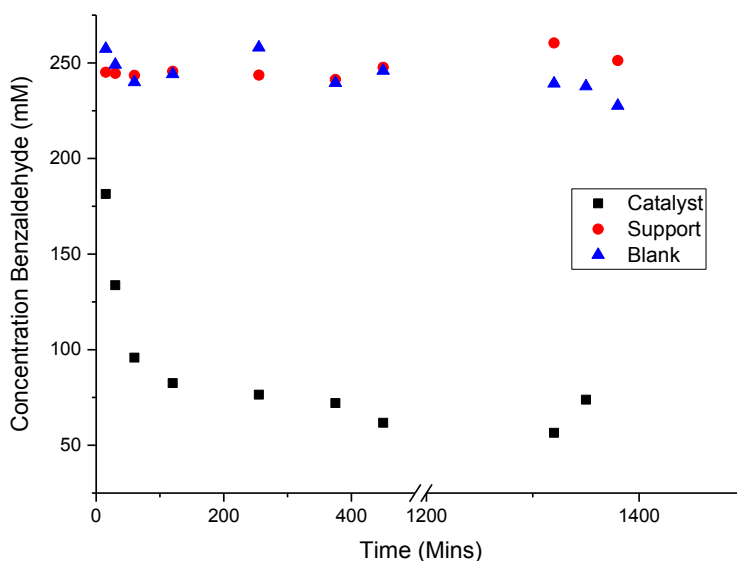
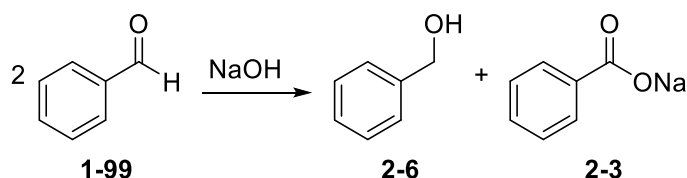


Figure 2-2. Autoxidation reaction of **1-99** ('Blank') compared to **1-99** oxidation with the addition of Au/ γ - Al_2O_3 ('Catalyst') or γ - Al_2O_3 ('Support')

In the absence of a AuNP catalyst, the oxidation of benzaldehyde in solution is very slow; the concentration of aldehyde remained unchanged over 24 hours with or without the support. In the presence of Au/ γ - Al_2O_3 , however, rapid consumption of benzaldehyde was observed, reaching 50% conversion within the first 60 min of the reaction.

Considering the low concentration of O₂ in toluene and water, 9.26 mM and 0.45 mM respectively (Table 2-5), the autoxidation of benzaldehyde in solution is expected to be limited by the rate of O₂ dissolution (mass transfer). Thus, the initial rapid consumption of benzaldehyde catalysed by Au/ γ -Al₂O₃ is undoubtedly due to a surface catalysed process (followed by the slower diffusion-limited process). The oxidation of benzaldehyde may proceed through three different pathways:

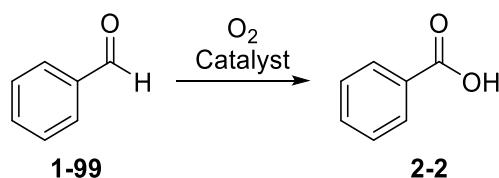
- 1) Cannizzaro reaction – a surface catalysed disproportionation of benzaldehyde with hydroxide



Scheme 2-6. Disproportionation of benzaldehyde in strongly basic conditions

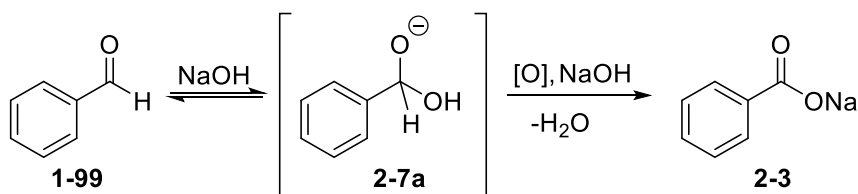
Heating benzaldehyde **1-99** in the presence of a strong base can result in a disproportionation reaction yielding benzyl alcohol **2-6** and sodium benzoate **2-3** (Scheme 2-6), in a process known as the Cannizzaro reaction. However, the absence of **1-99** conversion under O₂ free conditions (Chapter 2.3.3) eliminates this hypothesis.

- 2) Direct oxidation of benzaldehyde by an activated O₂ molecule on the AuNP surface (Scheme 2-7)



Scheme 2-7. Catalysed direct oxidation of benzaldehyde to benzoic acid

- 3) The oxidation of benzaldehyde **1-99** to benzoic acid **2-2**, proceeding via the formation of a surface-bound hydrated aldehyde **2-7** (Scheme 2-8)



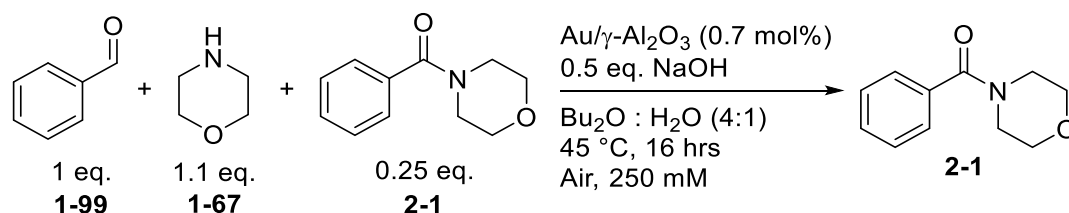
Scheme 2-8. Catalysed oxidation of benzaldehyde to benzoic acid via a gem-diol

In the presence of Au/ γ -Al₂O₃, the oxidation of **1-99** occurs rapidly, but slows and ceases as the conversion approaches 50%. A possible explanation is the consumption of NaOH due to the

competitive formation of benzoic acid **2-2**, which subsequently reacts with base forming sodium benzoate **2-3**. As **1-99** conversion reaches 50%, the amount of benzoic acid formed is enough to completely consume the starting 0.5 equivalents of NaOH. Whilst the consumption of NaOH (and adsorption of benzoic acid to the catalyst surface) is the most likely reason for catalyst inhibition it is not possible to distinguish between the two oxidation pathways proposed (**2** and **3**) above.

2.4.4 Catalyst Inhibition – Amides

Nitrogen-containing compounds are Lewis-basic and can bind to gold surfaces.^{103,132} The amide lone pair is not nucleophilic, but the addition of an amide has been previously shown to reduce yields obtained for a Au-catalysed oxidation of secondary alcohols.¹⁰¹ To investigate product inhibition in the reaction system, the initial rate of both aldehyde **1-99** conversion and amide **2-1** formation were compared with the initial rate of the same reaction conducted with the addition of 0.25 equivalents of amide **2-1** (Scheme 2-9, Figure 2-3).



Scheme 2-9. Addition of 0.25 equivalents of amide to the AuNP catalysed oxidative amidation

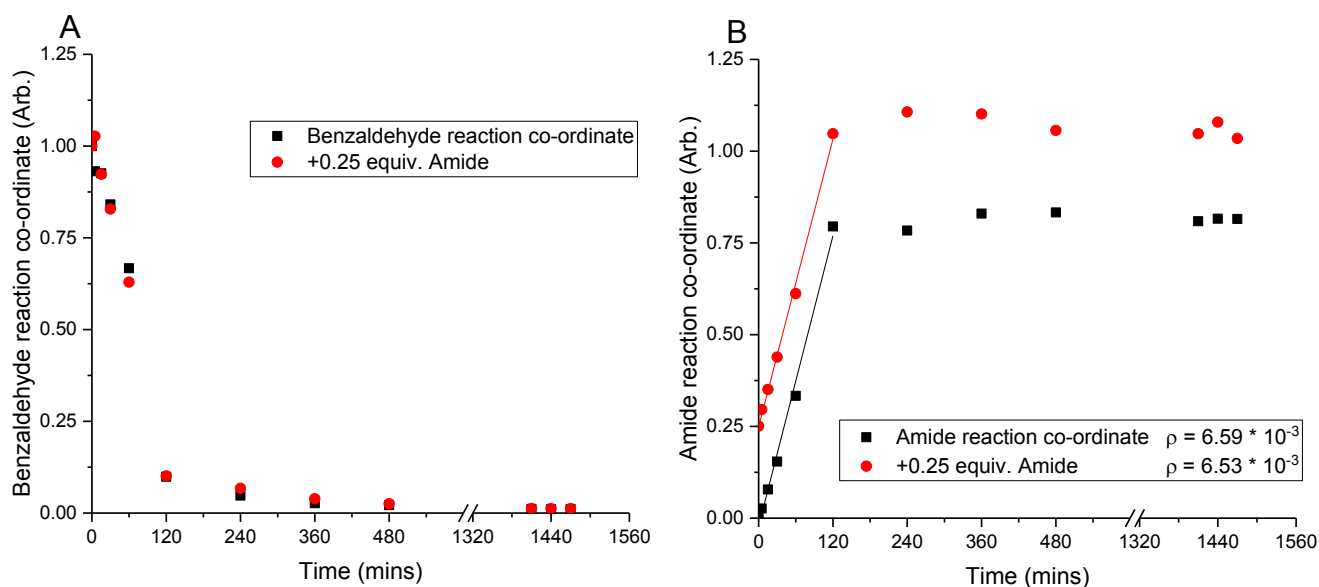


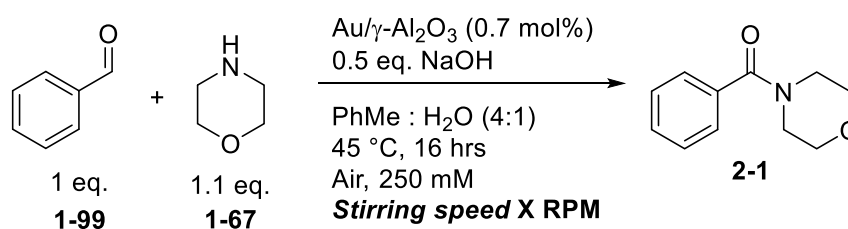
Figure 2-3. Effect of the addition of 0.25 equivalents of amide on reaction rate A) Rate of aldehyde conversion B) Rate of amide formation

The results showed no significant impact on the rate (Figure 2-3A) or selectivity of the reaction (Figure 2-3B) with the addition of 0.25 equivalents of the amide product. Therefore, product inhibition can be ruled out in the AuNP catalysed oxidative amidation under these reaction conditions.

2.5 Reaction Optimisation

2.5.1 Stirring Control

The homogeneity of the reaction mixture is described by the macromixing of a vessel and is primarily influenced by changing the stirring rate. Macromixing describes the mixing of the phases, the distribution of substrate concentration, and the thermal profile of the reaction.¹³³ Increasing the stirring speed will increase the effective contact area between the reaction mixture and the gas-phase, hence increasing the available surface area for O₂ dissolution. Due to the dependence of O₂ concentration in the reaction, an experiment was conducted to establish the effect of stirring speed on the AuNP oxidative amidation. The Au/γ-Al₂O₃ catalysed oxidative amidation of benzaldehyde **1-99** and morpholine **1-67** was performed under the specified conditions at stirring rates of 150, 300, 450, 550, and 650 RPM (Scheme 2-10). All reactions were performed in a Radleys Carousel using a 16.5 mm cross shaped stir bar (Radleys RR98091).



*Scheme 2-10. Au/γ-Al₂O₃ catalysed oxidative amidation reaction between **1-99** and **1-67** conducted at different stirring speeds of 150, 300, 450, 550, and 650 RPM*

Reactions at each stirring speed were performed in triplicate and the concentrations of **1-99** and **1-67** were monitored via HPLC and UV-Vis analysis for the first 2 hours of reaction time (Figure 2-4).

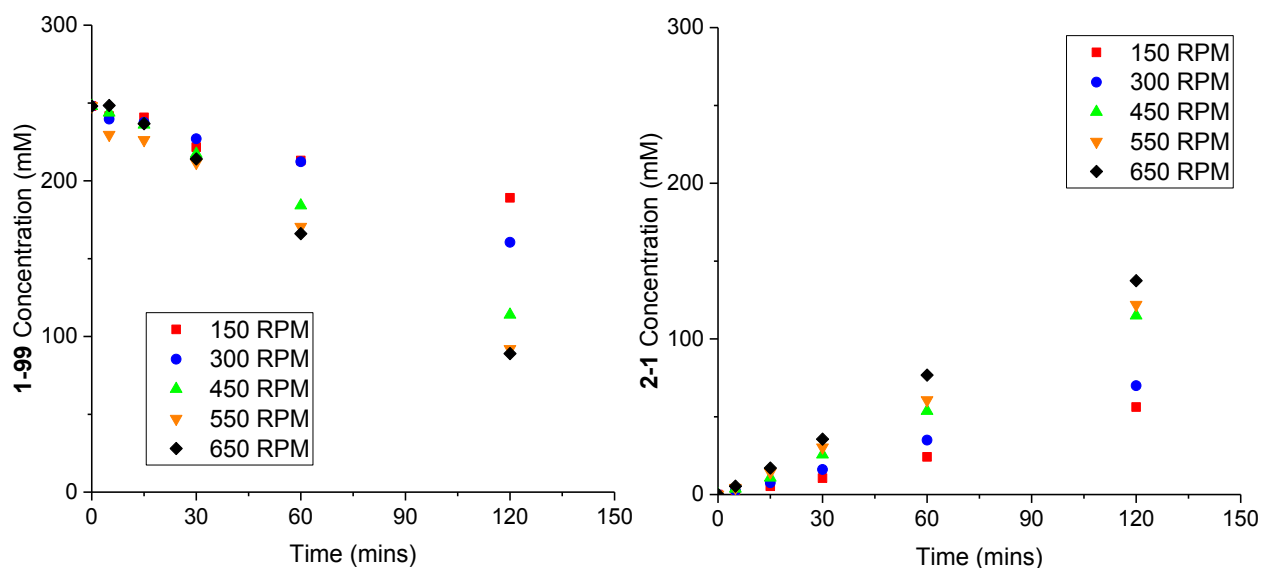


Figure 2-4. Concentrations of **1-99** and **2-1** in $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ catalysed oxidative amidation at stirring rates of 150, 300, 450, 550, and 650 RPM

The rates of **1-99** conversion and **2-1** formation were determined by fitting a linear curve to the average concentration profiles obtained for each stirring rate reaction. The selectivity was calculated as the ratio between the rate of amide formation and the rate of aldehyde conversion for stirring rate (Figure 2-5).

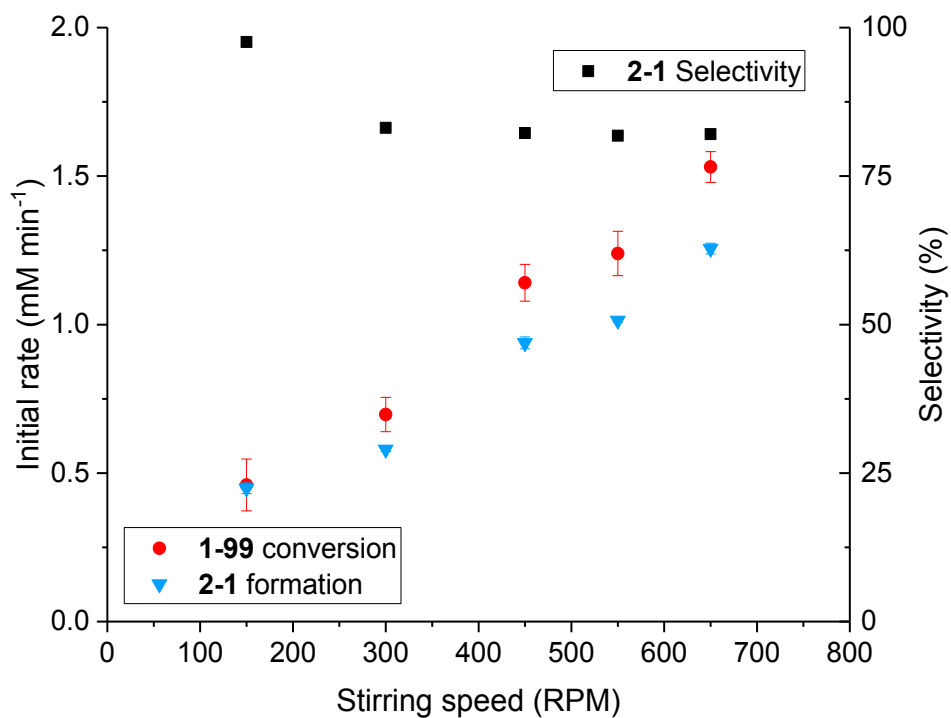


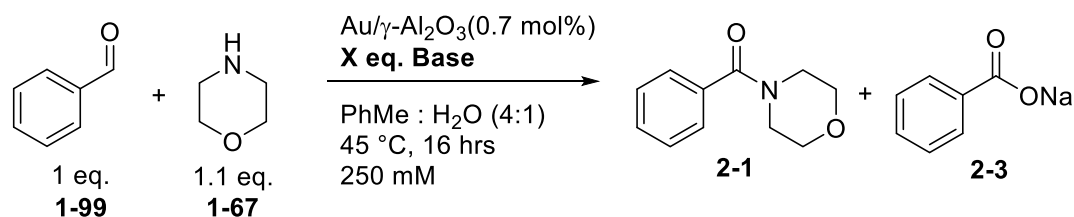
Figure 2-5. Rate of **1-99** conversion and **2-1** formation and selectivity in $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ catalysed oxidative amidation at stirring rates of 150, 300, 450, 550, and 650 RPM

Increasing the stirring rate resulted in a proportional increase in both the rate of aldehyde conversion and amide formation, however the increased stirring rate also reduced the selectivity of the reaction. Stirring at a rate of 300 RPM was enough to achieve a homogeneous mixing of the organic and aqueous layers. The Au/ γ -Al₂O₃ catalyst exists as a suspension in the aqueous phase, hence stirring does likely not impact the concentration of hydroxide at the catalyst surface. Instead the most likely explanation for the increased reaction rate, yet reduced selectivity is that the increased rate of stirring results in a greater effective concentration of O₂. Therefore, it appears that the rate of reaction is limited by the O₂ concentration in solution. All subsequent reactions were performed at 550 RPM due to practicality reasons; stirring at 550 RPM provided a balance between an acceptable reaction rate and selectivity. Increasing the stirring speed to 650 RPM and above in Radleys reaction vessels often resulted in the magnetic stir bar failing.

2.5.2 Base Screening

Having established the roles to of the base in the reaction, the next part of the investigation involves the screening of various bases at stoichiometric and sub-stoichiometric amounts (Table 2-8). A previous report proposed that the base could be intercalated within the Au surface to form a mixed metal oxide.⁹⁸ As such, different cations were also included in this study.

Table 2-8. Amidation in biphasic alkaline conditions, screening equivalence, cation effects



Entry	Base	Base Equiv. X	Conversion 1-99 (%)	Yield 2-1 (%)
1	NaOH	0.5	95	83
2	KOH	0.5	98	80
3	CsOH	0.5	97	82
4	NaOH	1	97	81
5	KOH	1	97	75
6	CsOH	1	97	72
7	Na ₂ CO ₃	0.5	57	59
8	K ₂ CO ₃	0.5	76	67
9	Cs ₂ CO ₃	0.5	72	71
10	Na ₂ CO ₃	1	42	44
11	K ₂ CO ₃	1	68	67
12	Cs ₂ CO ₃	1	71	71

^aReaction conditions: Au/γ-Al₂O₃ (150 mg, 0.7 mol%), benzaldehyde (1 mmol), morpholine (1.1 mmol), PhMe (4 mL), and specified aqueous base solution (1 mL) ^bConversion of aldehyde and yield of amide were determined by HPLC

The results unequivocally demonstrated that hydroxide bases (entries 1 to 6) outperformed their carbonate counterparts (entries 7 to 12), affording higher 1-99 conversions and 2-1 yields. No appreciable cationic effect was observed among the hydroxide bases. The necessity of a strong base for AuNP catalysed oxidative amidation is consistent with previous literature,^{101,104,105} and suggests that base is not only neutralising acidic by-products.

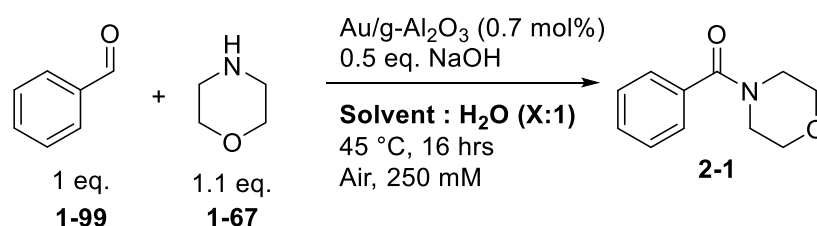
Greater amide yields were obtained when 0.5 equivalents of hydroxide were employed (entries **1** to **3**) compared to when a stoichiometric amount of base was added (entries **4** to **6**). Referring to previous experiments on Au-catalysed acid formation (section 2.4.3), the lower selectivity observed with higher concentrations of hydroxide is attributed to competitive formation of the carboxylic acid by-product. Carboxylic acid formation could occur via an analogous surface catalysed oxidation to oxidative amidation invoking hydroxide as a nucleophile.

Hereafter, 0.5 equivalents of NaOH is employed in all further optimisation and the development of the substrate scope.

2.5.3 Solvent Screening

Different organic solvents were screened while keeping the volume, ratio, and NaOH concentration of the aqueous component constant. Solvents were selected for their practicality and based on their green credentials and reputation.^{134–136} Chloroform was tested despite its very negative environmental impact, with the intention of performing validation NMR experiments *in-situ*.

Table 2-9. Screening alternative solvents



Entry	Solvent	Solvent Water Ratio (X:1)	Conversion 1-99 ^b (%)	Yield 2-1 ^c (%)
1	Bu ₂ O	4:1	>99	82
2	TBME	4:1	>99	82
3	PhMe	4:1	98	80
4	<i>n</i> -Heptane	4:1	>99	78
5	<i>t</i> -Amyl Alcohol	4:1	98	84
6	Trifluorotoluene	4:1	30	33
7	Chloroform	4:1	10	10

^aReaction conditions: Au/γ-Al₂O₃ (150 mg, 0.7 mol%), benzaldehyde (1 mmol), morpholine (1.1 mmol), specified solvent (4 mL), and 0.5 M aqueous NaOH (1 mL) ^bConversion of aldehyde were determined by HPLC ^cIsolated yield

Ethereal and hydrocarbon solvents (Table 2-9, entries **1** to **4**) afforded good conversions and selectivity for the amide product; with the added advantage of easy separation into distinct phases at the end of the reaction. *t*-Amyl alcohol, a non-nucleophilic tertiary alcohol, also allowed the amidation to proceed with similar results; however, *t*-amyl alcohol is only immiscible with water at high pH.

The poorest reaction outcome was observed with chloroform (entry **7**), with nearly complete inhibition of catalytic activity. The inhibition of Au in chloroform is therefore likely due to an interaction between chloroform and the AuNP surface: is known to abstract halogen atoms from halogenated solvents.¹³⁷

For this study, dibutyl ether (entry **1**) was selected to assess the reaction scope, as it provided a good yield for the amide product while remaining immiscible with water, facilitating separations and product purification steps. Furthermore, it is less volatile compared to the other top-performing solvents, so that the ratio of the biphasic mixture can be maintained throughout the reaction. GSK's expanded solvent selection guide¹³⁶ raises no significant issues with dibutyl ether. Applying the CHEM21 selection criteria, however, results in a 'problematic' rating (Table 2-10), missing the 'recommended' rating by having an autoignition temperature (AIT) 6 °C below the recommended temperature of 200 °C. The potential to form peroxides is unknown as the EUH019 is not explicitly stated on the SDS database, but this should not be disregarded.

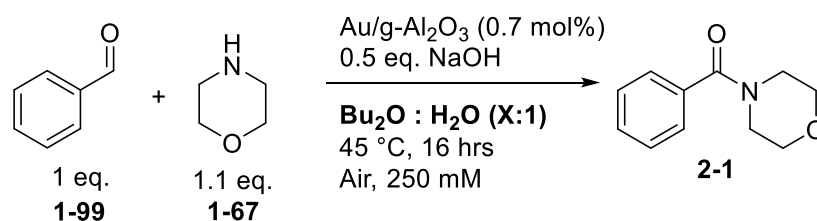
Table 2-10. CHEM21 Survey of the 'green-ness' of dibutyl ether

Criteria	Score	Justification
Safety score	4	Flashpoint 25 °C and H226 – Flammable liquid and vapour (3), AIT 194 °C (+1)
Health score	2	H315, H319, H335 – Causes irritation to the eyes, skin, and respiratory system (2)
Environmental score	5	Boiling point 141 °C, H412 – Harmful to aquatic life with long-lasting effects (5)

2.5.4 Water-to-Solvent Ratio

Water is important in the reaction as it dissolves the inorganic base, and it is also known to affect the chemistry of surface-catalysed AuNP. Varying the water-to-solvent ratio while maintaining 0.5 equivalents of hydroxide allow us to investigate the effect of changing the working concentration of hydroxide (Table 2-11).

Table 2-11. Screening the effect of the ratio of water to organic solvent



Entry	Bu ₂ O-H ₂ O Ratio (X:1)	Volume of H ₂ O added (mL)	Yield 2-1 ^b (%)
1 ^c	No water	N/A	15
2	16:1	0.25	44
3	8:1	0.5	67
4	4:1	1	82
5	2:1	2	71
6	0.8:1	5	33

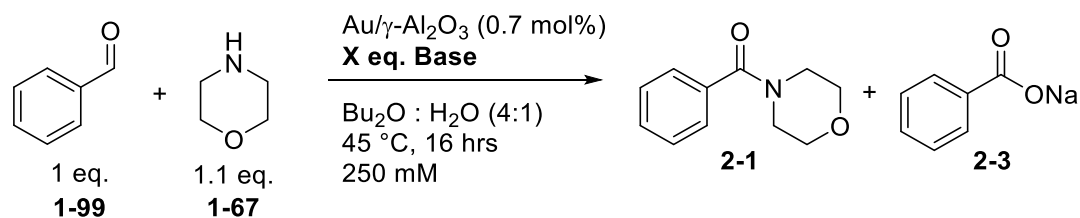
^aReaction conditions: Benzaldehyde (1 mmol), morpholine (1.1 mmol), Bu₂O (4 mL), and specified aqueous NaOH ^bIsolated yield

Without the addition of water, the addition of solid NaOH (Table 2-11, entry **1**) was an ineffective method of introducing base into the system. Gradual increases of water (entries **2** to **4**) resulted in an increased yield of amide **2-1**, and the optimum ratio of organic solvent to water was found to be 4:1 (entry **4**); above this the amide yield decreases (entries **5** and **6**). The optimum amount of water is a balance between the partition of reactants (substrates and base) between the liquid layers, and mass transfer of the reactants with the surface of the catalyst – which is suspended in the aqueous layer.

2.5.5 Base Equivalence

In this part of the study, the stoichiometry of NaOH was found to have a noticeable impact on the outcome of the oxidative amidation reaction (Table 2-12).

Table 2-12. Screening effect of changing the equivalence of NaOH



Entry	Base	Base Equiv. X	Conversion 1-99 ^b (%)	Selectivity 2-1 ^b (%)
1	—	0	74	60
2	NaOH	0.1	32	100
3	NaOH	0.25	84	71
4	NaOH	0.5	>99	82
5	NaOH	1	>99	38
6	NaOH	2	98	9

^aReaction conditions: Au/ γ -Al₂O₃ (150 mg, 0.7 mol%), benzaldehyde (1 mmol), morpholine (1.1 mmol), Bu₂O (4 mL), and aqueous NaOH (1 mL)

^bConversion of aldehyde and selectivity of amide were determined by HPLC

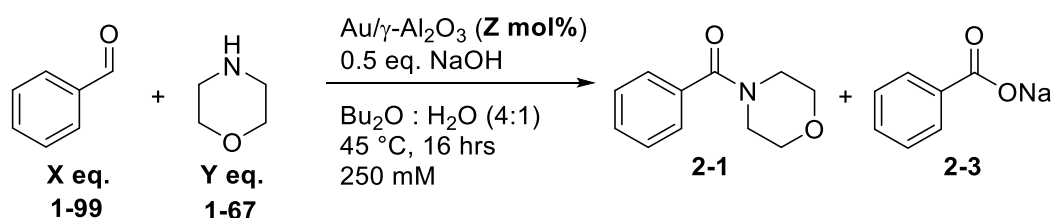
The absence of base, as expected, led to catalyst deactivation (Table 2-12, entry **1**). Below 0.5 equivalents of base (Table 2-12, entries **2** and **3**), the conversion of **1-99** did not reach completion, but proceeded with high selectivity for **2-1** formation. 0.5 M NaOH (Table 2-12, entry **4**) was found to be optimal, affording >99% conversion of the aldehyde and a high selectivity toward **2-1**. By comparison, a stoichiometric or excess amount of NaOH (Table 2-12, entries **5** and **6**), led to complete conversion of **1-99** but resulted in a lower selectivity toward **2-1** formation. It should be noted that the disparity in **2-1** selectivity between Table 2-12 and previous results would suggest that the choice of organic solvent also appears to influence the outcome of the oxidative amidation reaction at different concentrations of NaOH.

2.5.6 Reagent Stoichiometry

Previous reports on the Au catalysed oxidative amidation reaction employ an excess of alcohol and base,^{97,104,105,138} presumably to compensate for the competitive formation of carboxylic acid by-products. The use of excess aldehyde is wasteful and becomes problematic if the aldehyde is either expensive or requires a multi-step synthesis.

In this part of the study, the relative stoichiometries of benzaldehyde **1-99** and morpholine **1-67** were varied independently (Table 2-13, entries **1** to **5**). The use of excess aldehyde is expected to give greater amide yields but will continue to react to form **2-3**. In parallel, the effect of catalyst loading was investigated by varying the amount of Au/ γ -Al₂O₃ added to the reaction (entries **6** to **9**).

Table 2-13. Screening effect of changing substrate equivalence and catalyst loading



Entry	X Equiv.	Y Equiv.	Z (mol%)	Conversion 1-99 ^b (%)	Yield 2-1 ^c (%)
1	1	1	0.7	97	78
2	1	2	0.7	>99	81
3	1	3	0.7	96	70
4	2	1	0.7	73 ^d	92
5	3	1	0.7	53 ^d	95
6	1	1.1	0.4	>99	70
7	1	1.1	0.7	>99	82
8	1	1.1	1.4	>99	89
9	1	1.1	1.7	>99	85

^aReaction conditions: Au/ γ -Al₂O₃ (150 mg, 0.7 mol%), benzaldehyde (1 mmol), morpholine (1.1 mmol), Bu₂O (4 mL), and aqueous NaOH (1 mL) ^bConversion of aldehyde and yield of amide were determined by HPLC ^cIsolated yield

^dConversion values for excess aldehyde are calculated with respect to total quantity of aldehyde added

Keeping the same catalyst loading, the use of 1 to 2 equivalents of amine led to near-complete conversions of the aldehyde and good amide selectivity (Table 2-13, entries **1** and **2**). However, a reduced amide yield was obtained with 3 equivalents of amine (entry **3**), which could be attributed to competitive binding of the amine to active sites.

As expected, using an excess of aldehyde led to higher yields of amide, and the excess benzaldehyde was converted into benzoic acid/sodium benzoate (entries **4** and **5**). The amount of benzoic acid cannot be quantified reliably due to their solubility in the aqueous phase, but it appears that aldehyde conversion continues until the NaOH is consumed (by the formation of benzoic acid). Hence, when 2 equivalents of aldehyde are employed (entry **4**) ~1 equivalent of amide and ~0.5 equivalents of acid are formed (i.e. $1.5/2 = 75\%$ conversion).

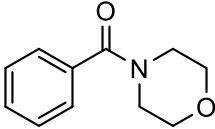
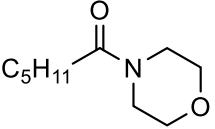
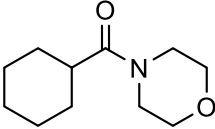
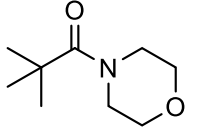
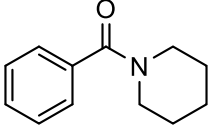
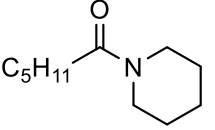
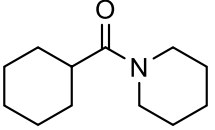
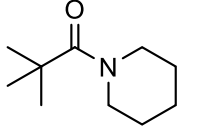
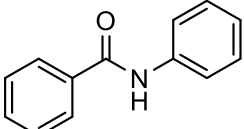
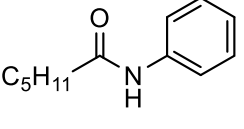
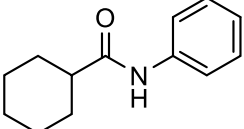
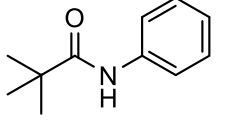
Increasing the catalyst loading in the oxidative amidation reaction only has a slightly beneficial effect on the amide yield (entries **6** to **9**), and the selectivity is similar when using loadings greater than 0.7 mol% (entries **7** to **9**). This suggests that the catalytic activity is largely limited by the mass transfer processes, present in the multiphasic system.

2.6 Reaction Scope

Having established the optimal conditions, the reaction scope was expanded to different aldehydes and amines. The AuNP catalysed amidation reaction was investigated for benzaldehyde, and aliphatic aldehydes of increasing steric encumbrance were initially investigated (Table 2-14). All reactions were performed at 45 °C on the 1 mmol scale using a Radley's carousel utilising air as the terminal oxidant.

Firstly, using two secondary cyclic amines, morpholine (**2-1**, **2-8** to **2-10**) and piperidine (**1-62**, **2-11** to **2-13**) known to be challenging in homogeneous Ru catalysed amidation and aniline (**1-42**, **2-14** to **2-16**), which is electron deficient and challenging for the Au-PICB catalysed oxidative amidation published by Kobayashi and co-workers. Each amine was reacted with benzaldehyde and aliphatic aldehydes: Hexanal, cyclohexanecarboxaldehyde, and pivaldehyde to investigate the influence of steric encumbrance at the α -carbon position.

Table 2-14. Steric effects of amidation reaction using Au/ γ -Al₂O₃ and biphasic conditions

$ \begin{array}{c} \text{R}-\text{CHO} \\ \text{1 eq.} \end{array} + \begin{array}{c} \text{R}'-\text{NH}-\text{R}'' \\ \text{1.1 eq.} \end{array} \xrightarrow[\text{Bu}_2\text{O} : \text{H}_2\text{O} (4:1), 45^\circ\text{C, 16 hrs, 250 mM}]{\text{Au}/\gamma\text{-Al}_2\text{O}_3 (0.7 \text{ mol\%}), 0.5 \text{ eq. NaOH}} \begin{array}{c} \text{R}-\text{C}(=\text{O})-\text{N}(\text{R}')\text{R}'' \end{array} $			
 2-1 85%	 2-8 63%	 2-9 65%	 2-10 0%
 1-62 67%	 2-11 80%	 2-12 59%	 2-13 0%
 1-42 0%	 2-14 58%	 2-15 53%	 2-16 27%

^aReaction conditions: Au/ γ -Al₂O₃ (150 mg, 0.7 mol%), aldehyde (1 mmol), amine (1.1 mmol), Bu₂O (4 mL), and aqueous 0.5 M NaOH (1 mL) ^bIsolated amide yields

Good yields were obtained for the coupling between morpholine and piperidine with both aryl and aliphatic aldehydes, affording amide products (**2-1**, **2-8** – **2-13**, **1-62**) in moderate to good yields, with no evidence for competing aldol condensation products. Tertiary substitution at the α -carbon of the aldehyde, however, prevented the formation of the pivalamides **2-10** and **2-13** – no pivaldehyde was recovered from the reaction mixture.

Employing aniline resulted in disappointing yields for all aldehydes (**1-42**, **2-14** to **2-16**). Reactions typically formed imines in preference to undergoing the desired oxidative amidation. The selectivity of amide formation appears to be dependent on the steric encumbrance and stability of the imine product. Amide products could be isolated from each reaction employing aliphatic aldehydes (**2-14** to **2-16**) however yields were reduced as the substitution at the α -carbon position increased. No amide formation was detected by NMR in the reaction between benzaldehyde and aniline (**1-42**), and the significant formation of imine can be rationalised by the increased stability of the extended π -system resulting from the condensation reaction. Attempts to increase yields by increasing the equivalence of either substrate or catalyst loading were unsuccessful.

Next, the oxidative amidation reaction was attempted for substituted benzaldehyde bearing either electron donating or electron withdrawing substituents (Table 2-15). The reaction of substituted benzaldehydes and morpholine (Table 2-15, **2-17**, **2-18**, **1-68**) resulted in high (>90%) conversions of aldehyde and the formation of other side products was not detected in the crude NMR. It is assumed the aldehyde that does not undergo the oxidative amidation reaction is converted into the corresponding sodium benzoate salt. The salts are either retained in the aqueous catalyst layer or adsorbed to the catalyst surface and cannot be recovered from the reaction mixture without dissolution of the catalytic material. Addition of either electron donating or electron withdrawing groups resulted in a reduction in amide yield and further substitution of the aryl ring another electron rich group reduced the amide (**2-19**) yield further to 40%.

The highest yields obtained were afforded when using secondary amine nucleophiles. This is particularly interesting, as piperazine motifs are commonly found in many active pharmaceutical ingredients (APIs) (Figure 2-6).¹³⁹ An excellent amide yield was obtained for the oxidative amidation of N-methyl piperazine (Table 2-15, **2-22**) and a slightly lower yield was obtained for the amidation of N-benzyl piperazine with benzaldehyde (**2-23**).

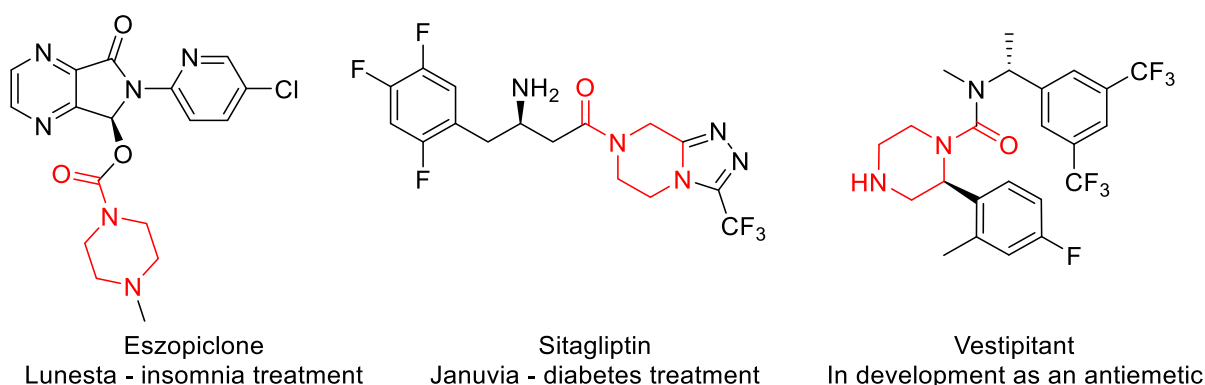
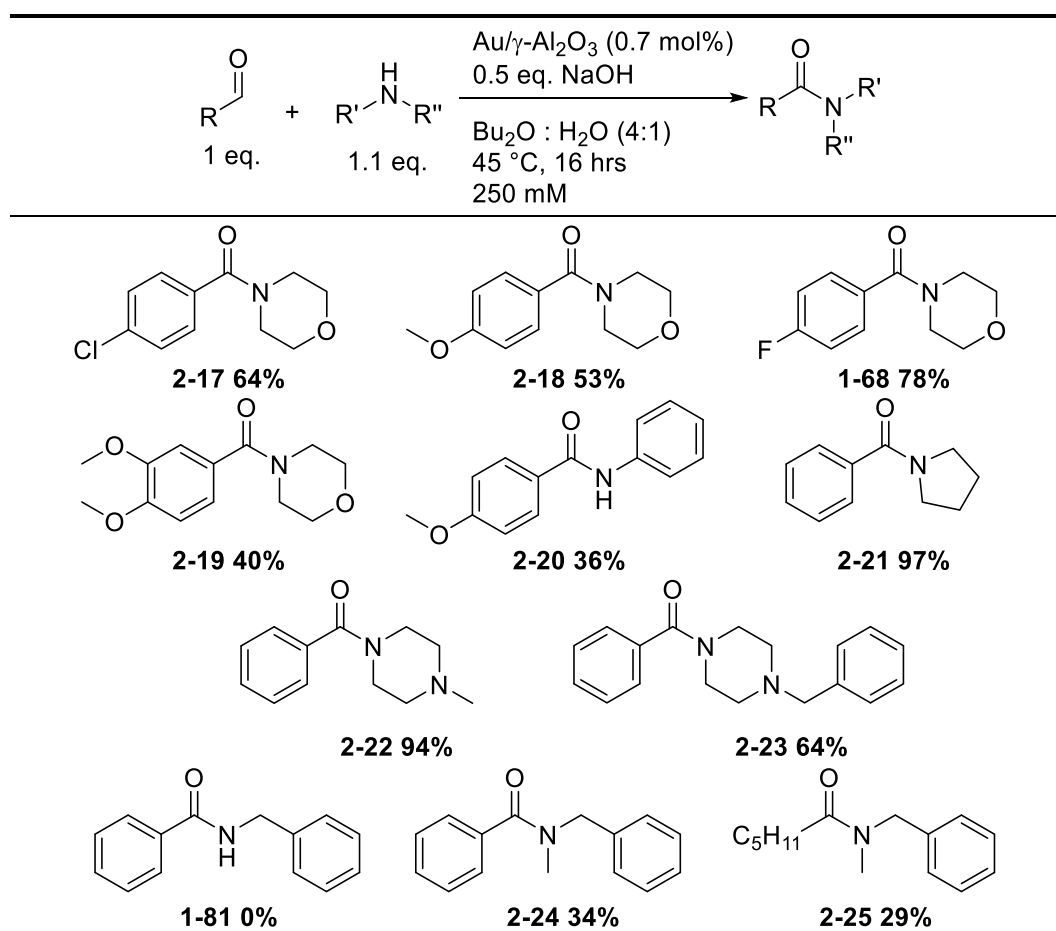


Figure 2-6. Piperazine amide motif containing FDA approved molecules

Table 2-15. Scope of amidation reaction using Au/ γ -Al₂O₃ and biphasic conditions

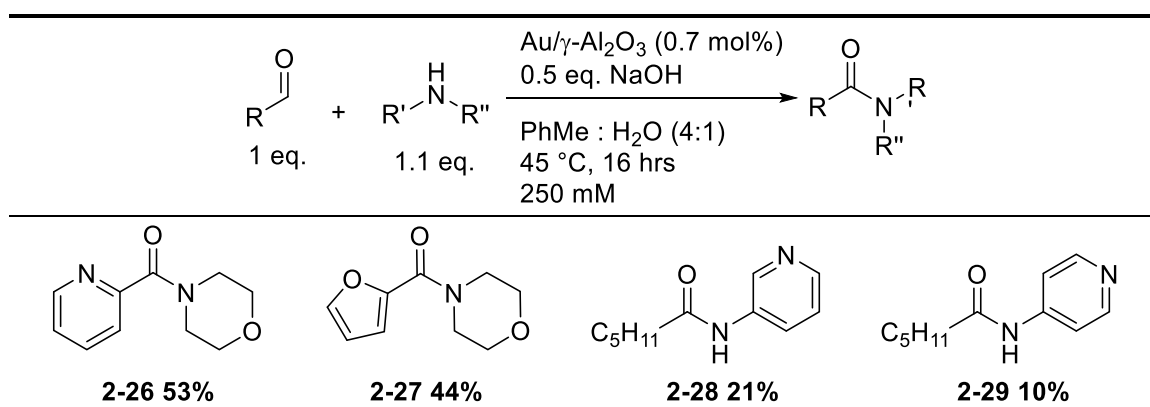


^aReaction conditions: Au/ γ -Al₂O₃ (150 mg, 0.7 mol%), aldehyde (1 mmol), amine (1.1 mmol), Bu₂O (4 mL), and aqueous 0.5 M NaOH (1 mL) ^bIsolated amide yields

Attempts using benzylamine also led rapidly to imine formation. This can be prevented by using a secondary amine (*N*-methyl benzylamine), but the low yields obtained, despite >90% conversion of the aldehyde, suggest either the oxidative amidation reaction is outpaced by the oxidation of the aldehyde to the acid or that the product was not isolated effectively from the reaction mixture.

The versatility of this chemistry was also demonstrated in the application to heterocycle containing aldehydes (Table 2-16). Problems with limited solubility of the heterocycle-containing aldehydes were overcome by substituting dibutyl ether with toluene (which was an equally effective solvent, see Table 2-9). This allowed the isolation of amidated heterocycles **2-26** and **2-27** in moderate yields without further optimisation. Reduced yields of **2-28** and **2-29** were obtained with electron-deficient amino-pyridines.

Table 2-16. Heterocyclic examples of amidation reaction using Au/ γ -Al₂O₃ and biphasic conditions

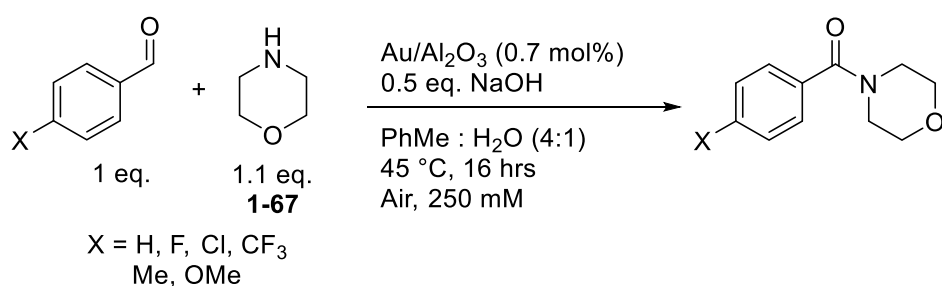


^aReaction conditions: Au/ γ -Al₂O₃ (150 mg, 0.7 mol%), aldehyde (1 mmol), amine (1.1 mmol), PhMe (4 mL), and aqueous 0.5 M NaOH (1 mL) ^bIsolated amide yields

2.6.1 Hammett Analysis

To date, no Hammett studies on oxidative amidation systems have been reported. The yields obtained with substituted benzaldehyde substrates (Table 2-15, **2-17**, **2-18**, **1-68**) prompted us to conduct a Hammett analysis with different para-substituted benzaldehyde substrates. Correlation between the rates of reaction and electronic effects of different para-substituted benzaldehydes can be used to offer mechanistic insights to the oxidative amidation reaction.

Previous Hammett analysis for AuNP-catalysed oxidation of benzyl alcohols to aldehydes reported a strong negative correlation,¹⁴⁰ inferring a build-up of positive charge around the benzylic carbon of a surface-bound intermediate, consistent with the elimination a benzylic hydride being the rate limiting step.



Scheme 2-11. Hammett analysis of the AuNP catalysed oxidative amidation reaction

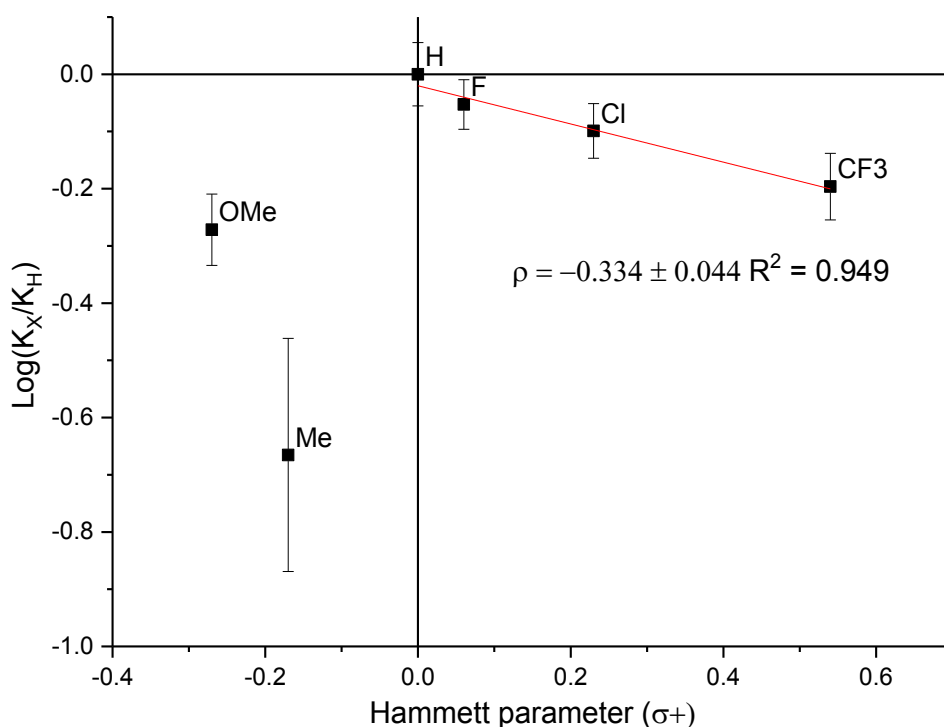


Figure 2-7. A plot of Hammett (σ_p) parameters¹⁴¹ against the log of the ratio between the rate of conversion of substituted benzaldehydes with benzaldehyde in the AuNP catalysed oxidative amidation. Error bars display the standard error associated with the correlation of the aldehyde concentrations to the linear fit.

Reactions to determine the rates of conversion of para-substituted benzaldehydes in the Au-catalysed oxidative amidation with morpholine **1-67** were performed independently and were analysed by HPLC at increasing intervals over 8 hours (Scheme 2-11). Concentrations of each para-substituted benzaldehyde were determined using a UV-vis detector and rates were calculated using a linear fit for the first 2 hours of the reaction.

The Hammett analysis plot showed no correlation between the rate of aldehyde conversion and the effects of electron-donating para-substituents (Figure 2-7). The lack of correlation between the rate of conversion and the electronic environment suggests that the rate-limiting step of the catalytic system does not involve reactions at the benzylic carbon.

However, the rates for substituted benzaldehyde systems bearing electron withdrawing groups ($R = \text{H, F, Cl, CF}_3$) show a small negative correlation ($\rho = -0.334 \pm 0.044$) between the Hammett parameter and relative rate. This would be consistent with the elimination of a negatively charged hydride species from a hemiaminal type intermediate. A similar negative correlation has been reported for a Au/TiO₂ catalysed alcohol oxidation, although this is a much more pronounced electronic effect ($\rho = -1.10$).¹⁴⁰

However, it is worth noting this study was conducted in a pure O₂ atmosphere, so it can be assumed that the rate was not limited by catalyst regeneration.

The results from the Hammett analysis are inconclusive. The lack of a linear correlation suggests that the results may be influenced by the bulk properties of the substituted aldehydes and complex physical interactions in the multiphasic system.¹⁴² The independence of the rate-limiting step to the rate of reaction may also support our previous hypothesis that the reaction is limited by the solubility and mass transfer effects of molecular oxygen in the reaction medium. However, a higher concentration of oxygen leads to a low selectivity and catalyst deactivation, which prevented further studies.

2.7 Conclusions

This chapter describes the development of a general synthetic procedure for the amidation of amines and aldehydes using Au/ γ -Al₂O₃ that can potentially be applied to other metal oxide supported Au catalysts. By examining the effect of each component, reaction conditions have been identified that can be applied to a range of substrates.

The role of base in gold catalysis is often poorly understood and investigations to explain its necessity are not normally undertaken. During the initial stages of this project the addition of base was observed to increase the catalytic activity of many supported AuNP systems in the oxidative amidation reaction. This result suggests a common mechanism for oxidative amidation.

We have highlighted the complex equilibria that exist in the multiphasic oxidative amidation reaction and propose how individual reaction components, fulfil more than one role in the catalytic system. In short, the addition of a sub-stoichiometric amount of hydroxide to the oxidative amidation reaction prevents the condensation of aldehydes and amines to amins/imines in the bulk solution and neutralises carboxylic acid by-products. The lack of product formation in under anaerobic conditions confirms that O₂ is the terminal oxidant. However, excess hydroxide and pure O₂ atmospheres appear to favour carboxylic acid formation. Both amide and carboxylic acid formation are surface-catalysed reactions. Hence, the selectivity of the reaction is dependent on the stoichiometry of base, as well as catalyst structure, reagents, and reaction conditions.

Using our AuNP catalyst we were able to efficiently perform amidation reactions with various benzylic and aliphatic aldehydes, with reasonable tolerance toward electron-donating and -withdrawing groups. Secondary amines were shown to be effective nucleophiles. However, couplings that utilised primary amines were more challenging and disappointing yields were obtained under the standard reaction condition. The formation of imines with extended conjugation systems proved impossible to drive towards the amide product.

The lack of any apparent relationship between reaction rate and electronics led to investigate alternative mechanistic pathways further. The preliminary investigations into possible mechanistic pathways provide the foundation for further discussion in subsequent chapters.

3 Catalyst Supports and Treatment Effects

3.1 Introduction

3.1.1 Background

Arguably, the greatest restriction in the development of heterogeneous catalysts is identifying the physicochemical properties that contribute to catalytic activity and translating these to an improved catalyst design. A significant amount of effort is usually dedicated to developing the preparation and pre-treatment of catalytic materials for specific processes.

The decision to identify a suitable heterogeneous catalyst for oxidative amidation was driven by one of our key objectives, to develop a *continuous* catalytic oxidative amidation process. Heterogeneous catalysts are ideally suited to continuous processing, as the catalyst can be isolated in either a plug or tank reactor and reagents can be continuously introduced.

Chapter 2 described the optimisation and scope of Au/ γ -Al₂O₃ catalysed oxidative amidation utilising a catalyst that was prepared via a sol-immobilisation method. It is known that this method affords AuNP catalysts, with a degree of consistency in the NP size and morphologies across a range of metal oxide supports. In this Chapter, the factors that may affect the performance of the Au/ γ -Al₂O₃ catalyst are presented, including a discussion on the analytical techniques used to study these effects. A short investigation into the effect of calcination temperature is presented and rationalised using simultaneous thermal analysis techniques.

3.1.2 Supported Gold Nanoparticle Development

Most metal-based heterogeneous catalysts are comprised of expensive catalytic metal(s) dispersed as nanoparticles or nanoclusters on a large surface area support.^{143,144} The activity of metal nanoparticles is unique and often displays radically different behaviour to both the bulk and atomic level equivalents. Previously, it was thought that the size of the nanoparticle was the critical parameter in controlling a catalysts activity. For selective oxidation reactions, it is typically believed that smaller AuNP's are more active.¹⁴⁵ However, more recent research has revealed suggests there are other significant contributing factors to the overall reactivity of AuNP catalysts, including:

- Metal-support interactions: both in modulating the activity and stability of the nanoparticles.^{146,147}
- Nanoparticle morphology: the number of coordinatively unsaturated corner and edge sites are important contributors to catalytic activity.^{148–151}
- Surface defects: creating higher energy coordinatively unsaturated ad-atoms, ridges, and islands.^{152,153}
- Composition of the AuNP nanoparticle: dopant metals (Cu, Pd, Ag, Pt, Co)^{100,104,154–157} can radically change the overall electronic properties of a NP and allow access to different reactive pathways.
- Compositional structure: how dopant metals are integrated into structure, be that alloying,^{104,158} core-shell structures,¹⁵⁹ or as discrete nanoparticles on the surface.¹⁰⁰

Figure 3-1 presents a graphical representation of the factors described above. Many of these factors are closely related. For example, the size and morphology of the NP will dictate the number particles in intimate contact with the support surface. While the size and composition of a NP is relatively easy to control, it is typically much more challenging to produce a desired morphology.¹⁶⁰

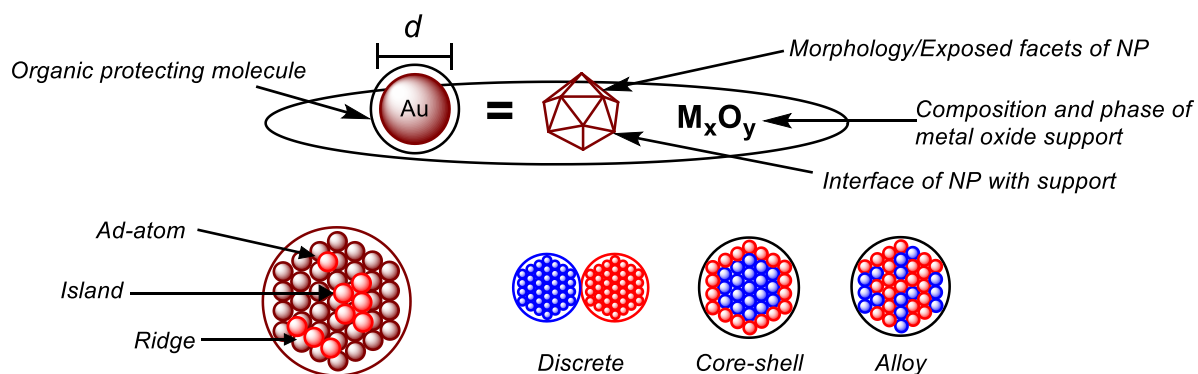


Figure 3-1. Factors affecting the activity of heterogeneous catalysts and schematic examples of NP surface defects and different mixed metal NP compositions

3.1.3 Synthesis Methods

As the interest in heterogeneous Au catalysis has grown, so has the variety of AuNP catalyst preparation methods. The preparation of supported AuNP catalysts tends to be a combination of two steps; firstly, the introduction of Au to the support material (as either pre-cursor or pre-formed nanoparticles), followed by a catalyst pre-treatment either to induce the formation of nanoparticles or to activate the catalyst.

It would be misleading to claim the importance of either the introduction of Au or the catalyst pre-treatment as greater than the other. The method of introducing Au to the support will influence the distribution of Au throughout the support material, and therefore the number of accessible active sites. Both the method of Au introduction and catalyst pre-treatment can influence the size and morphology of the resultant NP and hence the overall distribution of active sites.

The most commonly employed AuNP catalyst preparation techniques are impregnation, deposition-precipitation, coprecipitation and sol-immobilisation. Choosing a method is not solely about the properties of the NP - the nature of support will also influence the available methods; for example, deposition and sol-immobilisation methods are dependent on the point of zero charge of the surface, which is an inherent property of the support related to the surface's acidity/basicity. The Au precursor is typically chloroauric acid (HAuCl_4), but the presence of residual chloride ions has been shown to have detrimental effects in both thermal post treatment steps and can act as a poison in catalytic oxidation processes.^{161,162} The removal of chloride and other contaminants introduced during the preparation can be achieved by vigorous washing,¹⁶³ mild heating under aqueous reflux, or by higher temperature calcination/sintering steps.

Impregnation Methods

Impregnation is the one of the oldest methods for supported Au catalyst preparation,⁸⁷ the process consists of the addition of an aqueous solution of HAuCl_4 to a suspension of the support. The impregnation of the metal ions into the porous solid is achieved by evaporation of H_2O , and further drying steps are used to attain the final catalyst. Additional calcination or reduction steps can be applied following impregnation to change the properties of the resultant NPs.

The impregnation method is a rather crude preparation of AuNP catalysts, as it affords little control over the size or morphology; the NP size distribution tends to be wider, and the mean AuNP sizes tends to be larger ($> 5 \text{ nm}$), than catalysts prepared by other methods. Nevertheless, impregnation is arguably the best preparation method suited to large scale production. This method utilises fewer reagents and the catalytically active component is distributed homogeneously throughout the catalyst

material, as the support material is saturated by the catalytic component pre-cursor prior to nanoparticle formation.¹⁶¹

Impregnation has been largely superseded by other preparation methods, but an improved incipient-wetness (also known as double impregnation) method has been shown to yield highly active AuNP.^{161,164,165} The incipient-wetness preparation consists of impregnating the dry powder with a high concentration solution of HAuCl_4 , followed by the addition of the minimum amount of a Na_2CO_3 solution to form a slurry. This allows Au to be precipitated as the hydroxide salt, allowing more Cl^- to be washed from the material before calcination, allowing access to smaller particle sizes.¹⁶¹

Deposition-Precipitation Method

Deposition-precipitation, a technique developed and popularised by Haruta,^{145,166,167} was the first catalyst preparation optimised for AuNP oxidation catalysts. Compared to the impregnation method, the order of addition of Au precursor to support is reversed - the chosen support material is added to a solution of HAuCl_4 and precipitation is induced by adjusting the pH of the solution. In this method, AuNP formation is controlled by pH, aging time, temperature, or by the addition of co-ordinating species, such as urea.¹⁶⁸

Deposition-precipitation, like impregnation, results in a homogeneous dispersion of AuNP throughout the metal oxide support. While the greater control over the rate of Au precipitation facilitates the preparation of catalysts with much smaller (2 - 3 nm) nanoparticles desirable for catalytic CO oxidation, it can also lead to wide size distributions. Many active sites will also be embedded within the support material, which could hinder the access of larger molecules in liquid phase.

Coprecipitation Method

The coprecipitation method was reported by Haruta in 1989 for preparing Au catalysts for low temperature oxidation of H_2 and CO. In this case, catalyst formation is induced by precipitation of a mixture of HAuCl_4 and nitrate salt of the desired support material, such as $\text{Fe}(\text{NO}_3)_3$, $\text{Cu}(\text{NO}_3)_2$, or $\text{Al}(\text{NO}_3)_3$.¹⁶⁹ The mixed metal solution is poured into aqueous sodium carbonate resulting in the precipitation of a solid pre-catalyst, typically a carbonate or hydroxylate of the support material. The solid pre-catalyst is then thermally treated at high temperature to yield the active AuNP catalyst. Coprecipitation as a technique does not depend on a supports PZC. But the method has been largely been surpassed, as it offers poor control over both the size and distribution of the AuNPs.

Sol-Immobilisation Method

Sol-immobilised catalysts are prepared by the deposition of pre-formed nanoparticles onto the surface of a support material. The pre-formed AuNP sol is typically made by the addition of a reducing agent to a solution of HAuCl_4 in the presence of a stabilising molecule, such as a co-ordinating polymer or a capping agent, typically polyvinyl acetate (PVA) or polyvinylpyrrolidone (PVP).

The sol-immobilisation method was first described by Prati and Martra for the preparation of AuNPs supported on carbon (Au/C) to catalyse the liquid phase oxidation of ethane-1,2-diol.¹⁷⁰ The authors reported that Au/C prepared using the deposition-precipitation method resulted in large AuNPs (mean 13 nm) and poor catalytic activity ($\text{TOF } 430 \text{ mol}_{\text{subs}}/\text{mol}_{\text{cat}} \text{ h}^{-1}$); as the weak interaction between the carbon surface and the AuNP leads to aggregation during the catalyst synthesis. In comparison, the sol-immobilised Au/C, prepared with PVA, had a much smaller average AuNP size (mean 7.5 nm) and consequently displayed far superior activity ($\text{TOF } 1000 \text{ mol}_{\text{subs}}/\text{mol}_{\text{cat}} \text{ h}^{-1}$) for the oxidation of ethane-1,2-diol.

The sol-immobilised method was found to offer a high degree of both control and reproducibility over the size and morphology of the nanoparticle. As the AuNP is formed independently of the support, it is possible to achieve consistency in size and morphology across a range of materials. As the method deposits nanoparticles onto the support, it is reasonable to assume a much greater proportion of the Au is closer to the particle surface, increasing the number of accessible active sites. On the other hand, the sol-immobilisation technique is currently limited to smaller-scale batch production to ensure a uniform dispersion of NPs across the support surface. The stability of a sol-immobilised catalyst is also reliant on using a support that has a large surface area and a strong interaction between the NP and the surface, to prevent leaching or coagulation of the NP.

3.1.4 Catalyst Supports

Immobilisation of AuNP on a support material streamlines the recovery process and increases their stability against agglomeration. However, the support does not simply act as a high surface area scaffold, as the choice of support can also impact the outcome of a chemical process.^{120,145,171,172}

Metal-support interactions (MSI) were first reported in the 1930's as an 'electronic factor' to justify the activity of certain catalysts.¹⁷³ However, modern reports would suggest that the degree to which MSI impact a AuNP catalysed reaction are much more explicit. As discussed earlier, the properties of a support (e.g. PZC) can influence the available preparation methods, and thus the accessible AuNP sizes and morphologies.^{174,175} A support with a suitably high surface pH can alleviate the necessity for

a co-catalytic base¹⁷⁶ or they can participate directly in a reaction at the NP-support interface.¹⁵¹ For example, reducible metal oxides supports can be implemented to act as O₂ storage materials.¹⁷⁷

For a heterogeneous catalyst to retain its activity, it is important for the NP to remain bound to the surface during the course of a reaction. Leaching processes, either by the loss of single atoms or the desorption of whole nanoparticles,¹⁵ can both reduce the activity of the catalyst and contaminate the product. Leaching of supported AuNP catalysts can be further prevented by controlling reaction conditions or by increasing the strength of the interaction between the AuNP and the surface.

Metal oxides are rarely utilised as supports in the Au catalysed oxidative amidation reaction despite both physically and chemically robust. Metal oxide supports were chosen for investigation as they are typically compatible with the sol-immobilisation method and their resilience ensures the integrity of the catalyst can be retained during pre-treatments and under reaction conditions.

3.1.5 Treatment Effects

Pre-treatment of the 'fresh catalyst' is usually required to realise its optimum catalytic activity. The methods of pre-treatment depend on the synthesis method and desired catalytic application. The most common treatments are catalyst washing and thermal processes, such as drying or calcination under a reducing or oxidising atmosphere. Either chemical or thermal treatments can be used to induce NP formation or to remove water and residual contaminants.

Washing steps are routinely employed to treat catalysts prepared by deposition-precipitation, co-precipitation and sol-immobilisation methods. The isolated solid catalyst is washed repeatedly with water to remove residual ions, introduced during the preparation, that can have a detrimental effect on the catalyst structure. For example, the presence of Cl⁻ can reduce the activity of AuNP catalysts by accelerating the aggregation of AuNPs during thermal treatments.^{162,178} Thermal treatment in an atmosphere of H₂ has been shown to remove residual Cl⁻ while retaining small sized AuNPs. Alternatively, washing supported AuNP catalysts with ammonia solutions has been shown to be an equally effective method of removing Cl⁻.

Organic protecting molecules and capping agents, such as those used in sol-immobilisation procedures, cannot be removed by washing steps under ambient temperatures.¹²⁰ The key drawback to thermal treatment steps for removing organic molecules is the tendency of AuNP to aggregate at the higher temperatures required (>300 °C). To this end, Hutchings et al. have developed a method to remove excess organic stabilising ligand (PVA) from Au/TiO₂ by refluxing in water and filtration.¹⁷⁹

3.2 Sol-Immobilised Au/ γ -Al₂O₃

3.2.1 Au/ γ -Al₂O₃ Synthesis

In Chapter 2, Au/ γ -Al₂O₃ was identified from among other supported Au catalysts for the oxidative amidation reaction. γ -Al₂O₃ was investigated as the support of choice, based on the empirical observation that it outperformed other support materials under reaction conditions, and displayed limited reactivity even in the absence of base (section 2.5.5).

The Au/ γ -Al₂O₃ catalyst employed in this work was prepared on a 10 g scale, following a previously described procedure: Partially hydrolysed polyvinyl acetate (PVA) was added to an aqueous solution of HAuCl₄ to act as a stabilising molecule, followed by addition of NaBH₄ as the reducing agent to form a AuNP sol.¹²⁰ Following NP deposition, the sol-immobilised Au/ γ -Al₂O₃ was subjected to a gentle reflux in H₂O to remove excess PVA.¹⁷⁹ After washing the Au/ γ -Al₂O₃ was dried and ground to a fine powder before calcination.

3.2.2 Au/ γ -Al₂O₃ Characterisation

Relating a catalyst's physicochemical properties with its reactivity is not straightforward. Arguably, these difficulties are related to the complexity of the catalyst's physical structure, which requires multiple characterisation techniques. This Chapter presents a study of the key attributes of a sol-immobilised Au/ γ -Al₂O₃ catalyst that make it suitable for the oxidative amidation reaction.

Point of Zero Charge

The point of zero charge (PZC) reflects the overall acid-base characteristics of a materials surface, which can be analysed by using adsorption and titrimetric techniques. The average charge of the surface is the critical parameter for sol-immobilisation, where the deposition of AuNP on the support surface is achieved by electrostatic interactions. Reduction of the Au precursor using NaBH₄ (and PVA) results in the formation of AuNP decorated with hydroxyl and chloride anions. Hence, the surface of the support must be positively charged to affix the AuNP, and this is achieved by adjusting the pH of the AuNP sol solution to below the PZC of the chosen support.

In this work, PZC measurements of the support material (γ -Al₂O₃) and catalyst were made using a pH titration method,¹⁸⁰ where a range of NaNO₃ solutions with pHs in the range of 2 – 11 were prepared. A small amount of catalyst was added to solution and the suspension was allowed to equilibrate over 16 hours. The difference between the final pH and the starting pH was calculated and plotted against the starting pH (Figure 2). The PZC of the solid material is the x-intercept of the resultant plot (the point at which the pH of the solution and the surface are equivalent).

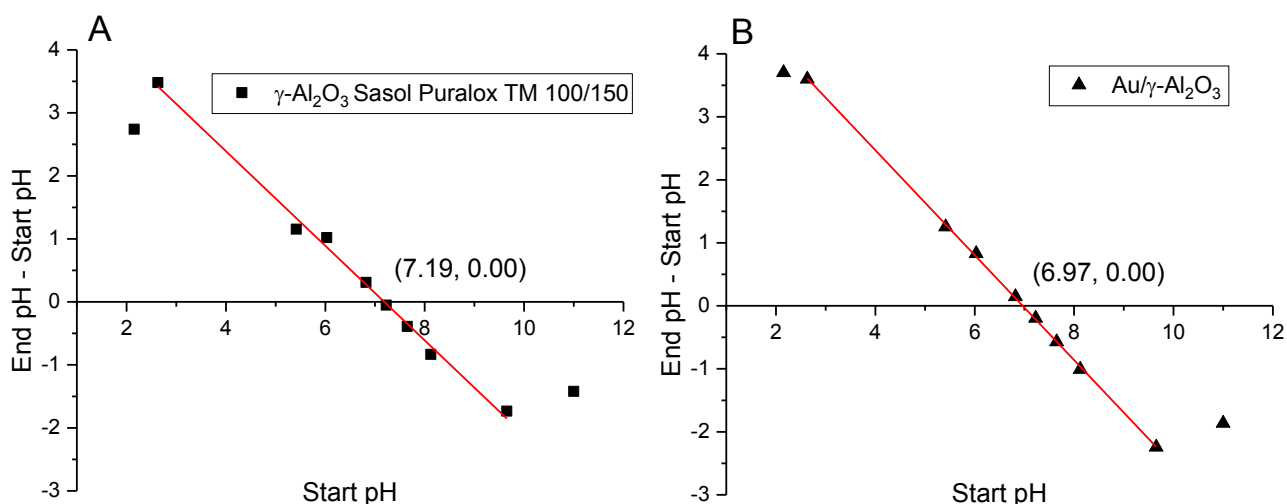


Figure 3-2. PZC plots of A) $\gamma\text{-Al}_2\text{O}_3$ (Sasol Puralox TM 100/150) B) Sol-immobilised $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ calcined at 500 °C

Table 3-1. PZC values for support materials and $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ catalyst

Entry	Material	PZC
1	$\gamma\text{-Al}_2\text{O}_3$ (Sasol TM 100/150)	7.19
2	$\text{Au}/\gamma\text{-Al}_2\text{O}_3$ - Calcined 500 °C	6.97

The PZC for the chosen support, $\gamma\text{-Al}_2\text{O}_3$ (Sasol Puralox TM 100/150) was determined to be 7.19 (Table 1, entry 1), which is consistent with expected values for $\gamma\text{-Al}_2\text{O}_3$, which can range from 6.9 to 9.7.¹⁸¹ Under these conditions, the formation of the AuNPs using NaBH_4 resulted in a sol with a pH between 5 - 6, therefore no adjustment was required to deposit the AuNP onto this support. The PZC of the $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ catalyst following calcination at 500 °C was found to be 6.97 (entry 2).

Brunauer-Emmett-Teller (BET) Analysis - Specific Surface Area

BET analysis is used to determine the specific surface area of a solid sample and is calculated using N_2 adsorption.¹⁸² Ideally, a catalyst support should possess a large surface area, so as to maintain the NP dispersion during the synthesis and pre-treatment. Particularly for catalysts prepared using sol-immobilisation, the weaker nature of the interaction between the NP and the support may lead to undesired aggregation to form larger NP's under catalytic conditions, resulting in a loss of activity.

BET analysis was performed to determine the surface area of the metal oxide support and the $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ catalyst, before and after calcination (Table 3-2).

Table 3-2. BET surface areas of γ -Al₂O₃ and Au/ γ -Al₂O₃ samples

Entry	Material	BET Surface Area (m ² /g)
1	γ -Al ₂ O ₃ support	147
2	Au/ γ -Al ₂ O ₃ - Uncalcined	139
3	Calcined ^a Au/ γ -Al ₂ O ₃	143

^a500 °C under air for 3 h

There is very little difference in values obtained for all three Au/ γ -Al₂O₃ samples (Table 3-2), showing that the preparation method and calcination steps have a negligible effect on the specific surface area of the catalyst. The measured specific surface area of the Au/ γ -Al₂O₃ catalyst (entry 3) is falls between the lower range reported for other Au/ γ -Al₂O₃ oxidation catalysts (137 to 314 m² g⁻¹).^{183,184}

X-Ray Diffraction (XRD)

Aluminum oxide (alumina) exists in different transitional polymorphic forms,¹⁸⁵ which can be obtained from thermal treatment of aluminium-containing ores. Each transitional polymorph has a distinct crystal structure, with physical and chemical properties that differ depending on their exposed facets. The most commonly used alumina materials are α -Al₂O₃ and γ -Al₂O₃. α -Al₂O₃ is the most thermodynamically stable crystalline form and can be obtained via the thermal treatment of any aluminium-containing ore and is typically employed for ceramic applications. By comparison, γ -Al₂O₃, is obtained from the thermal treatment of boehmite, is most commonly used as a catalyst support as it typically has the largest surface area of the transitional aluminas.¹⁸⁶ In this work, XRD was used to confirm the phases of alumina present in the support material and catalyst, before and after calcination.

The alumina support (Sasol Puralox TM 100/150) was found to be the gamma phase, confirmed by comparing the obtained XRD pattern with literature values,¹⁸⁷ and unchanged by deposition of AuNP onto the surface. As expected, calcination at 500 °C did not induce any phase changes; the transition of γ -Al₂O₃ into δ -Al₂O₃ is known to require temperatures above 750 - 850 °C.^{186,188}

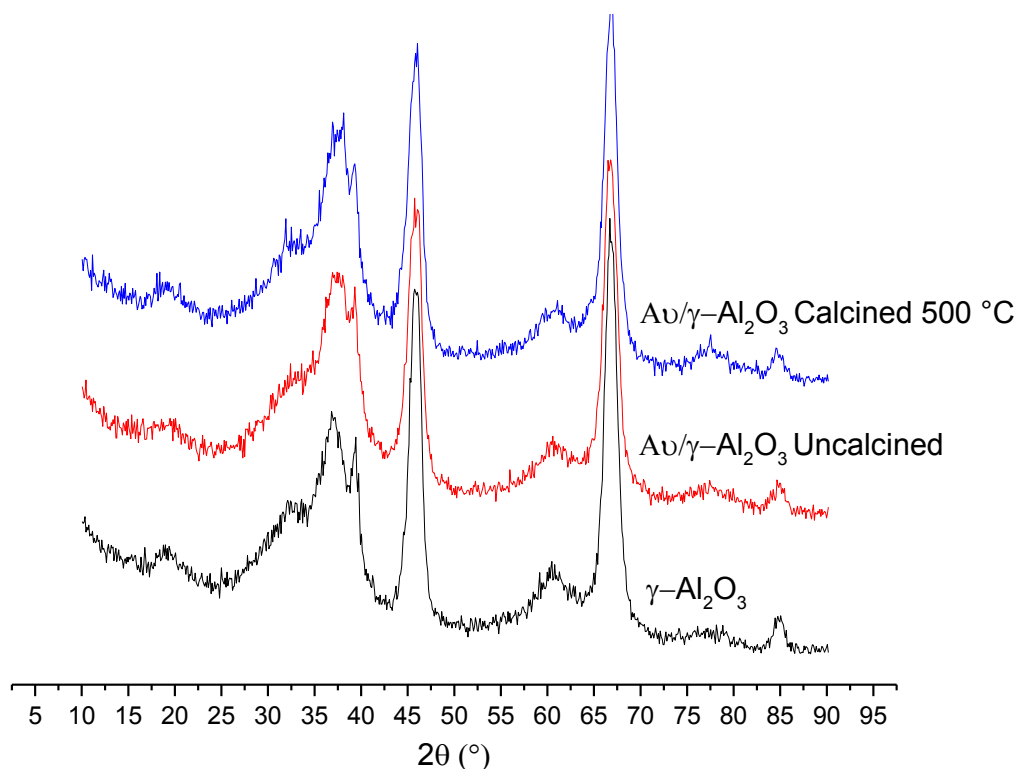


Figure 3-3. XRD diffraction patterns for blank $\gamma\text{-Al}_2\text{O}_3$, uncalcined $\text{Au}/\gamma\text{-Al}_2\text{O}_3$, and $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ calcined at 500 °C

Ion Coupled Plasma - Atomic Emission Spectroscopy (ICP-AES)

ICP-AES was used to measure the total Au content of the catalytic materials. Catalyst samples were digested in refluxing aqua regia to dissolve the Au. The amount of Au in each $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ catalyst employed in these oxidative amidation studies was between 0.85 and 0.95 wt%. ICP analysis was conducted on catalytic material obtained at each stage of the sol-immobilised $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ preparation (Table 3-3). Samples were collected after Au reduction/deposition (entry 1), after aqueous reflux to remove PVA (entry 2), and after calcination (entry 3). All samples were dried in a static oven at 80 °C prior to digestion in aqua regia.

Table 3-3. ICP analysis of $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ at different stages of the sol-immobilisation preparation

Entry	Material	Au content ^a (wt%)
1	$\text{Au}/\gamma\text{-Al}_2\text{O}_3$ - After deposition	1.03 ± 0.04
2	$\text{Au}/\gamma\text{-Al}_2\text{O}_3$ - After aqueous reflux (Uncalcined)	0.90 ± 0.04
3	$\text{Au}/\gamma\text{-Al}_2\text{O}_3$ - Calcined at 500 °C	0.95 ± 0.04

^aAu content error calculated from the error in the mass of catalyst digested (± 1 mg)

Comparing entries **1** and **2**, the apparent reduction in Au content following the aqueous reflux would suggest that the catalyst washing step results in removal of both PVA and weakly adsorbed Au species, such as unreduced Au(III) or small Au nanoclusters. As expected, calcination of the washed Au/ γ -Al₂O₃ sample (entry **3**) resulted in a small increase in the observed Au content due to dehydration of the support surface.

Transmission Electron Microscopy (TEM)

TEM uses an electron beam to obtain a two-dimensional image of a sample, by firing a highly-energetic electron beam through a thin sample. The resulting image shows a representation of both the thickness and composition of the sample: heavier atoms scatter more electrons resulting in a darker image. Hence, darker regions in the Au/ γ -Al₂O₃ images are due to either thicker sections of γ -Al₂O₃ or AuNP. For this work, AuNP are assigned as the distinctive dark spots against the alumina background (Figure 3-4). The exact chemical composition of the surface can be confirmed by supplementary Energy Dispersive X-Ray (EDX) analysis, although this does not form part of the routine catalyst analysis described in this thesis.

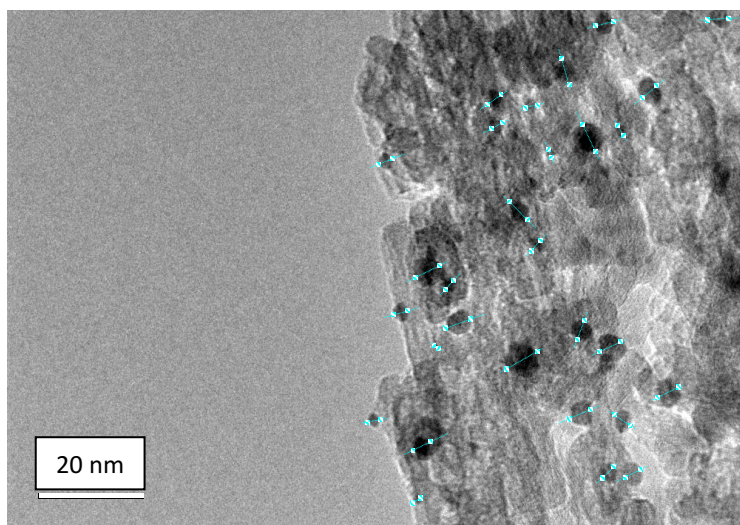


Figure 3-4. TEM image of Au/ γ -Al₂O₃ calcined at 500 °C

TEM is routinely used to provide statistical information about the NP size distribution, dispersion on the catalyst surface, and morphology of AuNPs. While TEM imaging is perhaps the most intuitive method of measuring AuNP sizes, the analysis of TEM images is subject to a degree of bias, as only selected areas of the catalyst surface are imaged and measurement of the AuNP sizes is performed manually. In this work, the statistical mean and distribution of AuNP sizes was calculated for samples of uncalcined Au/ γ -Al₂O₃ and Au/ γ -Al₂O₃ calcined at 500 °C (Figure 3-5).

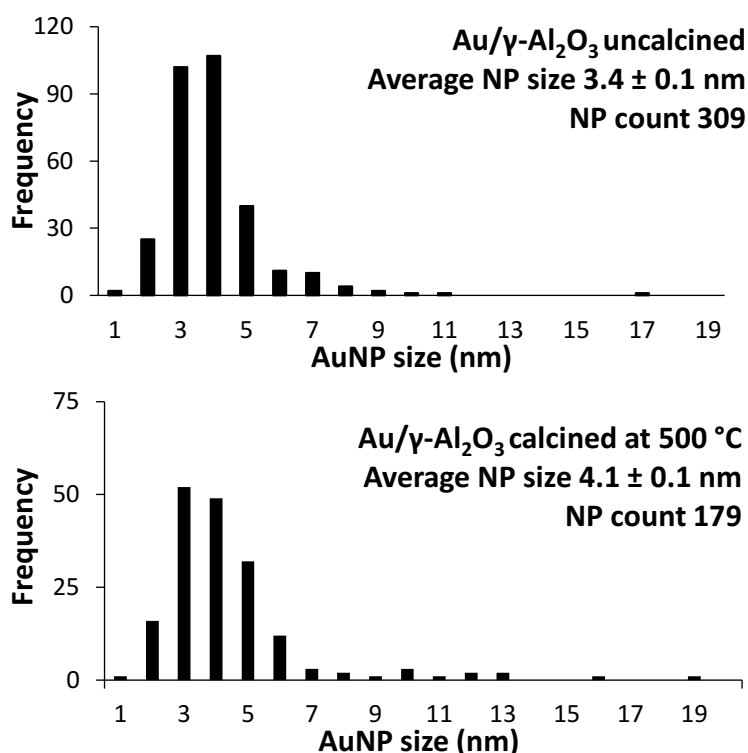


Figure 3-5. AuNP size distributions determined by TEM for Au/γ-Al₂O₃ A) Uncalcined B) Calcined at 500 °C.

The uncalcined Au/γ-Al₂O₃ catalyst exhibited an average AuNP size of 3.4 ± 0.1 nm. This value is consistent with sizes reported for AuNP catalysts supported on γ-Al₂O₃, TiO₂, and MgO, which were prepared using similar sol-immobilisation preparations.^{120,189,190} Calcination of the Au/γ-Al₂O₃ catalyst was conducted under air at 500 °C for 3 hours resulted in an increased average AuNP size of 4.1 ± 0.1 nm and a greater skewness toward larger particle sizes. The sintering of sol-immobilised AuNP catalysts is dependent on multiple factors, such as the dispersion of the NPs, the specific surface area of the support, and the strength of the interaction between the AuNPs and the support surface.¹⁸⁹ The relationship between calcination temperature, the sintering of the Au/γ-Al₂O₃ catalyst, and subsequent impact on the oxidative amidation reaction is discussed in more detail in Section 3.3.

3.2.3 Summary

The activity of supported AuNPs is determined by a range of complex structural features, not just the AuNP size. We have identified a commercial alumina (Sasol Puralox TM 100/150) as a suitable AuNP support material for the oxidative amidation of aldehydes. The PZC of the surface is approximately neutral, meaning that the number of acidic and basic sites is also approximately equal, and the pH of the gold sol does not require adjustment prior to the deposition step. We confirmed that Au/ γ -Al₂O₃ prepared by the sol-immobilised method has a high surface area, consisting of narrowly-distributed AuNP's of *ca.* 3 nm, supported on gamma phase alumina. Calcination at 500 °C resulted in a small increase in the average nanoparticle size; but, calcination of the 'freshly prepared' Au/ γ -Al₂O₃ at 500 °C resulted in a significant colour change, from red-brown to purple, leading to a more detailed investigation into the effect of calcination on sol-immobilised catalysts.

3.3 Thermal Pre-Treatment of Au/ γ -Al₂O₃

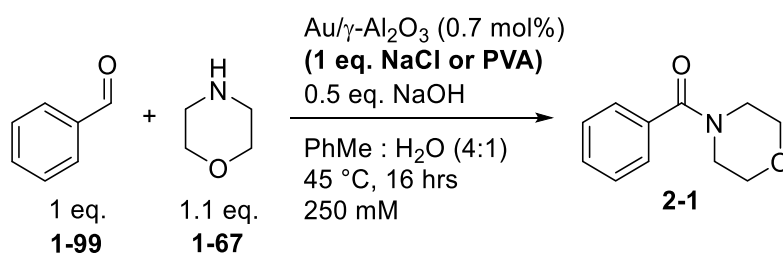
3.3.1 Aims

As discussed in the introduction to this chapter, optimal activity of AuNP catalysts prepared using a sol-immobilisation method typically requires a pre-treatment to remove the stabilising molecule employed to control the NP size. The removal of stabilising molecules, and other residual contaminants, is typically achieved by washing steps, chemical treatment, or thermal treatment. The use of catalyst washing and chemical pre-treatments typically employs mild conditions that allows optimal catalytic activity to be achieved without changing the AuNP structure.¹⁹¹

Thermal calcination was initially investigated as an alternative approach to regenerating spent Au/ γ -Al₂O₃. Calcination of 'freshly prepared' Au/ γ -Al₂O₃ at 500 °C resulted in a significant colour change, from red-brown to purple. Despite an increase in average AuNP size, the calcined Au/ γ -Al₂O₃ was found to be a more active catalyst in the oxidative amidation reaction. The aim of this short study was to examine this unexpected observation.

3.3.2 Effect of Residual Contaminants

Au/ γ -Al₂O₃ prepared via sol-immobilisation is washed and refluxed in H₂O to remove Cl⁻ ions and PVA stabilising ligand remaining from the synthesis. To establish if the presence of residual contaminants are detrimental to catalyst performance, the Au/ γ -Al₂O₃ catalysed oxidative amidation reaction between benzaldehyde **1-99** and morpholine **1-67** was performed with the addition of either 1 equivalent of NaCl or 5 mg PVA (corresponding to approximately twice the amount of PVA per gram of catalyst used during the sol-immobilisation method) (Scheme 3-1).



Scheme 3-1. Au/ γ -Al₂O₃ catalysed oxidative amidation reaction of benzaldehyde and morpholine performed with addition of possible contaminants from catalyst synthesis

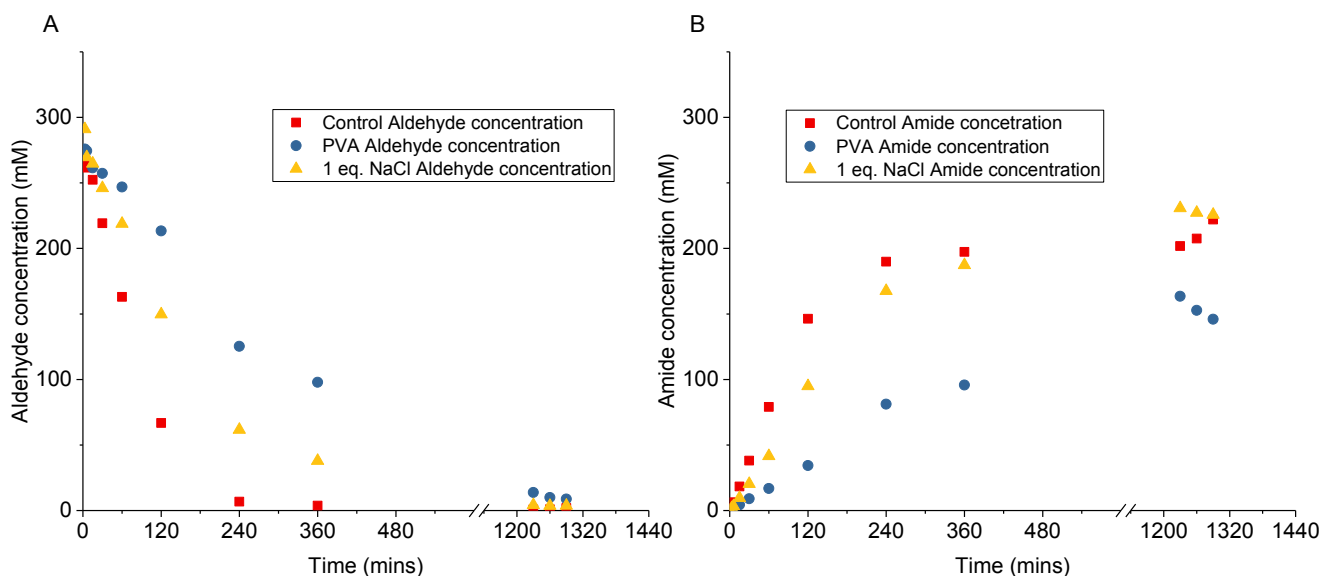


Figure 3-6. Concentration profiles for the Au/ γ -Al₂O₃ catalysed oxidative amidation reaction performed with possible contaminants from catalyst synthesis A) aldehyde concentration B) amide concentration

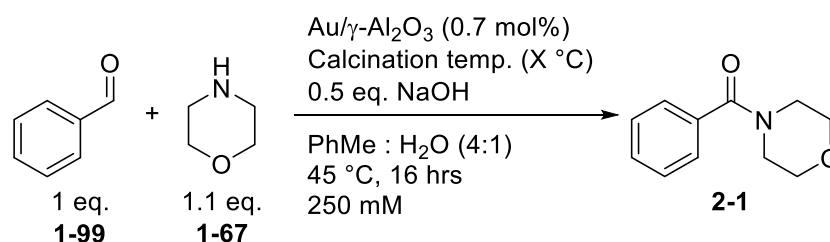
Interestingly, the addition of both NaCl and PVA reduced the catalytic activity of Au/ γ -Al₂O₃. The presence of Cl⁻ ions did not influence the selectivity of the Au catalysed oxidative amidation, inferring a reversible inhibition via the adsorption of Cl⁻ ions to the AuNP surface. On the other hand, the addition of PVA was found to have an inhibitory effect while also reducing the amide selectivity. The reduction in selectivity is likely due to the large size of the PVA molecule that restricts the surface mobility and combination of the bulky substrates.

3.3.3 Calcination Temperature

Catalyst calcination is performed under either reducing or oxygenated atmospheres and can be used to either change a catalysts physical structure or remove volatile or combustible contaminants. The choice of atmosphere and temperature is critical in controlling the properties of the obtained material. In the initial part of this study, catalysts calcined in a flowing or static air conditions were found to exhibit no difference in their catalytic activity.

Multiple samples of Au/ γ -Al₂O₃ were calcined under a flowing atmosphere of air at different temperatures up to 700 °C. Each calcined catalyst was employed in the oxidative amidation reaction between benzaldehyde **1-99** and morpholine **1-67** (Table 4). γ -Al₂O₃ undergoes a thermal transition into δ -Al₂O₃ at temperatures exceeding 850 °C, therefore it is reasonable to assume that calcination at temperatures of <700 °C will not result in a structural change in the support material.¹⁸⁸

Table 3-4. Results summary of the oxidative amidation reaction using Au/ γ -Al₂O₃ calcined at different temperatures



Entry	Calcination Temp. ^a (°C)	Conversion 1-99 ^b (%)	Yield 1-67 ^b (%)	Initial rate of 1-99 conversion ^c (mM min ⁻¹)
1	Uncalcined	99	69	0.593 ± 0.106
2	100	99	71	0.672 ± 0.111
3	300	99	80	1.080 ± 0.114
4	500	99	82	1.076 ± 0.070
5	600	99	78	0.998 ± 0.148
6	650	99	83	1.092 ± 0.081
7	700	91	73	0.405 ± 0.088

Reaction conditions: Au/ γ -Al₂O₃ (Calcined, 150 mg, 0.7 mol%), aldehyde (1 mmol), amine (1.1 mmol), Bu₂O (4 mL), and aqueous 0.5 M NaOH (1 mL) ^a500 mg of catalyst heated at specified temperature for 3 h under a flow of air (~20 mL min⁻¹) ^bAldehyde conversion and amide yield determined by HPLC ^cInitial rate of aldehyde conversion during first 2 h

Catalyst calcination was found to have a beneficial effect, employing Au/ γ -Al₂O₃ samples heated at temperatures between 300 and 650 °C resulted in an increased amide **2-1** selectivity and a faster initial rate of benzaldehyde conversion (Table 3-4, entries **1** vs. **3** to **6**). The initial rates of aldehyde

conversion were estimated by assuming a zero-order approximation for the concentration of aldehyde and fitting a linear curve to the first 2 hours of the aldehyde concentration profile (Figure 3-7).

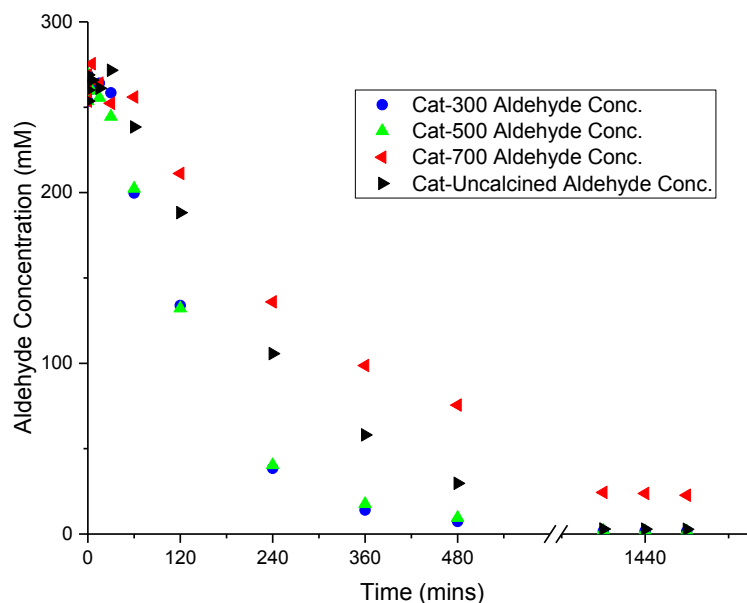


Figure 3-7. Benzaldehyde concentration profile for the oxidative amidation reaction employing calcined $\text{Au}/\gamma\text{-Al}_2\text{O}_3$, some aldehyde concentration profiles omitted for clarity

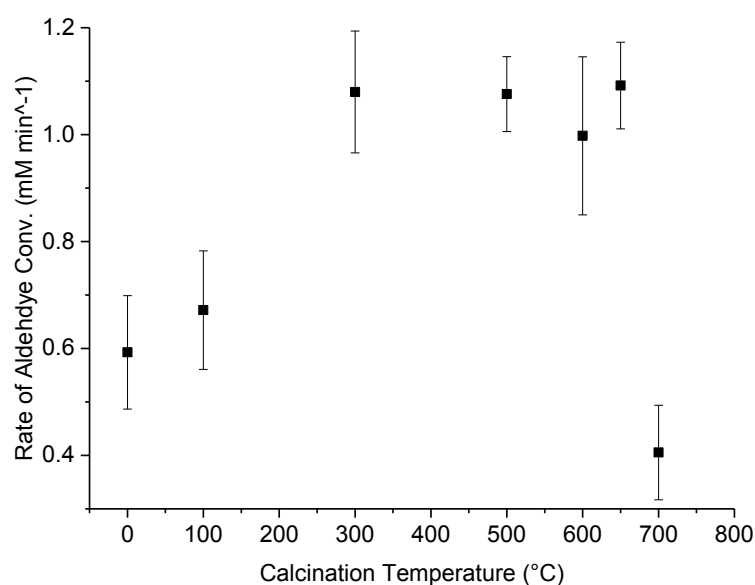


Figure 3-8. Rates of aldehyde conversion for the oxidative amidation reaction plotted against the maximum calcination temperature of the $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ used for each for each reaction

Plotting of the **1-99** conversion rates against the $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ calcination temperature (Figure 3-8) reveals that maximum catalyst activity is obtained when catalysts are calcined between 300 and 650 °C. At this stage, it is unclear at this stage whether this upper limit is corresponds to a maximum number of active sites, or the reaction may be limited by mass transfer effects (dissolution of O_2 in

solution). By comparison, the Au/ γ -Al₂O₃ calcined at 700 °C is far less active and selective, showing a similar performance to the uncalcined catalyst (Table 3-4, entries **7** and **1**).

In many cases, calcination of supported AuNP catalysts results in sintering, due to an increased mobility of metallic species on the support surface promoted by the elevated temperature. NP sintering can occur via two key mechanisms, either an Ostwald ripening type mechanism where particles break down into either atomic or nanocluster species and coalesce with nearby larger particles, or the merging of two NPs to form a single larger NP.¹⁹²

For each calcined catalyst the weight percentage of Au and average NP size were recalculated using ICP-AES and TEM respectively (Table 3-5 and Figure 3-9). The amount of Au in each sample is expected to increase due to both dehydration and the removal of organic material from the surface, while sintering will be apparent by an increase in the average AuNP size.

Table 3-5. Summary of Au mass by weight and AuNP size of calcined Au/ γ -Al₂O₃ samples

Entry	Calcination temp. (°C)	Au content by ICP ^b (wt%)	Average NP size ^c (nm)
1	Uncalcined	0.82 ± 0.04	3.4 ± 0.1
2	100	0.83 ± 0.04	3.4 ± 0.1
3	300	0.84 ± 0.04	3.6 ± 0.1
4	500	0.85 ± 0.04	4.1 ± 0.2
5	600	0.85 ± 0.04	6.3 ± 0.3
6	650	0.85 ± 0.04	9.6 ± 0.3
7	700	0.88 ± 0.04	41.6 ± 2.8

^a500 mg of catalyst heated at specified temperature for 3 h under a flow of air (~20 mL min⁻¹) ^bICP error calculated from error in mass of catalyst digested (± 1 mg) ^cStatistically determined average AuNP size and error in the mean value, number of AuNP counted for each sample reported in **Figure 3-9**

As predicted, both the Au content and average NP size of each Au/ γ -Al₂O₃ sample increased with the maximum calcination temperature (Table 3-5). The increase in Au wt% of each catalyst sample is relatively small (<10%) at calcination temperatures between 300 and 650 °C (entries **3** to **6**). Whereas, there is a significant increase in the average NP size from 3.6 to 9.6 nm, which corresponds with an almost two-fold increase in catalyst activity (Table 3-4). Calcination at temperatures ≥700 °C (entry **7**) result in an exponential growth in the size of the AuNP, and concomitant reduction in the activity of the catalyst.

This trend is consistent with earlier findings reported by Kobayashi and co-workers, who proposed that slightly larger particle sizes are optimal for oxidative amidation. The larger particles experience a weaker amine physisorption; which could otherwise inhibit the active catalyst sites.^{101,102} By controlling the AuNP formation, the authors established an optimal range of AuNP sizes (between 5 and 11 nm) for the oxidative amidation of aldehydes.

By using a thermally-stable metal oxide support, it has been shown that it is also possible to control AuNP size by careful selection of the calcination temperature (which is incompatible with the Au-PICB catalysts, due to the use of the organic matrix). At calcination temperatures above 700 °C, extensive sintering occurs to afford very large AuNP's which negates the beneficial effects observed with the mid-range NP's.

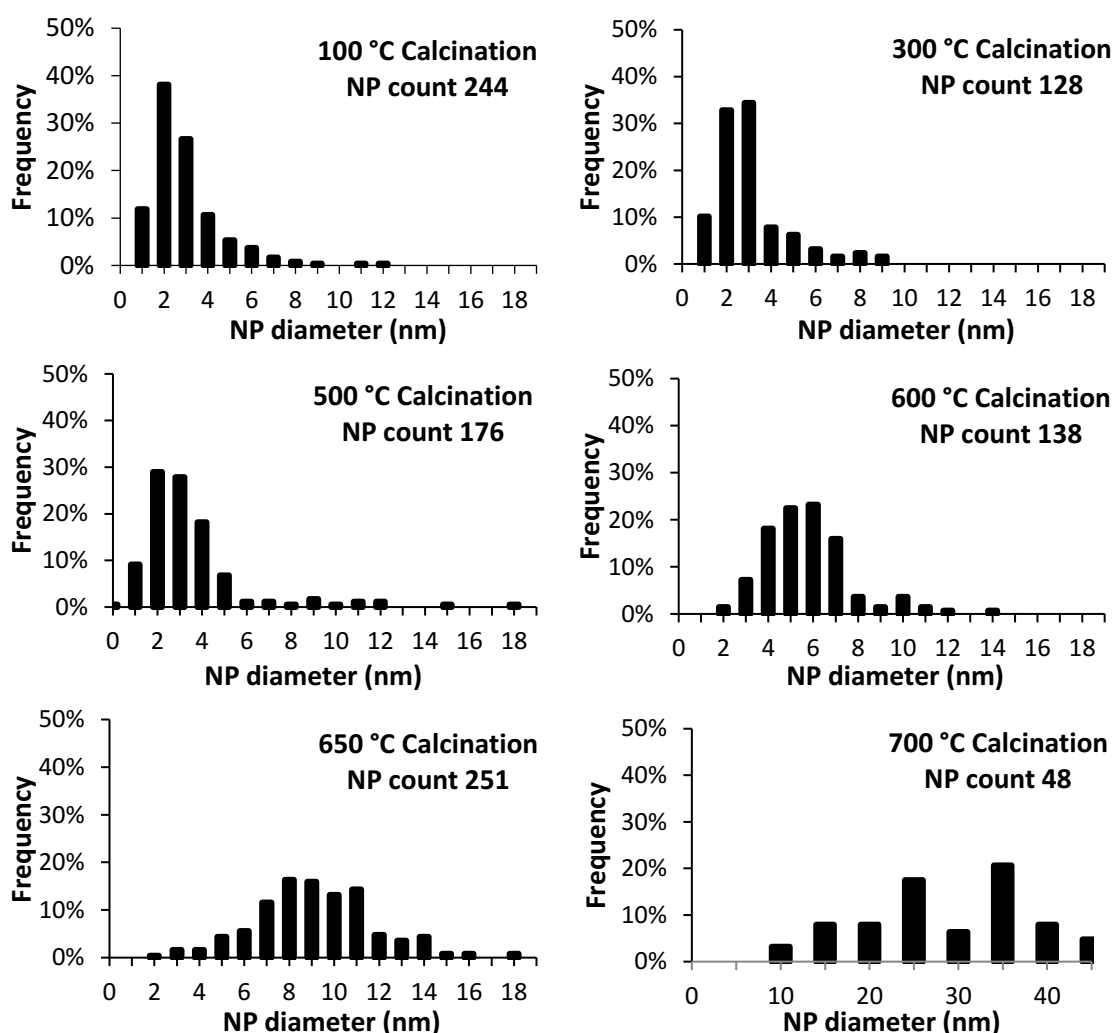


Figure 3-9. AuNP size frequency plots for each calcined Au/ γ -Al₂O₃ sample

To summarise, employing a Au/ γ -Al₂O₃ catalyst calcined between 300 and 650 °C in the oxidative amidation resulted in both an increased catalyst activity and selectivity. Calcined Au/ γ -Al₂O₃ catalysts

exhibit an increased average AuNP size and wider distribution of AuNP sizes that is proportionate to the maximum temperature of calcination. Previous literature reports suggest that the adsorption of both O₂ and amines is stronger on smaller AuNPs. Because of the significantly larger concentration of amine present in solution (compared to dissolved O₂), the adsorption of the amine molecule become a more prominent effect, which can irreversibly inhibit the surface of the AuNP under these oxidative amidation conditions.

There exists an optimal range of AuNP sizes for oxidative amidation where the activation of O₂ is energetically feasible, but, amine adsorption does not inhibit the surface. This range is accessible via the calcination of metal oxide supported AuNPs. Controlling the AuNP size by calcination avoids the arduous approach of synthesising multiple catalysts, as a single 'freshly-prepared' catalyst can be calcined at multiple temperatures to obtain Au catalysts with a range of AuNP sizes.

3.3.4 Thermal Analysis

To further understand the effect of calcination on sol-immobilised Au/ γ -Al₂O₃ catalysts, simultaneous thermal analysis techniques, thermogravimetric analysis coupled with either differential scanning calorimetry or mass spectrometry (TGA-DSC or TGA-MS respectively) were used to monitor how the mass and structural composition changes with increasing temperature.

TGA-DSC was used to continually monitor the change in mass and associated heat flow of each calcined Au/ γ -Al₂O₃ sample. The heat flow associated with the change in mass corresponds to the chemical or physical processes occurring in the catalyst sample. A negative heat flow represents an endothermic change and a net flux of heat into the Au/ γ -Al₂O₃ sample, which could indicate chemical changes such as evaporation of H₂O or melting. Conversely, a positive heat flow represents an exothermic change which could signify changes such as (spontaneous) combustion or crystallisation.

In these experiments, each calcined Au/ γ -Al₂O₃ sample was subjected to TGA-DSC using the same temperature programme. Each sample was heated to 150 °C and held isothermally to remove an excess or weakly adsorbed water molecules and then heated to 800 °C at a rate of 20 °C/min.

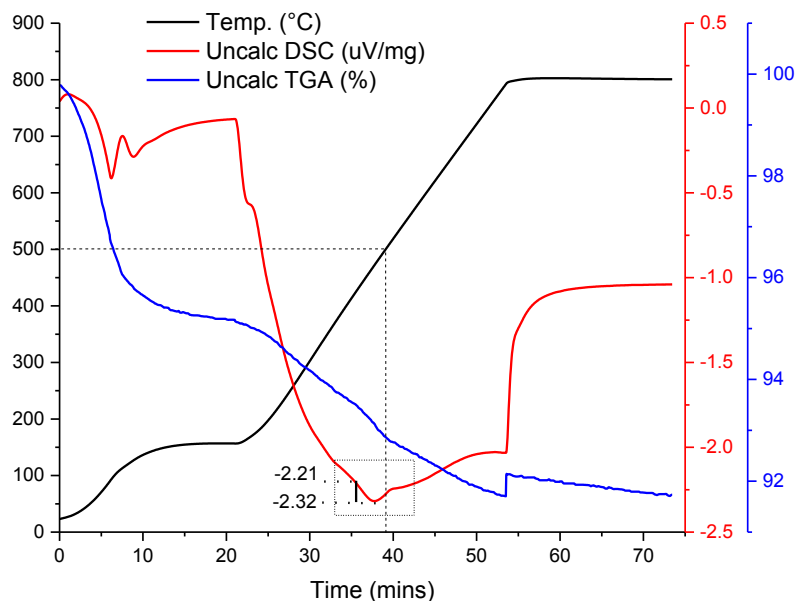


Figure 3-10. TGA-DSC analysis of uncalcined $\text{Au}/\gamma\text{-Al}_2\text{O}_3$

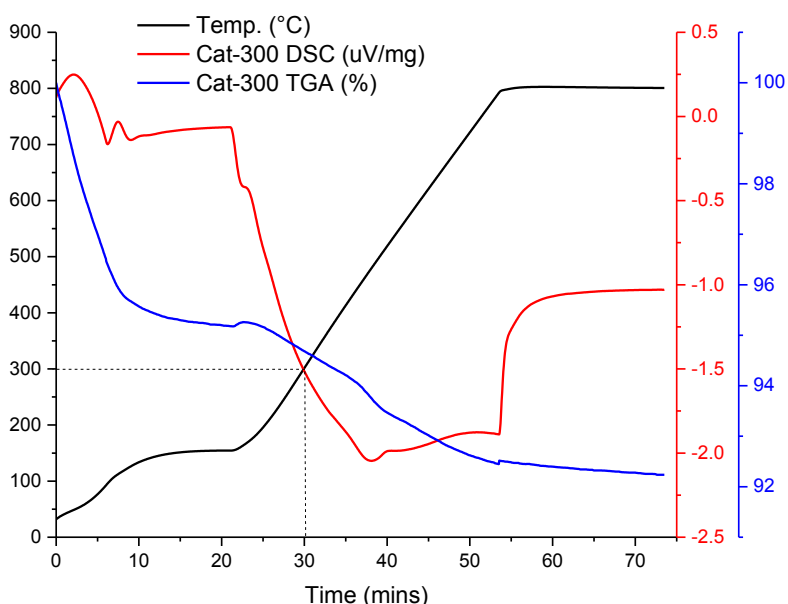


Figure 3-11. TGA-DSC analysis of $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ calcined at 300 °C

$\text{Au}/\gamma\text{-Al}_2\text{O}_3$ samples calcined at temperatures below 500 °C displayed very similar TGA and DSC profiles. As expected, the TGA traces for uncalcined $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ (Figure 3-10) and $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ calcined at 300 °C (Figure 3-11) both showed a continual decrease in mass. Firstly, a sharp decrease in mass as the temperature of the sample was raised to 150 °C, likely to be the result of desorption and evaporation of H_2O . This was followed by a slower decrease in mass as the temperature of the $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ sample is increased up to 800 °C.

The combustion of the polymeric stabilising molecule (PVA) employed in the $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ sol-immobilisation synthesis contributes to the loss of mass apparent in the TGA trace of uncalcined $\text{Au}/\gamma\text{-Al}_2\text{O}_3$.

Al₂O₃ (Figure 3-10); this would account for approximately 1% of the total weight loss (based on the amount employed in the catalyst preparation). The remaining ~2% of mass lost observed as temperature is increased from 150 to 800 °C results from dehydration of the metal oxide support material, which will require more energy than the desorption of adsorbed H₂O molecules. The difference between the TGA traces for uncalcined Au/γ-Al₂O₃ (Figure 3-10) and Au/γ-Al₂O₃ calcined at 300 °C (Figure 3-11) is small, but calcination at 300 °C is known to be sufficient to remove PVA from AuNP catalysts.¹⁷⁹ Close inspection of both traces would suggest a difference of ~0.5% in the final weight loss, corresponding to the removal of PVA in the calcined sample.

The heat flow trace from the simultaneous DSC analysis of each sample calcined below 500 °C is consistent with our proposals for the mass loss observed from the TGA traces. Although the most significant contributor to the overall profile of the heat flow trace is a large endothermic effect observed during the temperature ramp, which is attributed to the heating of the sample and dehydration of the γ-Al₂O₃ support.

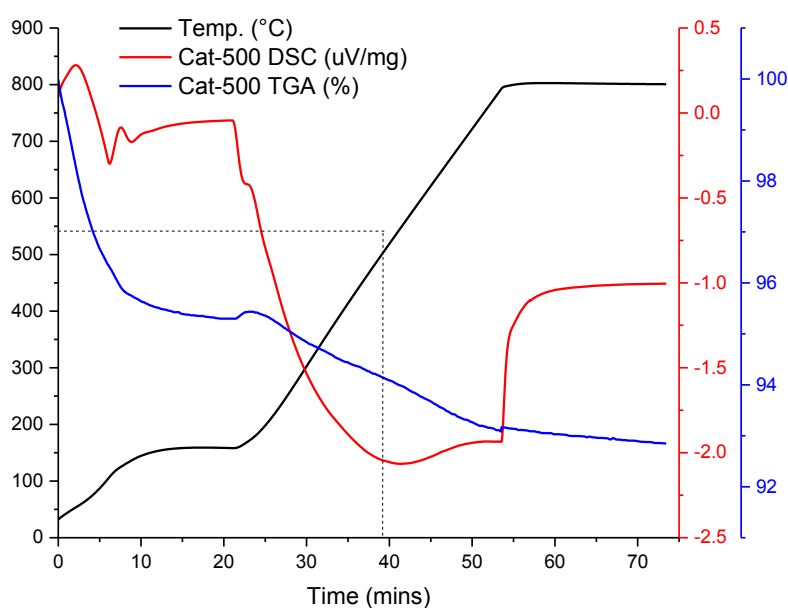


Figure 3-12. TGA-DSC analysis of Au/γ-Al₂O₃ calcined at 500 °C

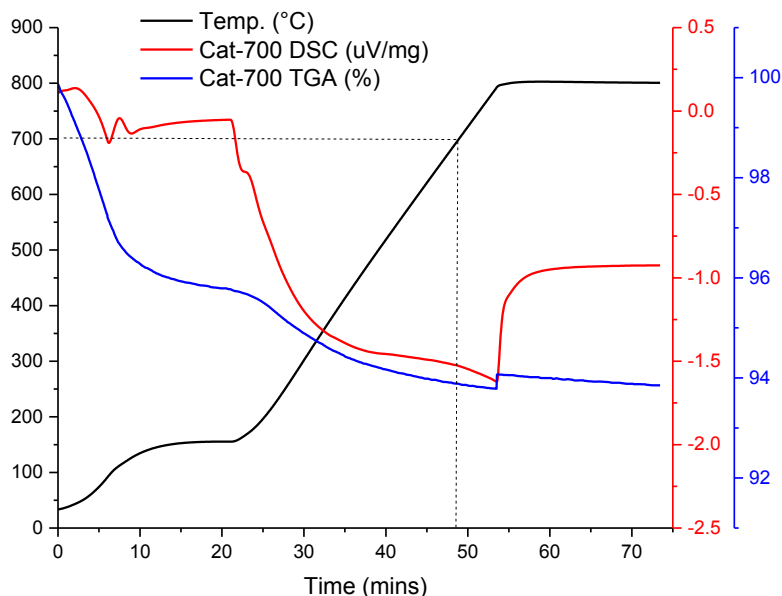


Figure 3-13. TGA-DSC analysis of Au/γ-Al₂O₃ calcined at 700 °C

A small endothermic effect was observed between 450 and 550 °C for the uncalcined or calcined below 500 °C Au/γ-Al₂O₃ samples, which was not detected for samples calcined at 500 °C (Figure 3-12) or 700 °C (Figure 3-13). Indeed, the TGA and heat flow traces obtained for Au/γ-Al₂O₃ calcined at 500 °C (Figure 3-12) were remarkably similar to the traces obtained for the uncalcined sample (Figure 3-10): a significant reduction in the mass as the catalyst sample was heated to 150 °C, attributed to evaporation of weakly adsorbed H₂O molecules; followed by a slower mass loss and a significant endothermic change as the temperature increased to 800 °C.

The TGA and heat flow traces obtained for Au/γ-Al₂O₃ calcined at 700 °C (Figure 3-13) follow a similar trend to other Au/γ-Al₂O₃ samples. There is a significant initial reduction in mass due to the removal of weakly adsorbed H₂O molecules, but a smaller mass loss due to dehydration of the support material compared to other Au/γ-Al₂O₃ samples. This result demonstrates that the dehydration of the support material is not reversible in the presence of atmospheric moisture.

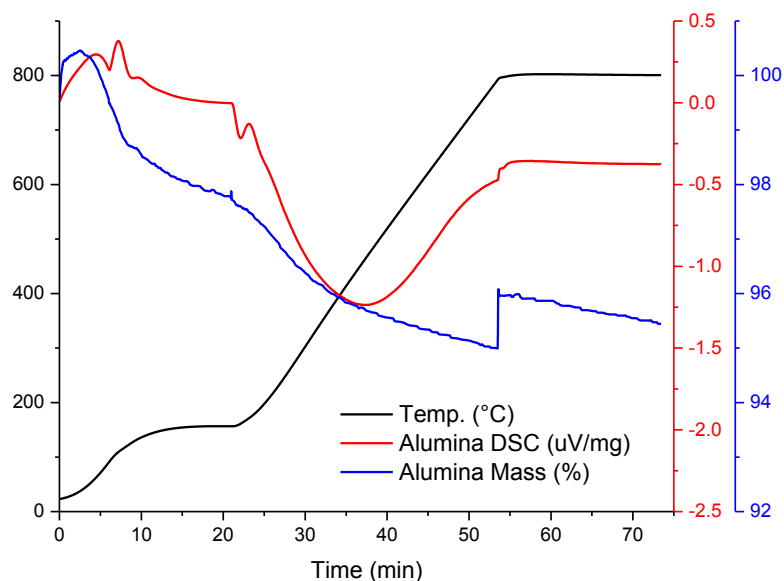


Figure 3-14. TGA-DSC analysis of uncalcined $\gamma\text{-Al}_2\text{O}_3$ support material

TGA and heat flow traces obtained for the $\gamma\text{-Al}_2\text{O}_3$ support material (Figure 3-14) demonstrated a similar trend but smaller loss of mass through evaporation of weakly adsorbed H_2O molecules and dehydration of the support. The smaller change in mass is expected as the blank support material has not been subjected to the aqueous catalyst synthesis conditions. It is also apparent from the heat flow trace of the blank $\gamma\text{-Al}_2\text{O}_3$ that the small endothermic change observed between 450 - 550 $^{\circ}\text{C}$ for $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ samples is related to a change in the structure or chemical properties of the supported AuNP.

TGA-MS is a complementary technique to TGA-DSC, by monitoring the mass change of the $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ sample while simultaneously analysing the effluent gas by mass spectrometry. Comparing the response of the mass values at 18 and 44 (H_2O and CO_2) to the TGA trace can be used to confirm whether mass changes are due to dehydration or combustion processes respectively. In this work, TGA-MS was employed to study the nature of endothermic change observed in samples of uncalcined $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ (Figure 3-15) and $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ calcined at 500 $^{\circ}\text{C}$ (Figure 3-16).

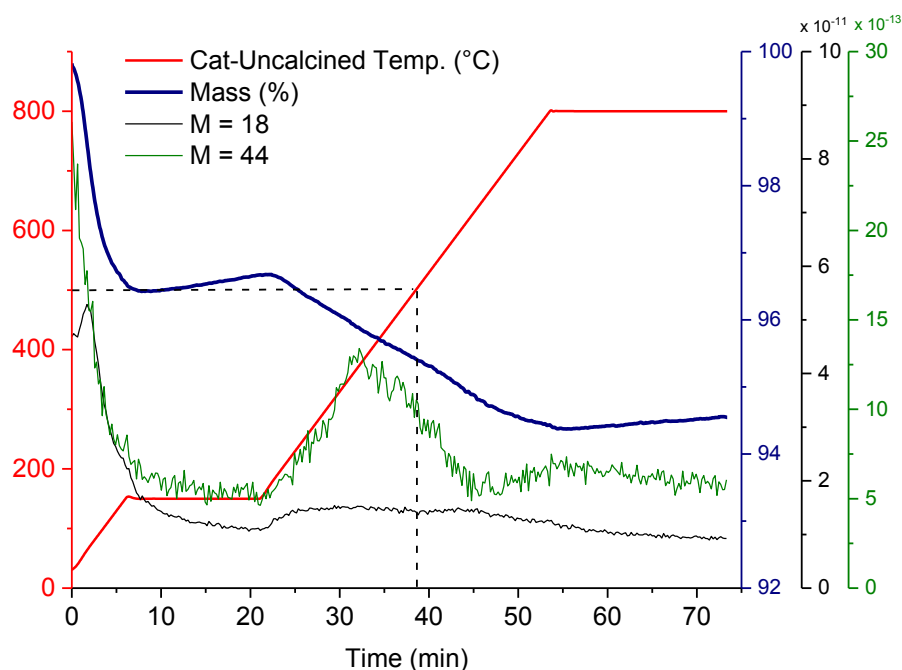


Figure 3-15. TGA-MS analysis of uncalcined $\text{Au}/\gamma\text{-Al}_2\text{O}_3$

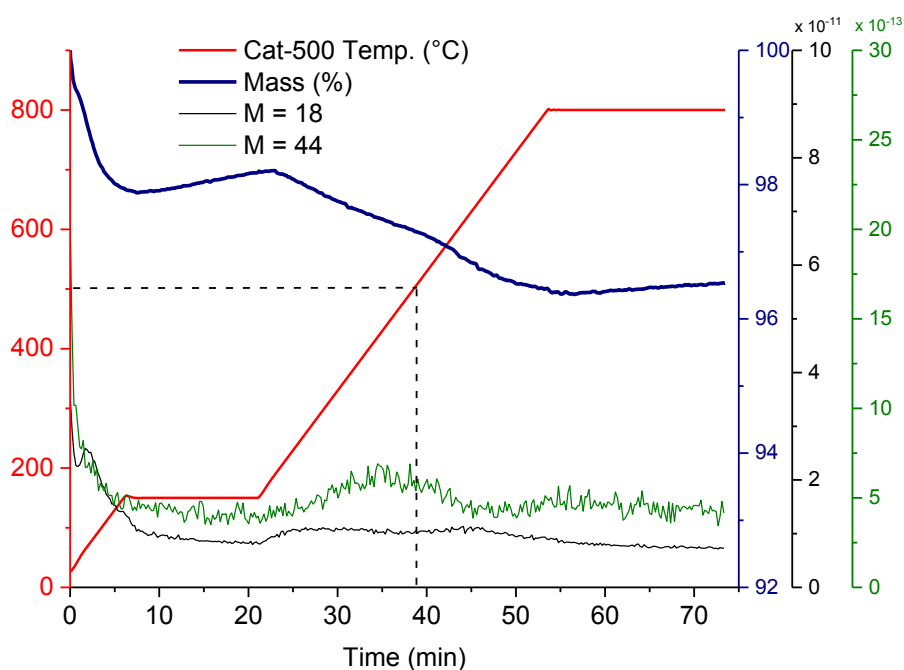


Figure 3-16. TGA-MS analysis of $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ calcined at 500 °C

These results show the initial mass decrease is due to desorption of H_2O and CO_2 from the catalyst surface. The loss of both H_2O and CO_2 continues as the temperature is ramped from 150 to 800 °C. Comparing the TGA-DSC analysis (Figure 3-10) with the TGA-MS analysis (Figure 3-15) of the uncalcined $\text{Au}/\gamma\text{-Al}_2\text{O}_3$, reveal a change in the AuNP which occurs after the majority of PVA has been removed from the catalyst surface. Indeed, it also appears that PVA is present even in $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ that has been calcined at 500 °C, as the formation of a small amount of CO_2 was observed when the temperature is increased above 400 °C (Figure 3-16). Therefore, the small endothermic change

observed could be due to the desorption/combustion of strongly bound PVA molecules. However, it seems counter-intuitive that a combustion reaction incurs a net exothermic change. An alternative explanation is that the removal of the remaining PVA molecules results in a change to the AuNP's morphology or interaction between the AuNP and metal oxide support.

Thermally-induced changes in morphology at temperatures of 600 °C are known to yield hemispherical AuNP's.^{193,194} Because of the suppressed melting point of AuNP compared to bulk Au,¹⁹⁵ it is possible that calcination temperatures of >500 °C result in restructuring of the NP on the surface the Au/ γ -Al₂O₃ catalyst (Figure 3-17).

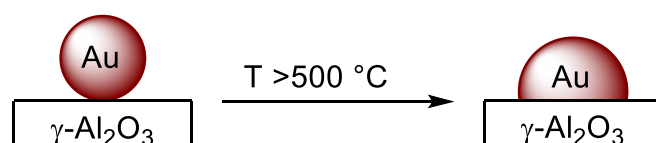


Figure 3-17. Proposed thermal change of AuNP morphology

However, it should be noted that the schematic representation of AuNPs presented in Figure 3-17 simplify the nature of the AuNP surface. AuNPs are multi-faceted structures and the thermally induced change may affect both the shape of the AuNP and the nature of the interface between the AuNP and support material (Figure 3-18).¹⁶⁰

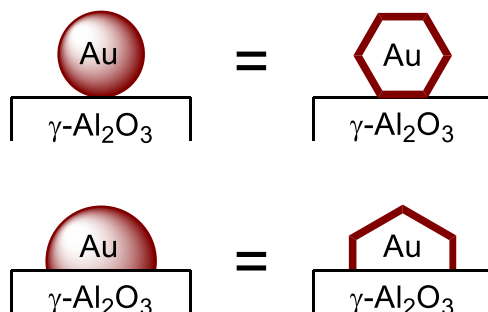


Figure 3-18. Simplified example of different AuNP morphologies

3.4 Conclusions

To conclude, the sol-immobilised Au/ γ -Al₂O₃ catalyst employed in our oxidative amidation reaction possesses many of the qualities typical of effective heterogeneous catalysts. Small sized AuNPs (2 – 4 nm) were deposited onto the γ -Al₂O₃ support surface without requiring adjustment of the Au sol pH. The γ -Al₂O₃ support has a large surface area and the structure appears to be unchanged by thermal treatment at temperatures up to 500 °C.

Calcination at temperatures >500 °C changed the catalyst colour and increased the size of the supported AuNP. Slight increases in the size of the AuNPs were accompanied by an accelerated rate of aldehyde oxidation and overall increases in the amide yield. Simultaneous thermal analysis suggests that the NP are most likely undergoing a morphological change at elevated temperatures. This hypothesis explains the endothermic event observed between 450 and 550 °C; however, the altered AuNP-support interface has not been spectroscopically confirmed. Optimal catalytic activity is achieved in when the catalyst is calcined at temperatures between 300 and 650 °C. Because of the mass transfer limitations of the catalytic system and the unknown nature of the active site, it is not possible for us to identify whether the proposed change in NP morphology facilitates an increase in catalytic activity.

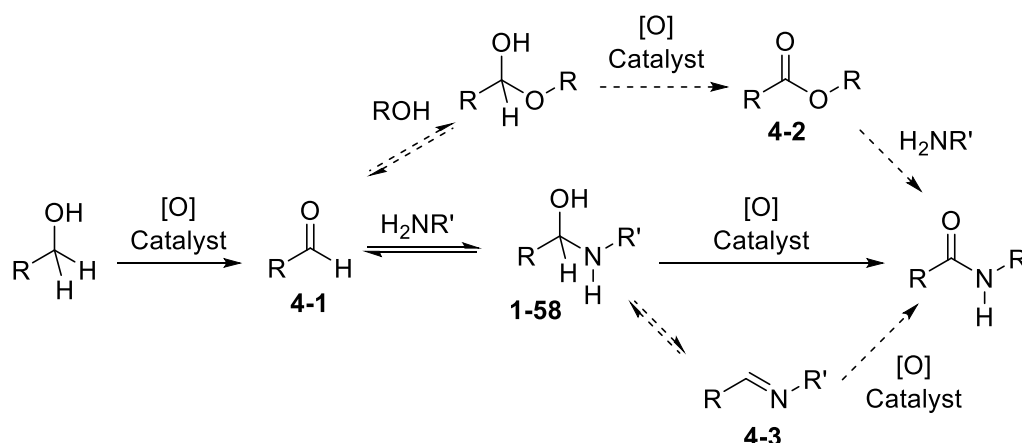
The loss of morphological control does eliminate one of the key benefits of afforded by sol-immobilisation. However, it may be possible to develop a greater understanding of metal-support interactions in AuNP catalysis by exploiting this change of AuNP on different support materials. If the change of morphology can be related to the Au atom environments can be quantified, then it may also be possible to determine a relationship between the morphology and activity of AuNP.

4 Mechanistic Studies of the TEMPO Accelerated AuNP Catalysed Oxidative Amidation

4.1 Introduction

Heterogeneous catalysis is widely employed for industrial applications. However, the relationships between a solid catalysts physical structure, chemical properties and their reactivity are usually poorly understood.^{196,197} The challenge in establishing a link between supported NP catalyst's structure and reactivity is two-fold: the active sites are both poorly defined and difficult to observe *in operando*.¹⁹⁸ As a result, it is difficult to predict trends in reactivity for supported NP catalysts, and most research tends to be performed iteratively based on empirical findings. A greater understanding of the AuNP catalysed oxidative amidation mechanism, and the specific contribution of the surface would facilitate a more rational approach to catalyst design.

Mechanistic investigations of the AuNP catalysed oxidative amidation from alcohols typically consist of testing the same catalyst and conditions with the intermediate aldehyde **4-1** or an ester/imine (**4-2/4-3**) to determine the possible mechanistic pathways (Scheme 4-1).^{97,100} Some efforts have been made to elucidate the specific reaction steps in the Au-catalysed oxidative amidation of aldehydes, but this understanding been achieved by investigating controlled Au surfaces rather than supported AuNPs.^{108,109}



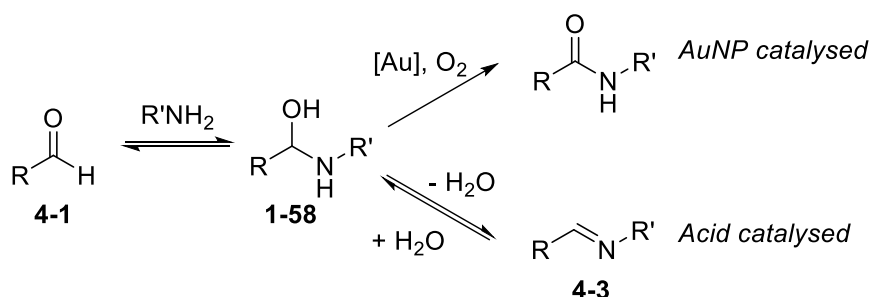
Scheme 4-1. Alternative pathways proposed for oxidative amidation of alcohols

This Chapter presents an investigation into the mechanism of AuNP catalysed oxidative amidation reaction. Firstly, the proposed mechanisms for oxidative amidation and the known reactivity of AuNPs is reviewed with relevance to oxidative amidation reactions. The effect of additives that are known to

inhibit or initiate radical reaction pathways are deployed to eliminate possible mechanistic pathways; and the results are used to propose a revised mechanism for Au catalysed oxidative amidation.

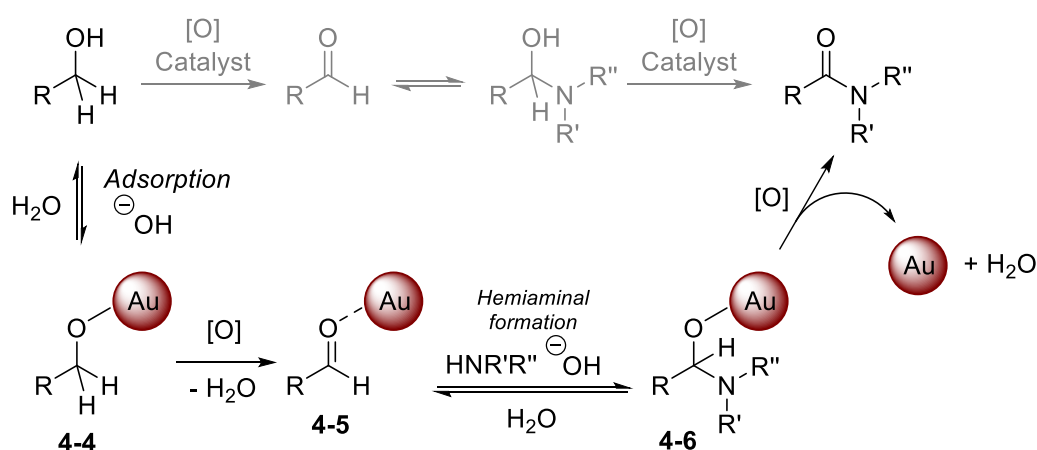
4.1.1 Mechanistic Investigations on AuNP Catalysed Oxidative Amidation

Simple generalisations of the Au catalysed oxidative amidation reaction omit intermediate adsorbed species and their interaction with the catalyst surface. Most reported AuNP catalyst systems for oxidative amidation resulted in almost selective imine formation **4-3** when aldehydes were employed as starting reagents, instead of alcohols.^{100,104,105} Both amide formation and imine formation proceed via the formation of a hemiaminal intermediate **1-58** (Scheme 4-2).



Scheme 4-2. Mechanism of the formation of both amide and imine via a hemiaminal intermediate

Intimate contact of the hemiaminal **1-58** with an active site on the catalyst surface is essential to amide formation, whereas the condensation of aldehydes and amines likely occurs at Lewis acidic point on the AuNP surface¹⁹⁹ or the metal oxide support.²⁰⁰ In light of this, a revised general mechanism is proposed for the Au catalysed oxidative amidation (Scheme 4-3).¹⁰⁴ At this juncture, the specific role of the Au catalyst is not clear.

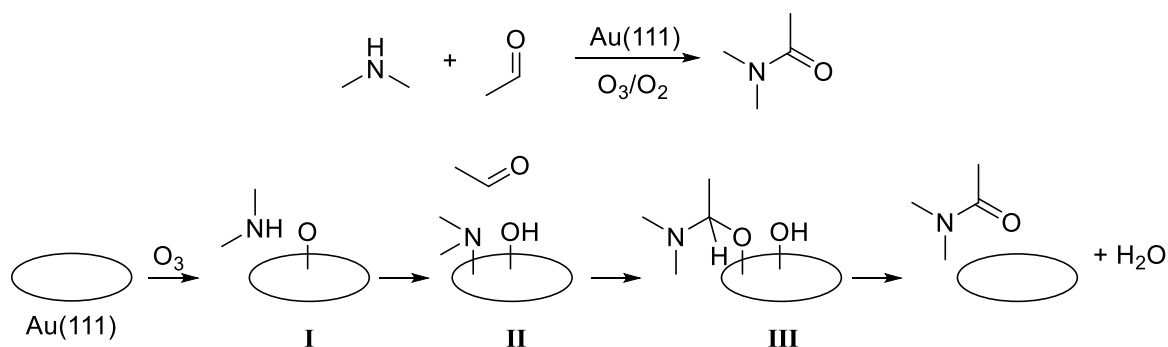


Scheme 4-3. The revised mechanism for the oxidative amidation of alcohols via the formation of an aldehyde

Given that both amide and imine formation share a common intermediate **1-58**, it is somewhat surprising that aldehyde substrates are ineffective under conditions employed for the oxidative amidation of alcohols. This implies that aldehyde **4-1** remains adsorbed to the AuNP surface or in close contact with the active site (**4-5**), prior to the formation of the hemiaminal (**4-6**).

A more detailed mechanism was proposed by Friend and co-workers for the gas-phase oxidative amidation of acetaldehyde with dimethylamine over an oxygenated Au(111) surface (Scheme 4-4),¹⁰⁹ involving three key steps:

- I. Oxygen-assisted amine adsorption to form a gold-amide species;
- II. Surface-mediated formation of a hemiaminal via reaction of a surface-bound amine with free aldehyde; and
- III. β -Hydride type elimination of the C-H bond of a surface-bound hemiaminal, resulting in the formation of dimethylacetamide and H₂O.



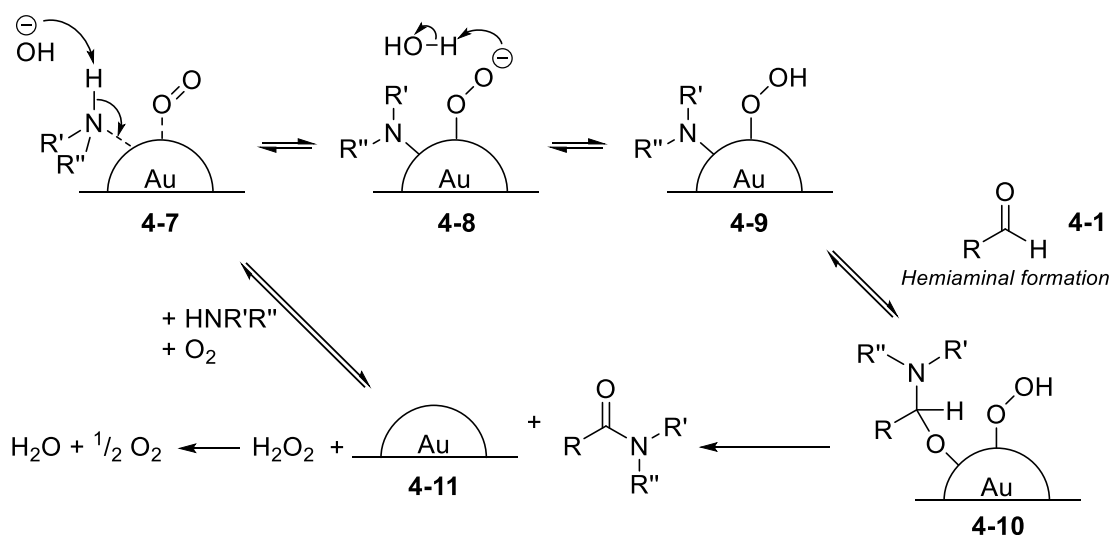
Scheme 4-4. Proposed mechanism for the oxidative amidation of dimethylamine and acetaldehyde on a Au(111) surface

The authors proposed mechanism is based on experiments conducted under high vacuum conditions over a Au (111) surface; ozone (O₃) was dosed into the chamber to control the initial surface oxygen coverage, followed by addition of dimethylamine and acetaldehyde in the vapour phase. Temperature programmed reactions and different dosing sequences were used to understand the reaction occurring at the surface. Analysis of the reaction products was performed via mass spectrometry.

The authors observed that no reaction occurred without the inclusion of either O₂ or O₃. However, increasing the initial surface oxygen coverage resulted in a lower selectivity toward amide. The necessity of O₂ or O₃ in initiating the amidation reaction and inverse relationship with selectivity introduces additional complexity to the mechanism of Au catalysed oxidative amidation. Our results thus far would suggest that the rate of reaction is limited by O₂ concentration, given that the increases

with stirring rate (section 2.5.1). However, performing the reaction under a pure O₂ atmosphere; increasing the concentration of O₂, has been shown to result in a decreased amide selectivity.

Kobayashi and co-workers proposed a mechanism for the liquid-phase amidation reaction, that incorporates the addition of a hydroxide base (Scheme 4-5).¹⁰¹



Scheme 4-5. Kobayashi's proposed mechanism for the AuNP catalysed oxidative amidation

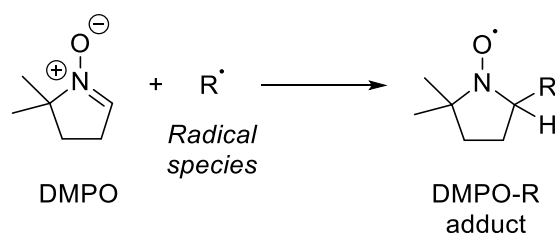
The key similarity between the two proposed mechanisms is the order of adsorption of reagents to the catalyst surface. Firstly, an amine is chemisorbed to the AuNP surface (**4-7**, **4-8**) via an oxygen-assisted reaction. This is followed by the generation of a surface-bound hemiaminal intermediate **4-10**, and finally, a β-hydride elimination leading to amide formation and regeneration of the AuNP surface **4-11**, liberating H₂O₂ as a by-product. The use of Au catalysts for the formation of hydrogen peroxide is a well-studied phenomenon,^{201–205} and the decomposition of H₂O₂ yielding H₂O and 1/2 O₂ is known to be accelerated by AuNPs²⁰² under strongly alkaline conditions.²⁰⁶

Kobayashi's proposal was derived on the original report published by Friend and co-workers, therefore understandably incorporates a broadly similar sequence of mechanistic steps. Neither of the proposed mechanisms provide an explicit mechanism for hemiaminal oxidation, nor the regeneration of the AuNP surface (Scheme 4-4, **III**, and Scheme 4-5, **4-10**).

The findings presented so far in this thesis are broadly in line with the proposed mechanisms by Kobayashi and Friend, with one notable exception: the poor amide yield obtained in CHCl₃ during a solvent screening of the Au/γ-Al₂O₃ catalysed reaction (section 2.5.3) prompted a more thorough investigation into the possible involvement of radical pathways.

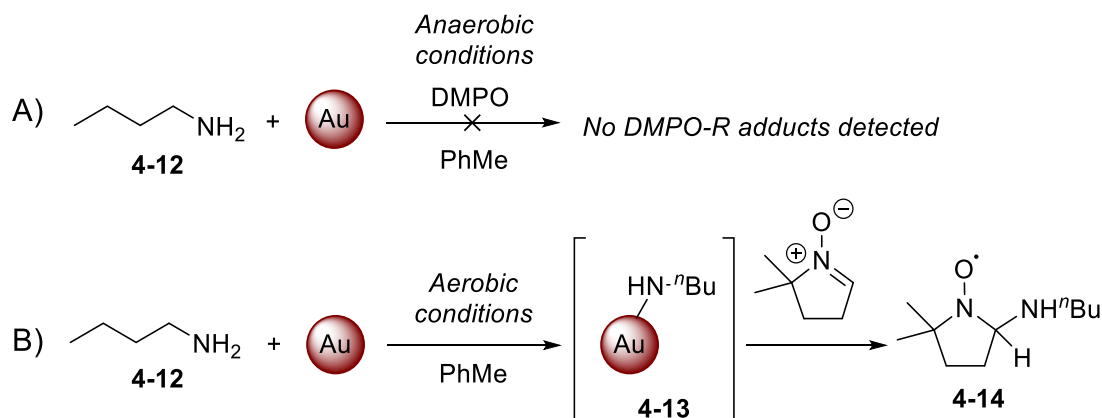
4.1.2 Adsorption of Amines to AuNP Surfaces

In 2007, Chechik and co-workers reported that AuNP would abstract halogen radicals from chlorinated solvents that subsequently results in the agglomeration of AuNP.¹³⁷ The abstraction of $\text{Cl}^\bullet$ radical and formation of $^\bullet\text{CHCl}_2$ was confirmed using 5,5-dimethyl-1-pyrroline-N-oxide (DMPO) as a trap for unstable radicals, to yield a DMPO-R adduct (Scheme 4-6),²⁰⁷ that can be identified using electron paramagnetic spectroscopy (EPR).



Scheme 4-6. Formation of persistent DMPO-R radical species using DMPO radical spin trapping technique

It is speculated that the poor catalytic activity observed for the $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ catalysed oxidative amidation reaction in CHCl_3 may be due to agglomeration of the AuNP. It may be possible that the mechanism of Au catalysed oxidative amidation proceeds via radical intermediates. This is partially substantiated by Chechik and co-worker's observation that butylamine **4-12** adsorbs to AuNP surfaces in the liquid phase via a radical mechanism (Scheme 4-7),¹³⁷ as opposed to a base-assisted process as proposed by Kobayashi and co-workers (Scheme 4-5).¹⁰¹

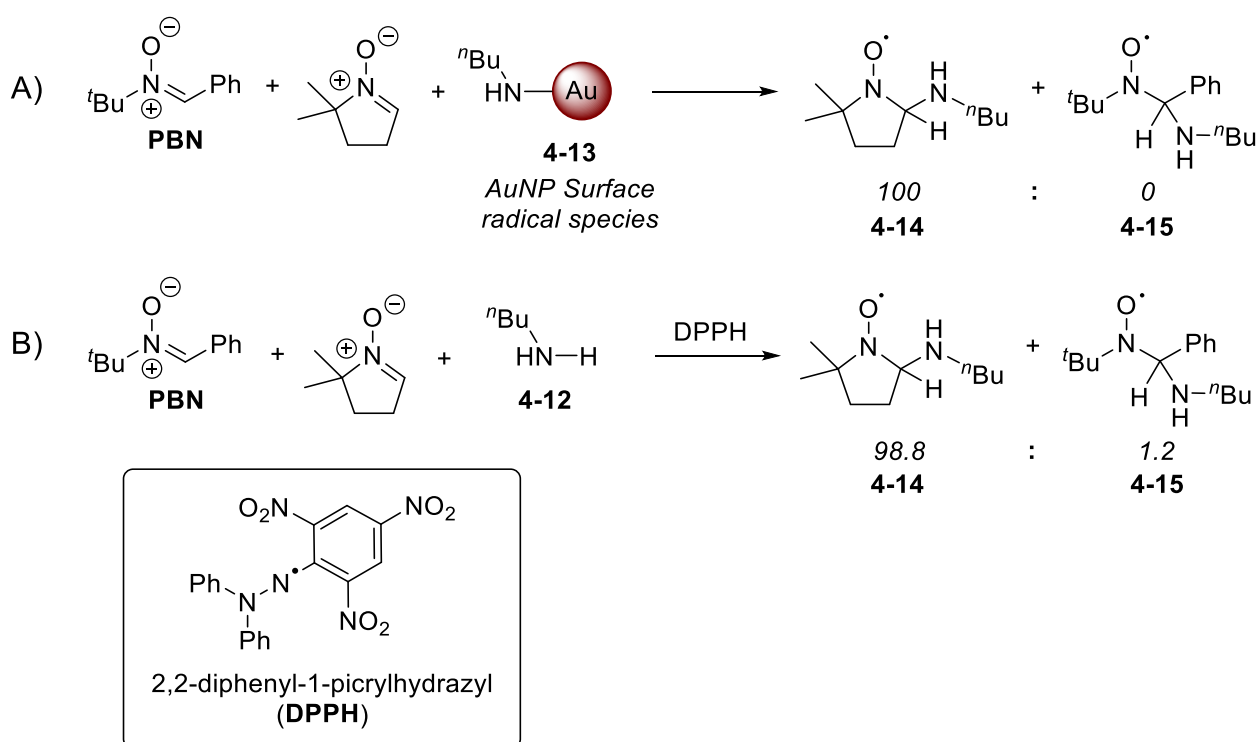


Scheme 4-7. A) Addition of butylamine to AuNP under anaerobic conditions B) Adsorption of butylamine to AuNP surface under aerobic conditions

Under anaerobic conditions, the authors reported that the addition of AuNP to a solution of **4-12** resulted in no detectable DMPO adducts (Scheme 4-7A), whereas the same spin trapping experiment in air resulted in the formation of DMPO-butylamine adduct **4-14** (Scheme 4-7B). Based on these results, Chechik and co-workers proposed that the formation of butylamine radicals at the AuNP

surface occurs via H atom abstraction, immediately followed by a chemisorption of the butylamine radical to the AuNP surface, rather than the dissociation of free radical species into solution. Adsorption of the N-centred radical species to the Au surface was evidenced using competitive radical trapping experiments with two different spin traps, DMPO and PBN (Scheme 4-8).

The authors compared the ratio of DMPO-N **4-14** and PBN-N **4-15** spin adducts obtained for the addition of **4-12** to solution phase AuNP (Scheme 4-8A), and for the generation of free N-centred radicals from **4-12** using 2,2-diphenyl-1-picrylhydrazyl (DPPH) (Scheme 4-8B). The rationale being that if addition of butylamine to AuNP forms free N-centred radicals then the ratio of DMPO and PBN spin adducts (**4-14** : **4-15**) will be identical to the ratio of spin adducts obtained when radicals are generated independently in solution by DPPH. The authors propose that the change in ratio of the DMPO-N **4-14** and PBN-N **4-15** spin adducts suggests that the N-centred radical does, in some part, exist as an adsorbed species on the AuNP surface. However, the lowest measurement uncertainties achievable with EPR are thought to be between 3 – 5%, therefore it could be possible to misinterpret minor signals or miss very low concentrations of adducts in mixtures of spin adducts.²⁰⁸



Scheme 4-8. Competitive radical trapping experiments employing DMPO and PBN in A) adsorption of butylamine to an O₂ activated Au surface and B) the formation of free N-centred radicals with DPPH

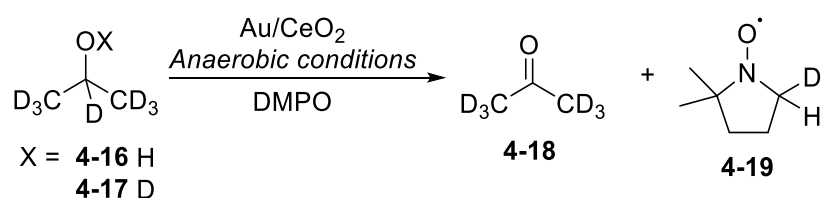
The necessity of O₂ for the adsorption of amine species is consistent with proposals made by Friend and co-workers for the adsorption of amines to Au (111) surfaces (Scheme 4). But the formation of the DMPO-NHⁿBu in Chechik's spin trapping experiments suggests that amines adsorbed to AuNP surfaces may have significant radical character.

4.1.3 Formation of Au-H

A collaboration between the Chechik and Kobayashi groups investigated potential radical pathways in the Au catalysed oxidation of alcohols.²⁰⁹ The authors propose two key findings from the investigation of the oxidation of secondary alcohols catalysed by Au/CeO₂:

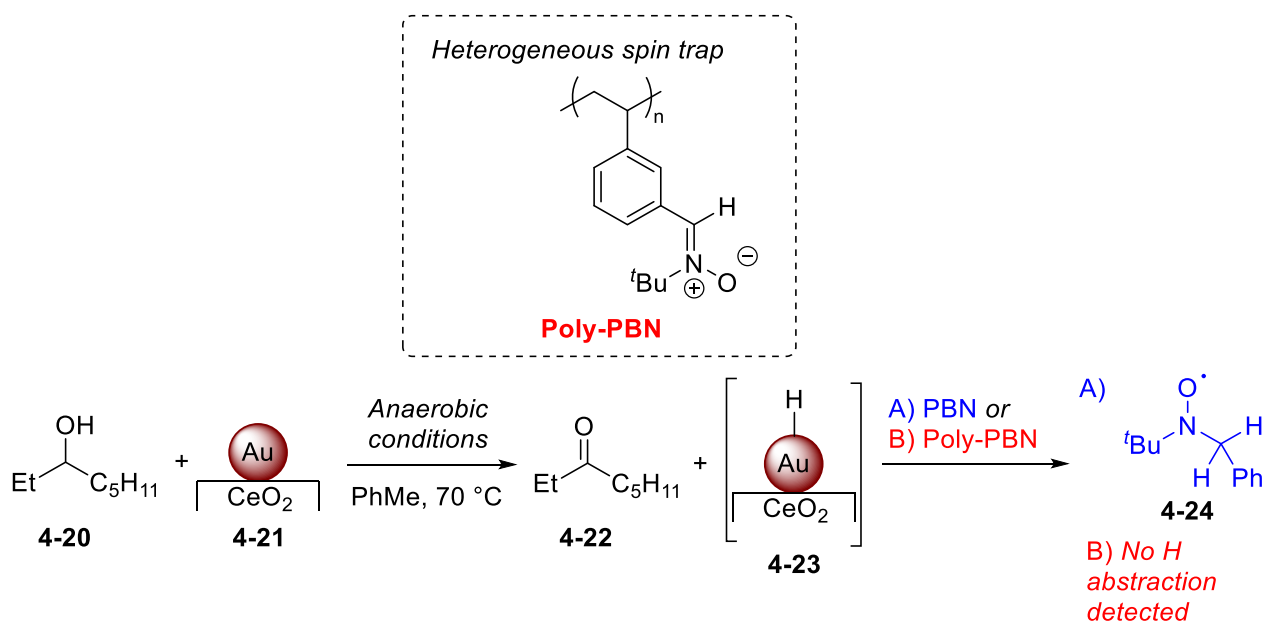
- Formation of Au-H surface species during Au catalysed alcohol oxidation
- Regeneration of Au-H surface species is achieved via a reaction with O₂

The formation of Au-H surface species was investigated using a combination of isotope-labelling and spin trapping experiments. The *anaerobic* oxidation of deuterated isopropanol (**4-16** or **4-17**) in the presence of DMPO yielded deuterated acetone **4-18** and DMPO-D **4-19** adduct exclusively, regardless of whether the alcohol functionality was protonated (**4-16**) or deuterated (**4-17**) (Scheme 4-9). This confirmed that the Au-H species resulted from the cleavage of the C-H bond, rather than the deprotonation of O-H.



Scheme 4-9. Anaerobic oxidation of deuterated isopropanol catalysed by Au/CeO₂ with the addition of DMPO radical spin trap

Next, the authors proceeded to investigate the source of the abstracted H atom: The oxidation of 3-octanol **4-20** was conducted using a solid Au/CeO₂ catalyst **4-21** under anaerobic conditions with the addition of either solution phase N-tert-Butyl- α -phenylnitrone (PBN) or heterogeneous Poly-PBN immobilised on a styrene resin (Scheme 4-10). Should radical H[•] species be formed in solution or originate from C-H abstraction, both scavengers would be equally effective.

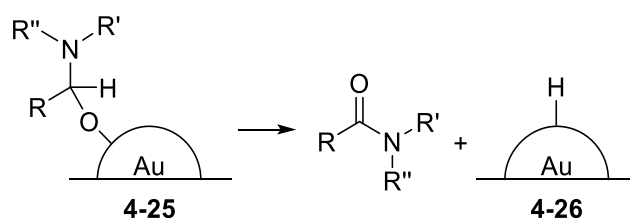


Scheme 4-10. Radical spin trap investigation of the Au/CeO₂ catalysed oxidation of 3-octanol using A) homogeneous PBN and B) heterogeneous poly-PBN radical spin traps

Au/CeO₂ (**4-21**) catalysed *anaerobic* oxidation of **4-20** with the addition of PBN (Scheme 4-10A) resulted in the formation of PBN-H adduct **4-24**. Whereas, the corresponding reaction in the presence of poly-PBN (Scheme 4-10B) resulted in no observable poly-PBN-R spin adducts. Therefore, it was concluded that the PBN-H adduct **4-24** observed in the Au catalysed anaerobic oxidation of **4-20** resulted from the abstraction of an H species adsorbed to the Au/CeO₂ surface **4-23**.

In the last part of the study, the authors demonstrated O₂ regenerates the catalyst surface via the oxidation of Au-H surface species: as evidenced by the *aerobic oxidation* of **4-20** with Au/CeO₂ and DMPO not resulting in the formation of DMPO-H adducts. Therefore, either the O₂ facilitated regeneration of the surface is faster than H atom abstraction, or the H atom abstraction is reversible, but reformation and regeneration of the Au-H species leads to the same conclusion.

Based on these studies, it is not unreasonable to assume that the oxidation of a hemiaminal intermediate **4-25** could also result in the formation of a similar Au-H species **4-26** (Scheme 4-11).

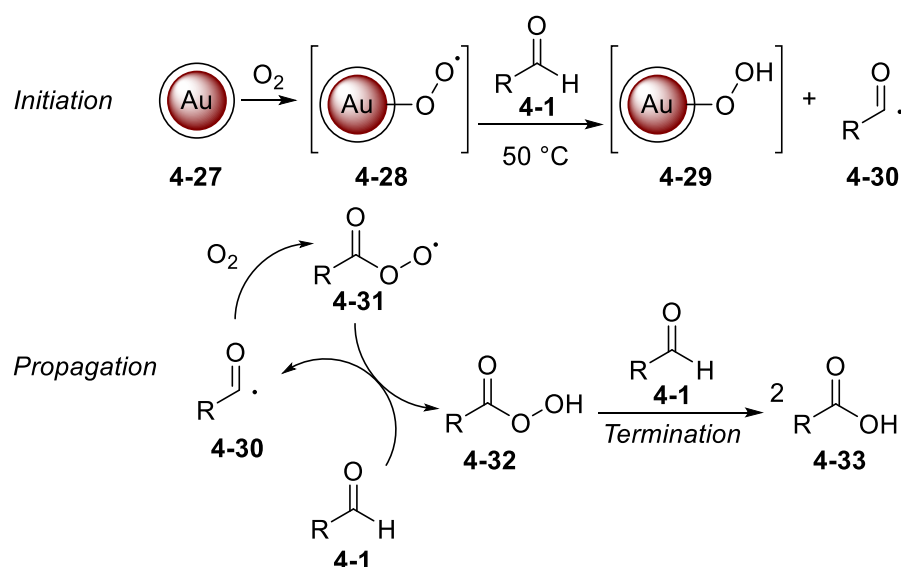


Scheme 4-11. Formation of Au-H species via the oxidation of a surface-bound hemiaminal

Observation of Au-H species has since been reported independently by Maldotti et al. using EPR and spin trapping, in the anaerobic oxidation of 2-pentanol with DMPO catalysed by Au/CeO₂.²¹⁰ Au-H species have been reported independently by Catlow and co-workers, using neutron scattering techniques to investigate the splitting of H₂ over Au/CeO₂.²¹¹ Catlow and co-workers suggest that further examples of Au-H species may be present in the literature but have gone falsely assigned or unnoticed due to their obscurity and due to often being disguised by other stronger signals.²¹²

4.1.4 Au Catalysed Acyl Radical Formation from Aldehydes

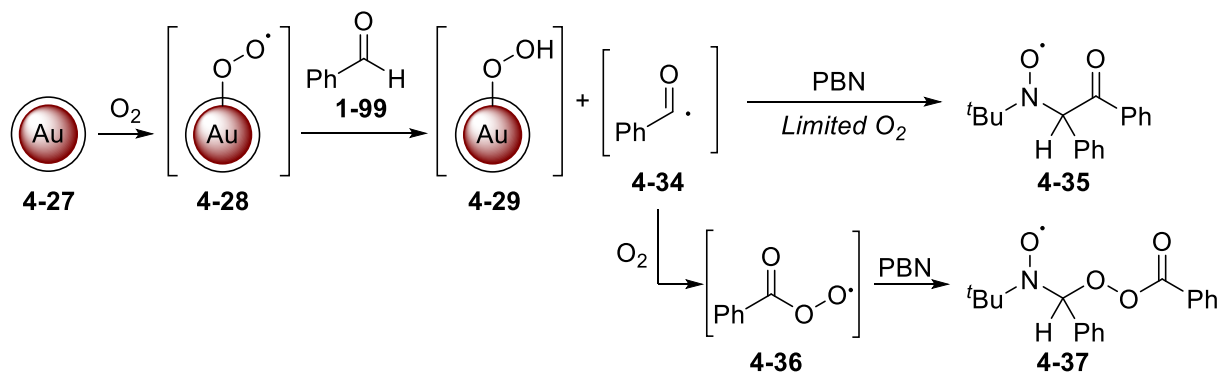
Following the initial studies with Au/CeO₂, the Kobayashi-Chechik team showed that polymer-incarcerated AuNP (PI-AuNP) catalysts initiate the autoxidation of aldehydes to carboxylic acids *via* a radical pathway (Scheme 4-12).²¹³ Initiation occurs under aerobic conditions *via* the abstraction of the aldehydic H atom by PI-AuNP **4-27**, forming an acyl radical. The radical reaction is then propagated through the oxidation of **4-30** with dissolved O₂ yielding acyl-peroxy radical **4-31** that subsequently abstracts another aldehydic H atom, reforming the acyl radical and an organic peroxide **4-32**. The radical reaction terminates by the formation of a carboxylic acid **4-33**, resulting from the reaction of organic peroxide **4-30** with an equivalent of the starting aldehyde **4-1**.



Scheme 4-12. AuNP initiated radical autoxidation of an aldehyde

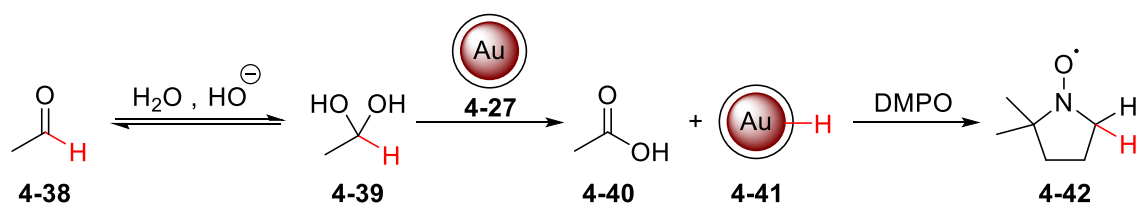
Like their previous reports, the authors evidenced their proposed mechanism using radical spin trapping experiments.²¹³ The addition of PBN to the PI-Au initiated oxidation of benzaldehyde **1-99** resulted in the formation of spin adducts PBN-C(O)Ph **4-35** and PBN-OOC(O)Ph **4-37**, under limited O₂ and aerobic conditions respectively (Scheme 4-13). However, they did not discuss whether the acyl radical species R(O)C· **4-34** can bind to the Au surface. To the best of our knowledge, there are no

other reports examining the formation of acyl radicals by AuNP, and reports to support the formation of surface-bound carbonyl species.



Scheme 4-13. Formation of PBN-C(O)Ph and PBN-OOC(O)Ph in the PI-Au initiated radical oxidation of benzaldehyde

In the same report,²¹³ the authors conducted the Au-catalysed oxidation of aldehyde **4-38** in the presence of NaOH and DMPO (Scheme 4-14), which resulted in the formation of DMPO-H spin adduct **4-42**. Citing their previous work,²⁰⁹ the authors propose that in the presence of base, the reaction of **4-38** with hydroxide generates a gem-diol intermediate **4-39**, which is subsequently oxidised to yield ethanoic acid **4-40** and Au-H species **4-41** (Scheme 4-14).



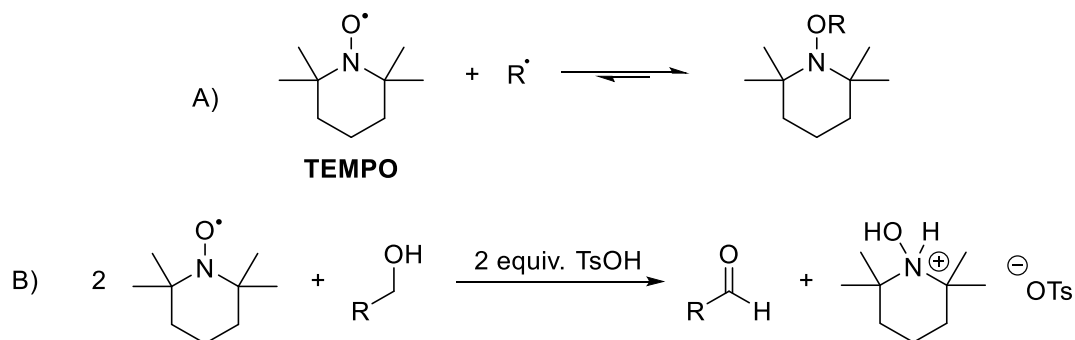
Scheme 4-14. Formation of DMPO-H adduct in the Au-catalysed oxidation of acetaldehyde

It was claimed that that the PI-Au catalysed oxidation of gem-diol (Scheme 4-14) is a minor pathway, and the oxidation of aldehyde to carboxylic acid occurs primarily via a AuNP initiated radical chain reaction (Scheme 4-12). The claim was supported by demonstrating that addition of a carbon radical scavenger, TEMPO, resulted in a significant reduction of aldehyde conversion. The suppression of aldehyde conversion was observed with or without the addition of catalyst, further substantiating the authors claim.

Earlier in this thesis, Au-catalysed oxidation of aldehydes to carboxylic acids was identified as an undesired side reaction (section 2.4.3). Should carboxylic acid formation result from a Au initiated radical chain mechanism then it is envisaged that the selectivity of amide formation could be improved by inhibiting the undesired radical pathway, provided that the formation of amide does not also depend on radical intermediates.

4.1.5 TEMPO Effect on Catalysed Oxidations

(2,2,6,6-Tetramethylpiperidinyl)-*N*-oxyl (TEMPO) is a stable nitroxide radical species that exists as a crystalline orange solid at ambient temperature. TEMPO is commonly used in organic synthesis as both a radical spin trap and a mild selective oxidant under acidic conditions (Scheme 4-15).^{214,215}

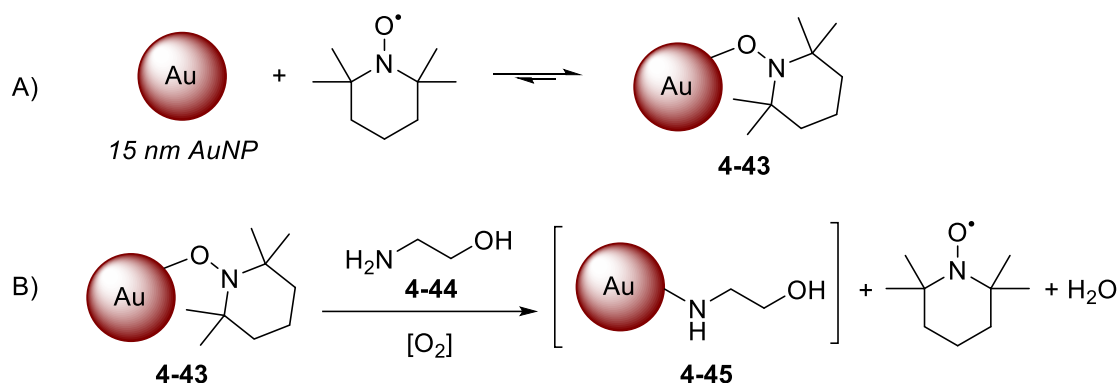


Scheme 4-15. Common applications of TEMPO as A) a radical spin trap and B) selective oxidation of alcohols under acidic conditions

The radical-trapping properties of TEMPO are complementary to that of DMPO and PBN discussed previously. The reaction of TEMPO with a free radical species results in the reversible formation of a diamagnetic TEMPO-adduct that can be identified by NMR spectroscopy. An example of using TEMPO as a radical spin trap to investigate the oxidative amidation of aldehydes was presented in the introductory Chapter to this thesis (section 1.4.2).⁸³

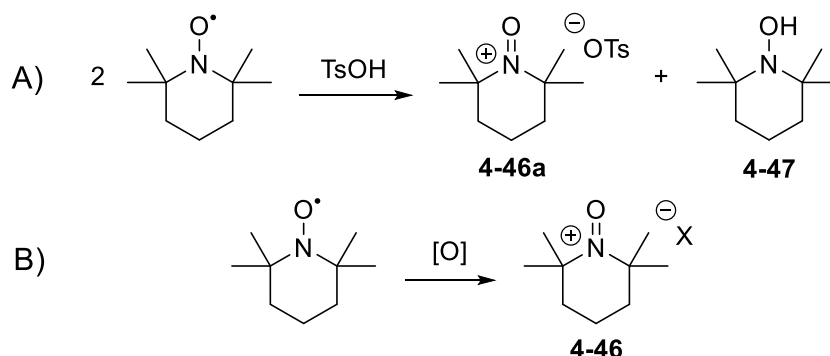
Meisel and co-workers reported that the addition of AuNP to a solution of TEMPO results in a proportional decrease in the intensity of the EPR signal of the free-radical species.²¹⁶ The authors attributed this to the adsorption of TEMPO to the Au surface (**4-43**, Scheme 4-16A), citing a similar effect observed for the adsorption of free radicals to bulk Au surfaces.

The EPR signal of the free radical species can be almost completely regenerated via the addition of 2-aminoethanol **4-44** under aerobic conditions (Scheme 4-16B). While the precise mechanism by which **4-44** liberates TEMPO from the AuNP surface (**4-45**) was not discussed, it could conceivably proceed via an oxygen-assisted adsorption process, as presented previously in Scheme 4-7B.¹³⁷



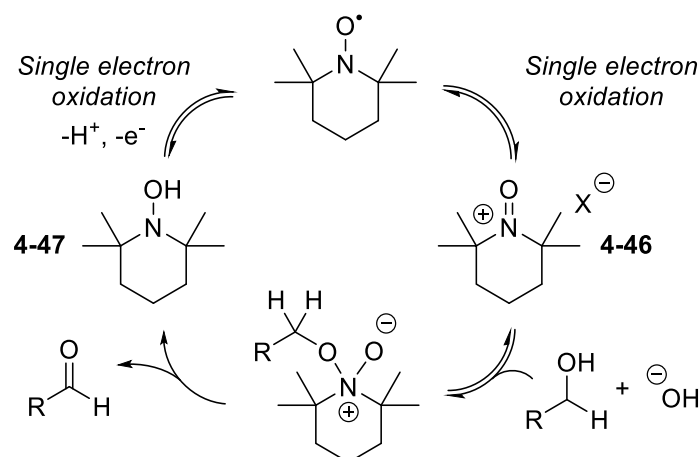
Scheme 4-16. A) Reversible addition of TEMPO to the surface of solution phase AuNP B) Proposed liberation of TEMPO from the surface of AuNP by addition of ethanolamine, observed by EPR spectroscopy

TEMPO is commonly employed as a selective oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones respectively.²¹⁷ In most cases, the oxidations proceed through single electron transfer (SET), via the formation of oxoammonium salt **4-46** either by acid-catalysed disproportionation (Scheme 4-17A) or the reaction of TEMPO with a terminal oxidant (Scheme 4-17B).



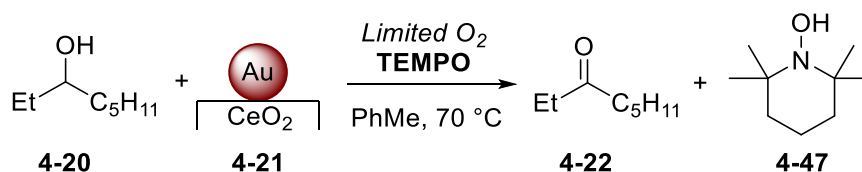
Scheme 4-17. Formation of an oxoammonium salt either by A) disproportionation in acidic conditions or B) addition of an external oxidant

Under basic conditions, TEMPO can be employed catalytically in the presence of stoichiometric oxidants, such as hypervalent iodine reagents.^{218,219} Or, more atom-economically, using O₂ as a terminal oxidant in the presence of a co-catalyst, such as Cu^{220,221} or Fe.^{222,223} To the best of our knowledge, there are no known examples of Au catalysed **4-46** formation using O₂ for selective oxidation reactions.



Scheme 4-18. The proposed mechanism of oxidation of primary alcohols using TEMPO as a co-catalyst.^{224,225}

The addition of TEMPO in AuNP-catalysed oxidations has been examined previously by Chechik and co-workers in their reports on secondary alcohol oxidation²⁰⁹ and acyl radical formation.²¹³ Firstly, the Au/CeO₂-catalysed oxidation of 3-octanol was performed in a sealed system with the addition of TEMPO (Scheme 4-19).



Scheme 4-19. Au/CeO₂-catalysed oxidation of **4-20** with the addition of TEMPO, reaction was performed in a sealed atmosphere of air to limit the amount of O₂ available

TEMPO concentration was monitored via the intensity of its EPR signal and the sharpness of the peaks were used to monitor O₂ concentration, which sharpen as the O₂ concentration depletes. During the reaction, the EPR signal first became sharper, and then reduced in intensity. This result infers a gradual consumption of O₂, followed by the formation of TEMPOH; consistent with the formation of Au-H surface species and a reversible hydride abstraction by the stable free radical species.

Chechik and co-worker's earlier study demonstrated that TEMPO has an inhibitory effect on the Au-initiated radical autoxidation of aldehydes (Scheme 4-12).²¹³ The reaction was suppressed in the presence of TEMPO using both polymer-incarcerated AuNPs and a Au/ZnO catalyst. The inhibitory effect was not present in AuNPs pre-treated with TEMPO, leading the authors to propose that the reduced activity is due to the suppression of the (uncatalysed) radical side reaction, rather than due to any deactivation of the catalyst surface.

4.2 Aims

The original aim of the work described in this Chapter was to eliminate the possible involvement of radical intermediates in the Au catalysed oxidative amidation reaction. By adding TEMPO to the reaction, we were anticipating either no observable effect or suppression of catalyst activity. Contrary to these expectations, the addition of catalytic amounts of TEMPO was found to *accelerate* the rate of Au catalysed oxidative amidation. This unexpected result led us to examine the catalytic cycle and role of TEMPO in the reaction. This included kinetic experiments to elucidate the rate-limiting steps in Au-catalysed oxidative amidation, and how it changes with the addition of TEMPO.

All kinetic experiments were performed in a Radley's carousel reactor at the 1 mmol scale. All experiments were performed in duplicate, and a control reaction for each experiment is performed in parallel. The rate of aldehyde conversion was monitored by manual sampling of the reaction mixture. As the number of active sites is unknown, it is not possible to assign accurate values for TON and TOF. Additionally, the rate of the multiphasic reaction is inherently limited by the mass transfer of O₂ from the air into the solution, and diffusion to the active site. Under these conditions, it is not possible to obtain intrinsic reaction rates, although qualitative comparisons can still be made.

4.3 Initial Screen of Radical Initiators and Radical Quenchers

Under optimised conditions, the Au/ γ -Al₂O₃-catalysed oxidative amidation of benzaldehyde **1-99** and morpholine **1-67** was performed with inclusion of additives, known to either quench or initiate radical reactions (Table 4-1). A range of additives were included for their ability to intercept different radical centres: Cumene and triphenylmethane (Ph₃CH) (Figure 4-1) are known to form persistent tertiary-carbon centred radicals via hydrogen abstraction.^{226,227} α -Methyl groups at a benzylic carbon of cumene stabilise the formation of the tertiary radical, while the phenyl rings in triphenylmethane stabilise the formation of radical centres by delocalisation of the radical character through the multiple independent π -systems.

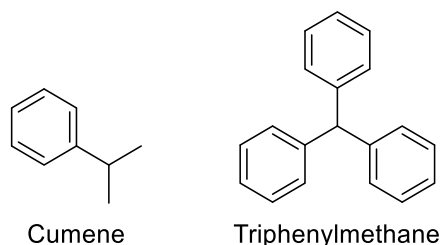
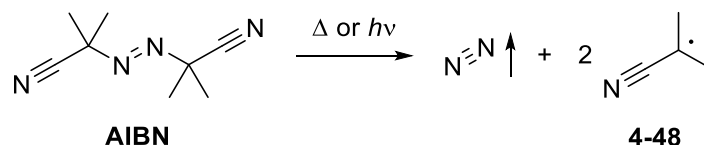


Figure 4-1. Structures of cumene and triphenylmethane

On the other hand, inorganic radical inhibitors sodium nitrite and sodium thiosulphate are effective quenchers of hydroxyl and hydroperoxyl radicals, respectively.²²⁸ Azobisisobutyronitrile (AIBN) was

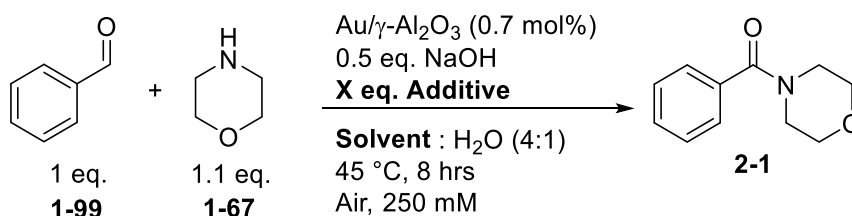
added as radical initiator, which has been shown to have a beneficial effect in AuNP-catalysed oxidations.²²⁹



Scheme 4-20. Homolytic cleavage of AIBN

AIBN is often used to initiate radical reactions, undergoing homolytic cleavage with loss of nitrogen when exposed to light or heat resulting in the formation of 2 equivalents of 1-cyano-1-methylethyl carbon radical **4-48** (Scheme 4-20).

Table 4-1. Effect of radical quenchers and radical initiators on the yield and initial rate of Au catalysed oxidative amidation



Entry	Additive	Solvent	Conversion 1-99 ^b (%)	Yield 2-1 ^b (%)	Selectivity (%)	Initial rate of 1-99 conversion ^c (mM min ⁻¹)
1	No additive	CHCl ₃	5	Trace	N/A	N/A
2	1 eq. Cumene	PhMe	74	58	78	0.674
3	1 eq. Ph ₃ CH	PhMe	81	68	84	0.850
4	No additive	Cumene	81	66	81	0.690
5	0.1 eq. NaNO ₂	PhMe	99	77	78	1.805
6	0.1 eq. Na ₂ S ₂ O ₃	PhMe	N.D.	N.D.	N/A	N/A
7	0.1 eq. AIBN	PhMe	56	41	73	0.623
8	1 eq. AIBN	PhMe	N.D.	N.D.	N/A	N/A
9	No additive	PhMe	98	74	76	1.819

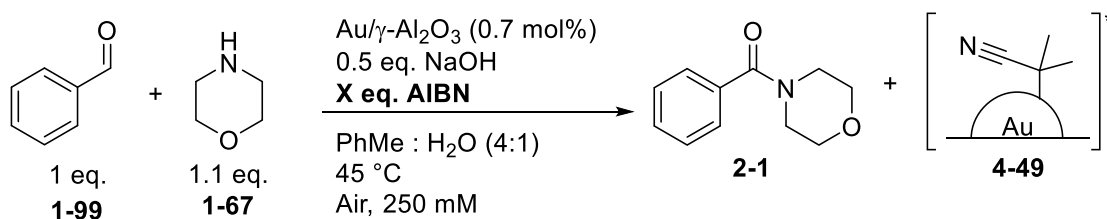
^aReaction conditions: Benzaldehyde (1 mmol), morpholine (1.1 mmol), PhMe (4 mL) ^bConversion of aldehyde and yield of amide were determined by HPLC after 8 h. ^cInitial rate was calculated by monitoring aldehyde consumption after 2 h (HPLC). ^dN.D. = not detected

As previously described, the use of CHCl₃ as a solvent resulted in almost complete inhibition of catalytic activity (Table 4-1, entry **1**). Presumably due to the competitive abstraction of Cl[•] by the AuNP catalyst. Addition of cumene or Ph₃CH led to reduced conversion of benzaldehyde, reduced yield of amide **2-1**, and significant reduction in the initial rate of benzaldehyde conversion compared to the control

reaction (entries **2** to **4** vs **9**). The reduced conversion rate of **1-99** may be explained by the competitive formation of stable carbon centred radicals from cumene and Ph₃CH via the abstraction of the tertiary C-H bond by Au species on the catalyst surface. A competitive reaction resulting in the temporary deactivation of the surface required for substrate adsorption would explain the reduction in catalyst activity, but the similar selectivity obtained when compared to the control reaction (entry **9**).

Sodium nitrite had no detectable effect on the reaction outcome (Table 4-1, entry **5** vs **9**); therefore, it is proposed that hydroxyl radicals is unlikely to be involved in the reaction. In contrast, the addition of sodium thiosulfate (entry **6**) completely inhibited the reaction; which could suggest the quenching of reactive peroxide species. However, inhibition of catalytic activity could also be due to homolytic cleavage of the S₂O₃²⁻ anion and adsorption of sulfate to the Au surface.

Addition of 0.1 equivalents of AIBN reduced the rate of aldehyde conversion and the overall amide yield after 8 hours compared to the control reaction (Table 4-1, entry **7** vs entry **9**), whereas the addition of 1 equivalent of AIBN completely prevented aldehyde conversion (entry **8**). Analysis of both reaction mixtures after an additional 12 hours of heating showed no change in their composition, suggesting that the adsorption of the **4-48** to the AuNP (**4-49**) results in an irreversible deactivation of the catalyst surface (Scheme 4-21).



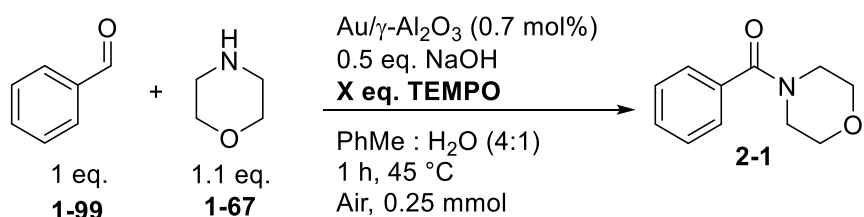
Scheme 4-21. Addition of AIBN to the Au/ γ -Al₂O₃ catalysed oxidative amidation of benzaldehyde and morpholine

4.4 TEMPO Acceleration of Au/ γ -Al₂O₃ Catalysed Oxidative Amidation

4.4.1 Stoichiometry of TEMPO

Based on literature reports and the effects of radical-inhibiting additives investigated thus far, it was hypothesised that addition of a free radical species would result in inhibition of the AuNP catalyst. A series of oxidative amidation reactions were performed in parallel with increasing equivalents of TEMPO, each reaction was heated at 45 °C under atmospheric conditions, and the concentrations of benzaldehyde **1-99** and amide **2-1** were determined by HPLC after 1 hour (Table 4-2). Reactions to investigate the stoichiometry of TEMPO were performed at a smaller scale in 2 mL microwave vials (Biotage 352016) using small-scale magnetic stirring (Biotage 355544). The addition of any amount of TEMPO to the reaction mixture increased the rate of aldehyde conversion.

Table 4-2. Effect of addition of increasing amounts of TEMPO on the AuNP catalysed oxidative amidation reaction



Entry	X eq. TEMPO	Conversion 1-99 ^b (%)	Yield 2-1 ^b (%)	Selectivity 2-1 (%)
1	0	49	35	72
2	0.1	60	46	76
3	0.5	59	45	75
4	1	67	51	77
5	2	78	63	81
6	3	77	60	78
7	4	94	70	75
8	5	93	70	75

^aReaction conditions: Au/ γ -Al₂O₃ (35 mg, 0.7 mol%), benzaldehyde (0.25 mmol), morpholine (0.28 mmol), PhMe (1 mL), NaOH_(aq) (0.25 mL, 0.5 M)

^bConversion of **1-99** and yield of **2-1** were determined by HPLC after 1 h

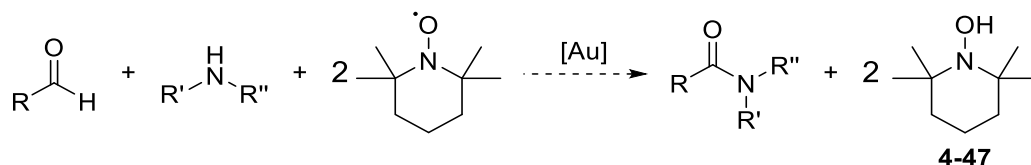
The addition of up to 5 equivalents of TEMPO to the Au/ γ -Al₂O₃ catalysed oxidative amidation resulted in a proportional increase in the conversion of the aldehyde to amide **2-1** after 1 hour (Table 4-2, entry **8**) with no observable change in selectivity.

4.4.2 Possible Mechanisms for TEMPO Acceleration

Our investigation into Au catalysed oxidative amidation of aldehydes has so far indicated that the reaction rate is limited by the mass transfer effects of O₂. However, employing pure O₂ atmospheres to increase the concentration of O₂ in solution is undesirable as higher O₂ concentrations favour the formation of carboxylic acids.¹⁰¹ The use of a recoverable additive, such as TEMPO, to accelerate the rate of Au catalysed oxidative amide formation, without sacrificing selectivity or requiring the use of stoichiometric reagents, merited further investigation.

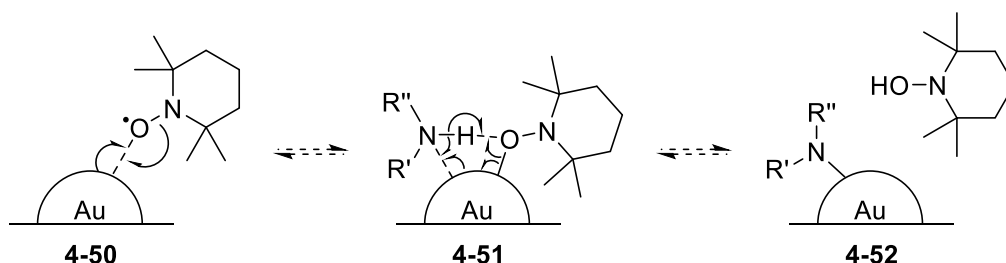
There are several possible explanations for the increase in rate of the Au catalysed oxidative amidation. Each proposed hypothesis circumvents the necessity for adsorption of O₂ to the AuNP surface. Based on the known interactions of TEMPO with AuNPs and common reactivity of TEMPO as either a mild oxidant or radical trap (outlined above in section 4.1) presented below are three hypotheses for the accelerating effect of TEMPO in AuNP catalysed oxidative amidation:

1. TEMPO could replace the role of O₂ in either activating or regenerating the AuNP surface (Scheme 4-22), and **4-47** can subsequently be oxidised by an oxygenated Au species or O₂ in solution to regenerate the TEMPO free radical.²³⁰



Scheme 4-22. General scheme for a TEMPO-accelerated Au-catalysed oxidative amidation of aldehydes and amines

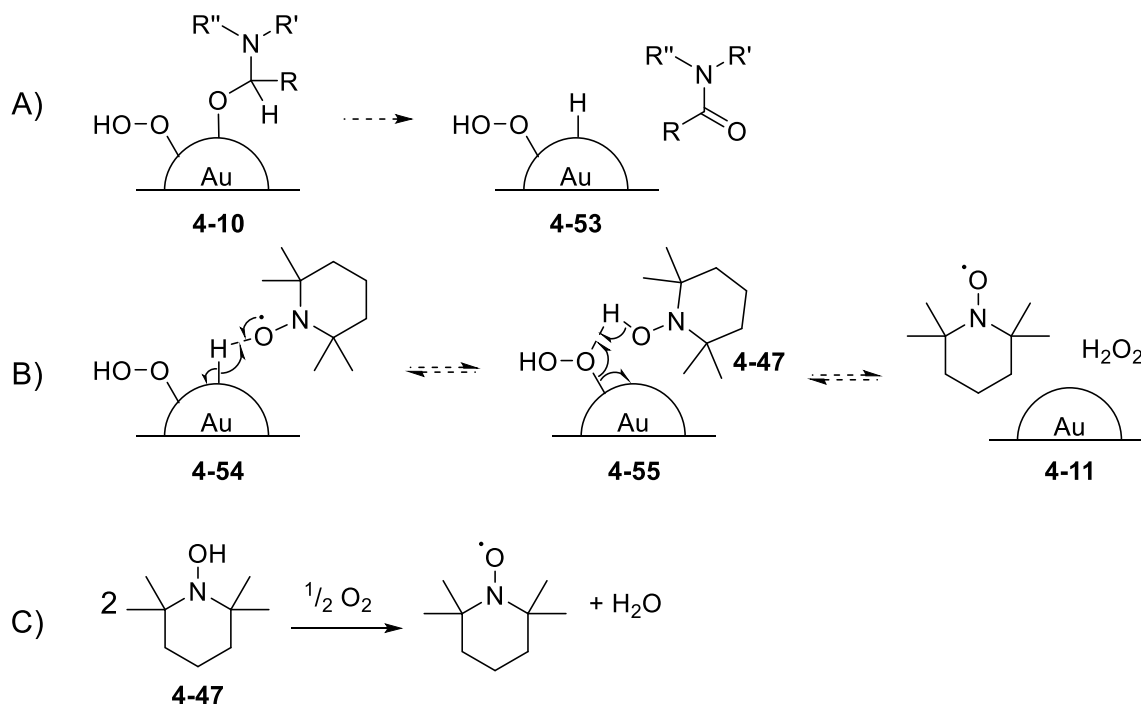
Previously, it was proposed that adsorbed O₂ on the AuNP surface is required both to initiate the oxidative amidation reaction possibly by the adsorption/activation of amines and for the regeneration of active sites. TEMPO could activate the surface in a similar manner (Scheme 4-23).



Scheme 4-23. Adsorption of an amine to the AuNP surface activated by TEMPO.

Alcohol oxidation is thought to result in the formation of Au-H species via β -hydride type eliminations.^{122,140,209} Oxidation of a hemiaminal intermediate (**4-53**) may also result in Au-H species,

such as **4-54** (Scheme 4-24A). TEMPO could regenerate the active sites on the AuNP via a hydride abstraction (**4-55**).

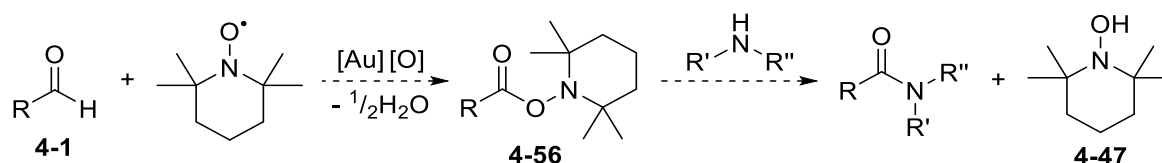


Scheme 4-24. A) β -hydride type eliminations of hemiaminal B) Accelerated regeneration of AuNP surface via hydrogen transfer mediated by TEMPO C) Regeneration of TEMPOH in solution by O_2

The regeneration of TEMPOH could proceed via a surface-catalysed reaction with an oxygenated Au species (**4-55**, **4-56**, Scheme 4-24B). Alternatively, 2 equivalents of **4-47** can be regenerated in solution by reaction with O_2 (Scheme 4-24C).²³⁰

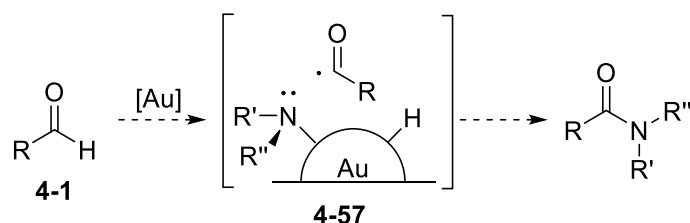
In both proposed regeneration pathways, the use of TEMPO alleviates the necessity for the reaction of Au-H species with O_2 adsorbed on the catalyst surface. Therefore, the mass transfer limitations of gaseous O_2 could be overcome, although O_2 would still be required as the terminal oxidant to regenerate TEMPO.

2. TEMPO could trap an acyl radical formed via hydride abstraction, yielding a TEMPO-derived hydroxylamine ester **4-56**; followed by aminolysis of **4-56** to yield the desired amide and TEMPOH **4-47**.



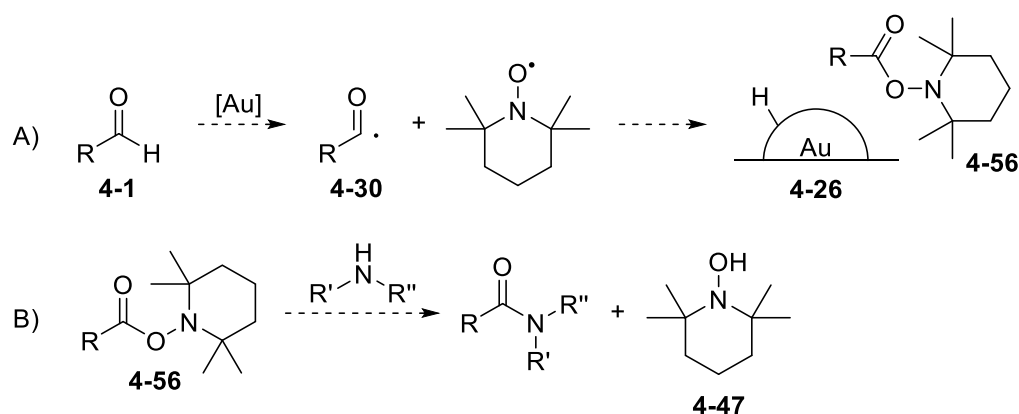
Scheme 4-25. Au-catalysed oxidative formation of a TEMPO ester

Based on the observation that addition of other radical scavengers appears to hinder the rate of amide formation (Table 4-1), the generation of acyl radicals is a plausible step in the oxidative amidation reaction (Scheme 4-26). Which is consistent with previous reports that AuNPs can initiate formation of acyl radicals.²¹³



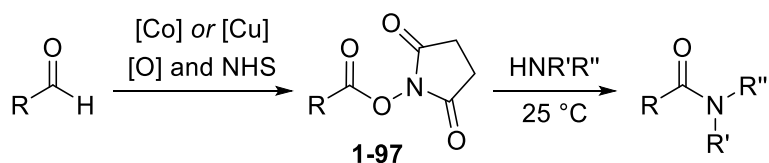
Scheme 4-26. Possible radical pathway for the AuNP catalysed oxidative amidation of aldehydes

TEMPO may accelerate the rate of the reaction via the formation of an intermediate hydroxylamine ester (Scheme 4-27). In combination with the proposed abstraction of $\text{H}^\bullet$ from the catalyst surface by TEMPO (Scheme 4-24), and proposed TEMPO regeneration pathways (Scheme 4-24), the formation of a hydroxylamine ester would also alleviate the necessity for O_2 to react with adsorbed Au-H species.



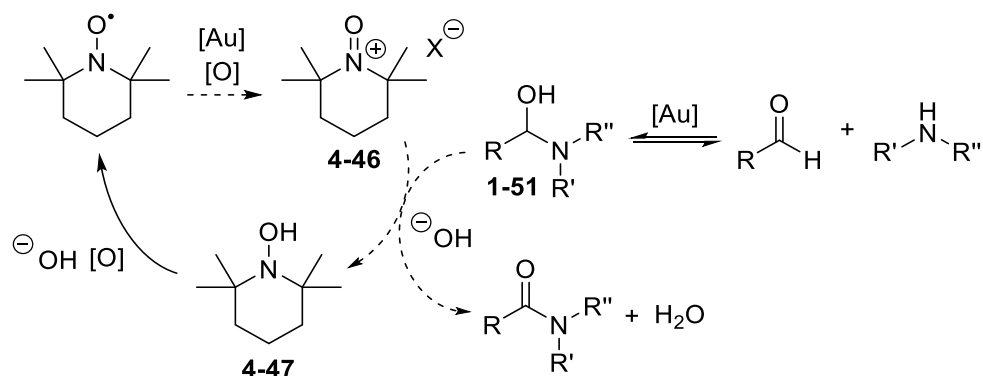
Scheme 4-27. Possible pathways for the formation of amide via the generation of a hydroxylamine ester A) Trapping of a AuNP generated acyl radical B) Aminolysis of hydroxylamine ester

The generation of hydroxylamine esters as intermediates in catalytic oxidative amidation of aldehydes was briefly discussed in the introduction to this thesis (section 1.4.2). Hydroxylamine esters can be generated by Co- or Cu-catalysed oxidative reaction between an aldehyde and NHS, and aminolysis yields the desired amide (Scheme 4-28).



Scheme 4-28. Formation of NHS-esters as intermediates in amide formation.^{82,83}

3. TEMPO could undergo oxidation to oxoammonium salt **4-46** and oxidise hemiaminal intermediate **1-51** to the amide, although the formation of hemiaminal may be dependent on the addition of a AuNP catalyst (Scheme 4-29).



Scheme 4-29. Oxidative amidation of an aldehyde via the oxidation of a hemiaminal intermediate using an oxoammonium salt derived from TEMPO

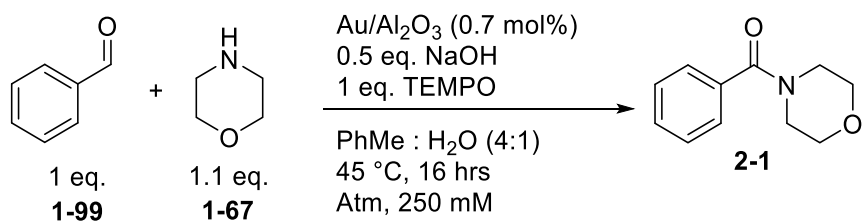
However, it is known that stable free radical species, such as TEMPO, preferentially adsorb to the AuNP.²¹⁶ There are no reported examples of Au-catalysed oxidation yielding the oxoammonium salt **4-46**.

In the following sections, each of these hypotheses is investigated to determine the accelerating effect of TEMPO and further understand the mechanism of Au catalysed oxidative amidation. Based on the available literature, the abstraction of H atoms from the AuNP surface, accelerating the regeneration of active sites seems the most likely explanation.

4.4.3 Controlled Reactions

Microwave vials were charged with Au/ γ -Al₂O₃, TEMPO and aqueous NaOH, before they were sealed, purged and filled at 45 °C with the specified gas. The reactions were initiated with the addition of the organic solvent and reactants: benzaldehyde **1-99** and morpholine **1-67** (Table 4-3, entries **1** and **2**). Three further reactions were performed, where each component was systematically omitted (entries **3** to **5**) and compared to the Au/ γ -Al₂O₃ catalysed oxidative amidation reaction without the addition of TEMPO (entry **6**).

Table 4-3. Au/ γ -Al₂O₃ catalysed oxidative amidation of benzaldehyde and morpholine performed with the addition of TEMPO, either under controlled atmospheres or with the removal of a component known to be required for the Au/ γ -Al₂O₃ catalysed oxidative amidation reaction



Entry	Conditions	Conversion	Yield 2-1 ^b	Conversion
		1-99 ^b (%)	(%)	TEMPO ^b (%)
1	Air atm. (Sealed microwave vial)	95	71	72
2	O ₂ atm. (Sealed microwave vial)	96	66	1
3	Air (Open), with H ₂ O, without NaOH	36	23	3
4	Air (Open), without H ₂ O, without NaOH	15	6	6
5	Air (Open), with Al ₂ O ₃ , without Au/γ-Al ₂ O ₃	N.D.	N.D.	N.D.
6	Air (Open), without TEMPO	83	61	N/A

^aReaction conditions: Au/γ-Al₂O₃ (75 mg, 0.7 mol%), benzaldehyde (0.50 mmol), morpholine (0.55 mmol), PhMe (2 mL), 0.5 M NaOH (0.5 mL) ^bConversion of aldehyde, yield of amide, and conversion of TEMPO were determined by HPLC

Au/ γ -Al₂O₃ catalysed oxidative amidation of **1-99** and **1-67** under atmospheres of air or pure O₂ were previously discussed in this work (section 2.3.2). Under an air atmosphere, benzaldehyde conversion and amide **2-1** yield were 25% and 28%, respectively, compared to 96% and 79%, when the reaction was performed under a pure O₂ atmosphere.

Performing the Au/ γ -Al₂O₃ catalysed oxidative amidation reaction with TEMPO under an atmosphere of air (limited O₂ conditions), significantly larger aldehyde conversion and amide yield (Table 4-3, entry **1**) were obtained, compared to the equivalent reaction without the addition of TEMPO. A significant conversion of TEMPO was observed when the reaction was performed in limited O₂ conditions, which was clearly indicated by a decolourisation of the reaction solution (Figure 4-2). The reaction mixture then slowly regained the distinctive orange colour upon exposure to air, suggesting the decolourisation is due to the formation of TEMPOH that is oxidised back to the orange free radical species in the presence of O₂.

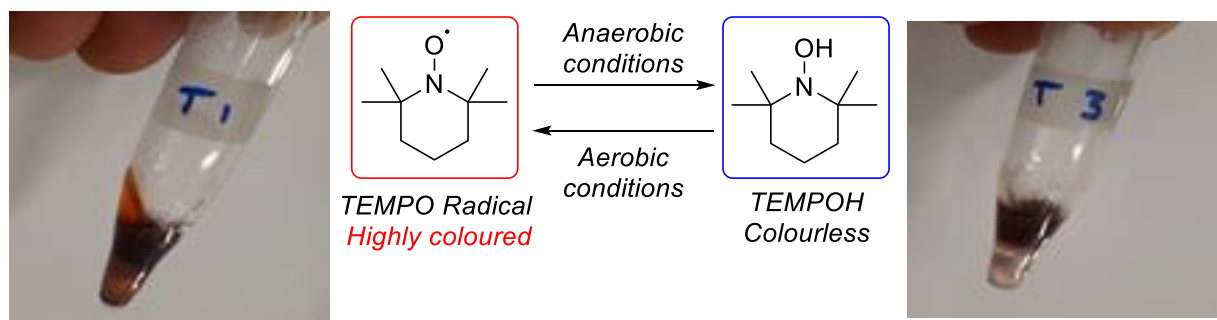
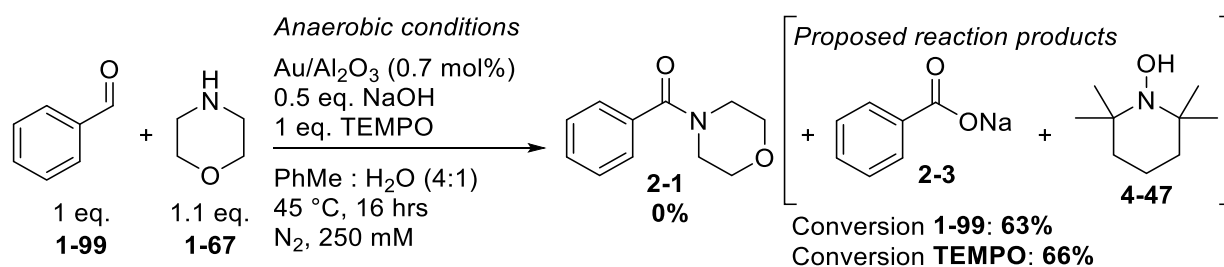


Figure 4-2. Colour change of TEMPO solution in Au/Al₂O₃ catalysed oxidative amidation T1) under O₂ atmosphere T3) under an air atmosphere

Under a pure O₂ atmosphere (aerobic conditions), a similar aldehyde conversion and amide yield are observed (Table 4-3, entry **2**), compared to the equivalent reaction without the addition of TEMPO; with no observable conversion of TEMPO. These experiments confirm that O₂ remains the terminal oxidant for Au/ γ -Al₂O₃ oxidative amidation reactions mediated by TEMPO. The critical roles of base and H₂O were confirmed (entries 3 and 4) and replacing the Au/ γ -Al₂O₃ with the blank Al₂O₃ support material (entry 5) showed that the oxidative amidation reaction could not be catalysed by TEMPO.

The Au/ γ -Al₂O₃ catalysed oxidative amidation reaction with the addition of TEMPO was also attempted under N₂ (anaerobic conditions) (Scheme 4-30).

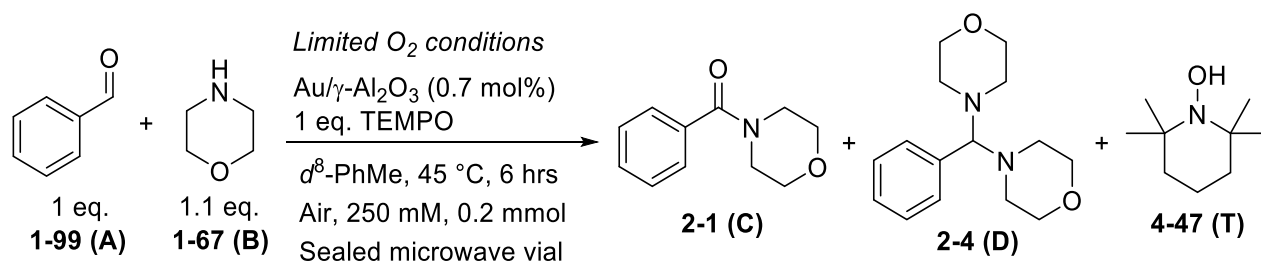


Scheme 4-30. Au/ γ -Al₂O₃ catalysed oxidative amidation performed with TEMPO under a N₂ atmosphere

Under an anaerobic atmosphere, consumption of both benzaldehyde and TEMPO were observed, but not the formation of **2-1**. The products could not be isolated from the multiphasic reaction mixture; however, it is proposed that benzoic acid was formed under these conditions, utilising TEMPO as the terminal oxidant. Benzoic acid is then neutralised in solution to form water-soluble benzoate **2-3**.

Under anaerobic conditions, the same decolourisation of the reaction mixture was observed, which could be regenerated via exposure to air. Therefore, it is proposed that TEMPOH **4-47** is a by-product of the reaction. However, **2-3** could not be separated from the aqueous catalyst slurry, and the regeneration of distinctive colour upon exposure of the reaction mixture to air prevented the isolation of **4-47**.

To confirm the formation of **4-47** during these reactions, the oxidative amidation reaction was performed in deuterated toluene. However, adequate NMR signals could only be observed in the absence of D₂O (Scheme 4-31). A base-free AuNP catalysed oxidative amidation of **1-99** and **1-67** was performed in a sealed microwave vial under air, and the crude mixture was analysed by NMR (Figure 4-3). While no special care was taken in the transfer of reaction mixture to the NMR tube to avoid exposure to O₂, the NMR sample was purged with N₂ and capped with a gas-tight rubber stopper before analysis.



Scheme 4-31. Au-catalysed oxidative amidation reaction performed with TEMPO under limited O₂ conditions in deuterated toluene without the addition of H₂O or NaOH.

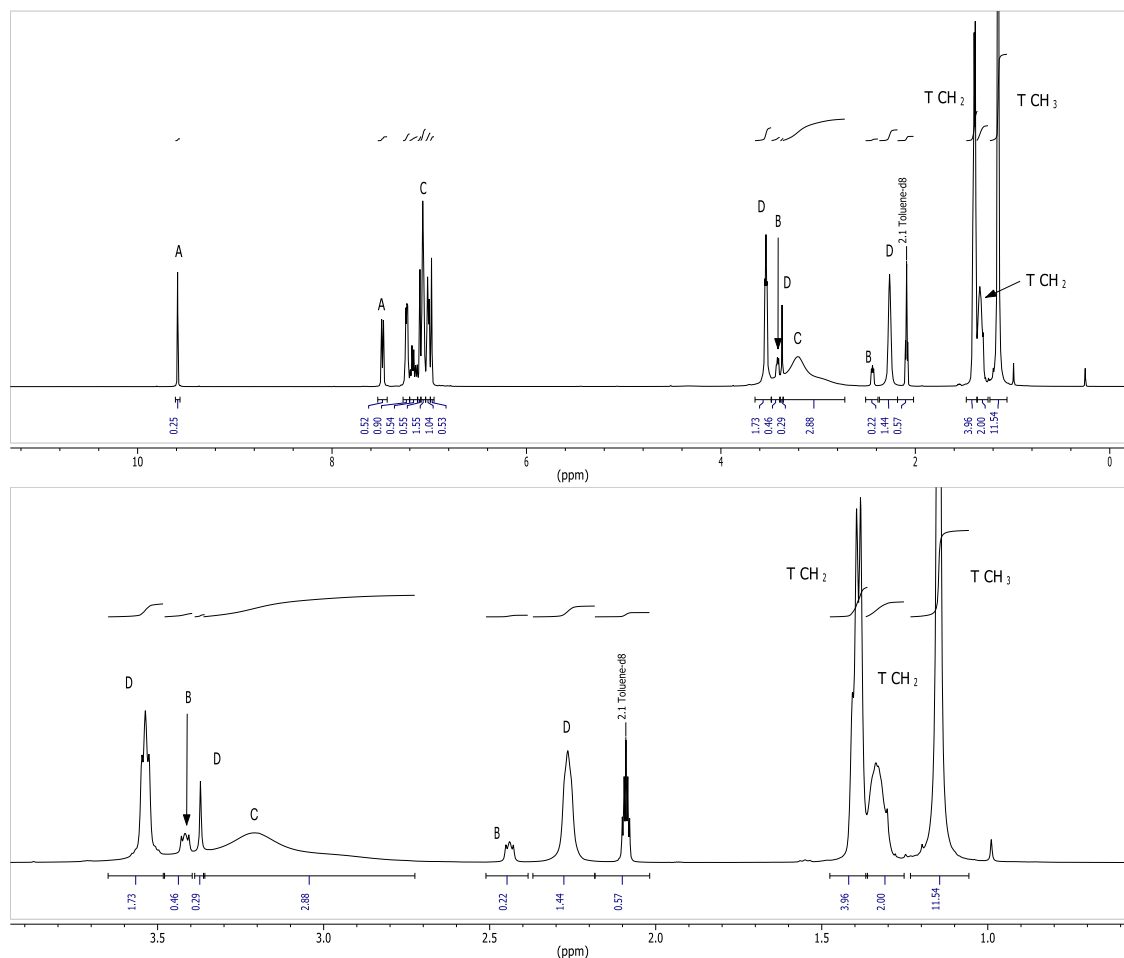


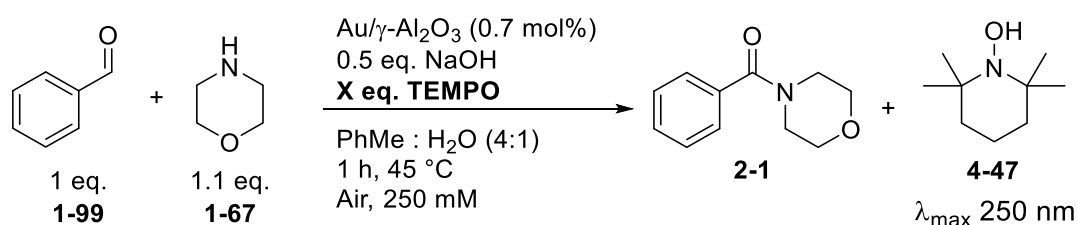
Figure 4-3. NMR spectra of reaction mixtures obtained under base-free and limited O₂ conditions, A) 1-99, B) 1-67, C) 2-1, D) 2-4, T) 4-47 (Scheme 4-31)

As expected, base-free AuNP catalysed oxidative amidation of **1-99** and **1-67** with TEMPO resulted in the incomplete conversion of **1-99**, and the formation of a mixture of amide **2-1** and aminor **2-4**. The incomplete conversion is consistent with previous observations and is attributed to the formation of benzoic acid that deactivates the catalyst in the absence of base.

After 6 hours, the reaction mixture visibly decolourised, indicating the conversion of the TEMPO free radical species to TEMPOH, confirmed by the observation of three ^1H signals in a ratio of 12:2:6 between 1.0–1.5 ppm, and consistent with reported literature values.²³¹

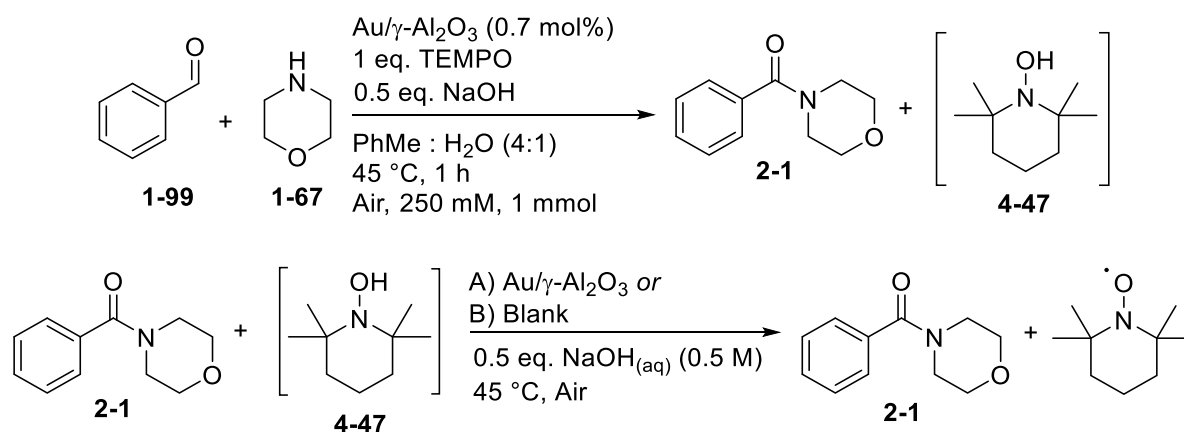
4.4.4 TEMPO Regeneration

Having visually observed the spontaneous regeneration of TEMPO, it was necessary to establish that the concentration of TEMPO remained constant between sampling and HPLC analysis. To this end, 50 μL reaction aliquots were sampled after 1 hour (Scheme 4-32) and immediately diluted 10-fold with methanol in a 2 mL 'snap-top' HPLC vial and sealed with a silicone/PTFE cap. For each HPLC sample, the concentration of TEMPO was determined by UV-Vis absorption at 250 nm,²³² relative to a biphenyl internal standard, the analysis of each HPLC sample was performed 3 times at 12-hour intervals. No change in TEMPO concentration was observed in either subsequent HPLC analysis. Therefore, it was concluded that TEMPO does not regenerate in diluted and sealed reaction samples for at least 24 hours.



Scheme 4-32. TEMPO accelerated $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ catalysed oxidative amidation of benzaldehyde and morpholine with varying equivalences of TEMPO

The oxidation of TEMPOH and regeneration of TEMPO by O_2 could occur on the surface of the catalyst or in solution (uncatalysed). To assess the effect of catalyst on the regeneration rate of TEMPO a 1 mmol scale $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ catalysed oxidative amidation of benzaldehyde **1-99** and morpholine **1-67** was performed in a sealed microwave vial under an atmosphere of air with the addition of 1 equivalent of TEMPO. After 1 hour, the reaction was interrupted by phase separation (isolating the organic compounds from the aqueous catalyst suspension). The organic layer was immediately partitioned between two vessels, and heated at 45 °C under an open atmosphere of air; containing either A) 0.25 mmol of aqueous NaOH (0.5 M) and 'fresh' $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ or B) 0.25 mmol of aqueous NaOH (0.5 M) (Scheme 4-33).



Scheme 4-33. Au catalysed oxidative amidation reaction utilising TEMPO stopped after 1 h to facilitate observation of TEMPO regeneration either by A) oxidation of **4-47** in the presence of 'fresh' Au/ γ -Al₂O₃ or B) background oxidation of **4-47** with dissolved O₂

The concentrations of benzaldehyde **1-99**, amide **2-1**, and TEMPO in each reaction were monitored using a HPLC equipped with a UV-Vis detector over 4 hours (Figure 4-4).

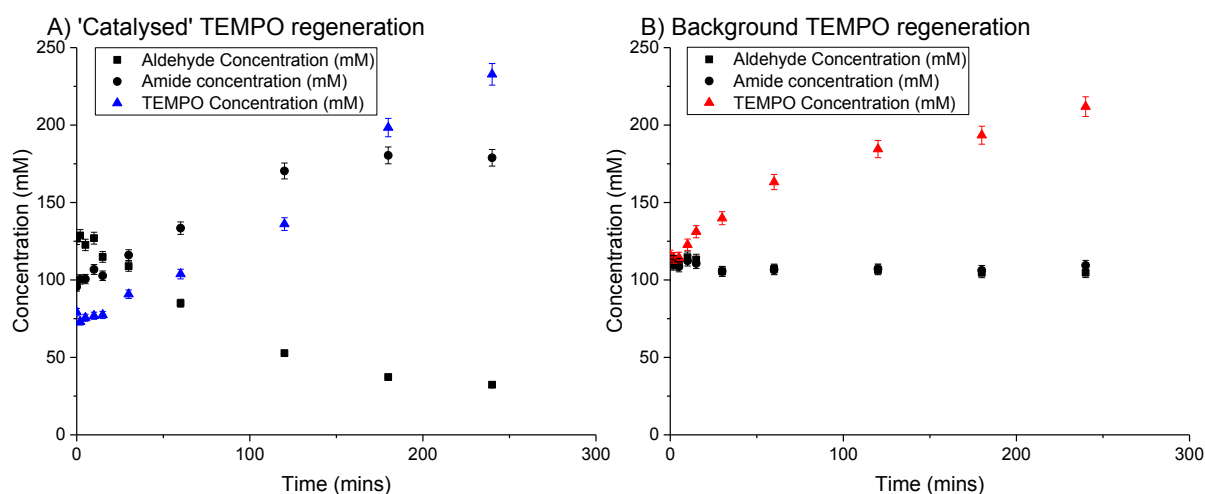


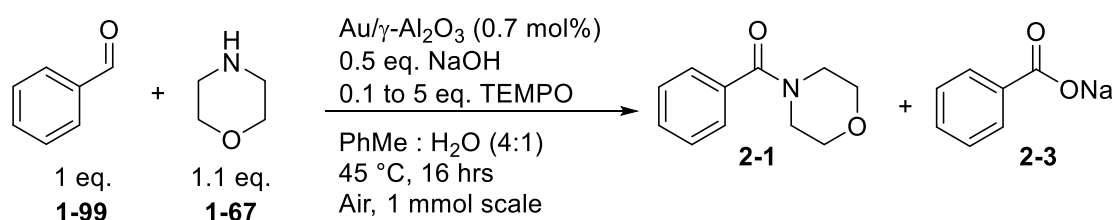
Figure 4-4. Regeneration of TEMPO by either A) oxidation of **4-47** in the presence of 'fresh' Au/ γ -Al₂O₃ B) background oxidation of **4-47** with dissolved O₂

TEMPO regeneration was observed when the isolated reaction mixture was stirred with or without the addition of 'fresh' Au/ γ -Al₂O₃. The addition of the mixture to 'fresh' Au/ γ -Al₂O₃ and aqueous NaOH resulted in catalytic turnover (Scheme 4-33A, Figure 4-4A), indicated by an increased concentration of amide **2-1**. In the absence of the catalyst (Scheme 4-33B, Figure 4-4B), TEMPO regeneration occurred with no detectable change in the concentrations of benzaldehyde and amide.

TEMPO regeneration most likely occurs via both a AuNP catalysed reaction and through reaction with dissolved O₂. Complete regeneration of TEMPO occurred within 4 hours both when the reaction solution was added to ‘fresh’ Au/ γ -Al₂O₃ (Scheme 4-33A, Figure 4-4A) or allowed to stand under air. This result is surprising as the addition of reaction solution to fresh catalyst resulted in the continued formation of amide and slower initial regeneration of TEMPO, suggesting that the catalyst is accelerating TEMPO regeneration.

4.4.5 TEMPO Reaction Profile

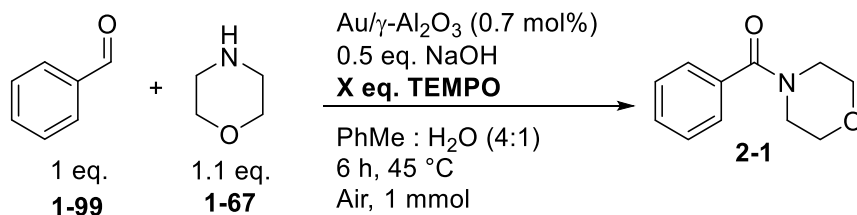
The next part of the investigation evaluates changes in TEMPO concentration during the AuNP catalysed oxidative amidation reaction. Amidation experiments were performed in the presence of between 0.1 and 5 equivalents of TEMPO (Scheme 4-34). Reaction vessels were charged with Au/ γ -Al₂O₃, 0.5 M aqueous NaOH, and TEMPO and heated to 45 °C in a Radley’s reaction carousel. The amidation reaction was initiated via addition of the substrates (benzaldehyde **1-99**, morpholine **1-67**) as a solution in toluene. Reactions were monitored by HPLC, and the concentration of TEMPO was determined by UV-Vis spectroscopy (Figure 4-5).



Scheme 4-34. Au/ γ -Al₂O₃ catalysed oxidation amidation in the presence of TEMPO.

For each reaction, complete conversion of **1-99** was observed after 6 hours reaction time. Under these reaction conditions, a lower selectivity of the amide **2-1** was observed while employing a large excess of TEMPO (Table 4-4, entries **7** to **9**). Previously the stoichiometry of TEMPO (section 4.4.1) was investigated by performing experiments in 2 mL microwave vials. The larger Radley’s reaction vessels facilitate a greater rate of O₂ mass transfer into solution due to more efficient macro-mixing between the organic and aqueous layers, and result in a reduced amide selectivity.

Table 4-4. Effect of addition of increasing amounts of TEMPO on the AuNP catalysed oxidative amidation reaction



Entry	X eq. TEMPO	Conversion 1-99 ^b (%)	Yield 2-1 ^b (%)
1	0	99	69
2	0.1	99	73
3	0.5	99	69
4	1	98	71
5	1.5	99	69
6	2	99	69
7	3	99	63
8	4	99	62
9	5	99	59

^aReaction conditions: Au/γ-Al₂O₃ (150 mg, 0.7 mol%), benzaldehyde (1 mmol), morpholine (1.1 mmol), PhMe (4 mL) ^bConversion of aldehyde and yield of amide were determined by HPLC after 1 h

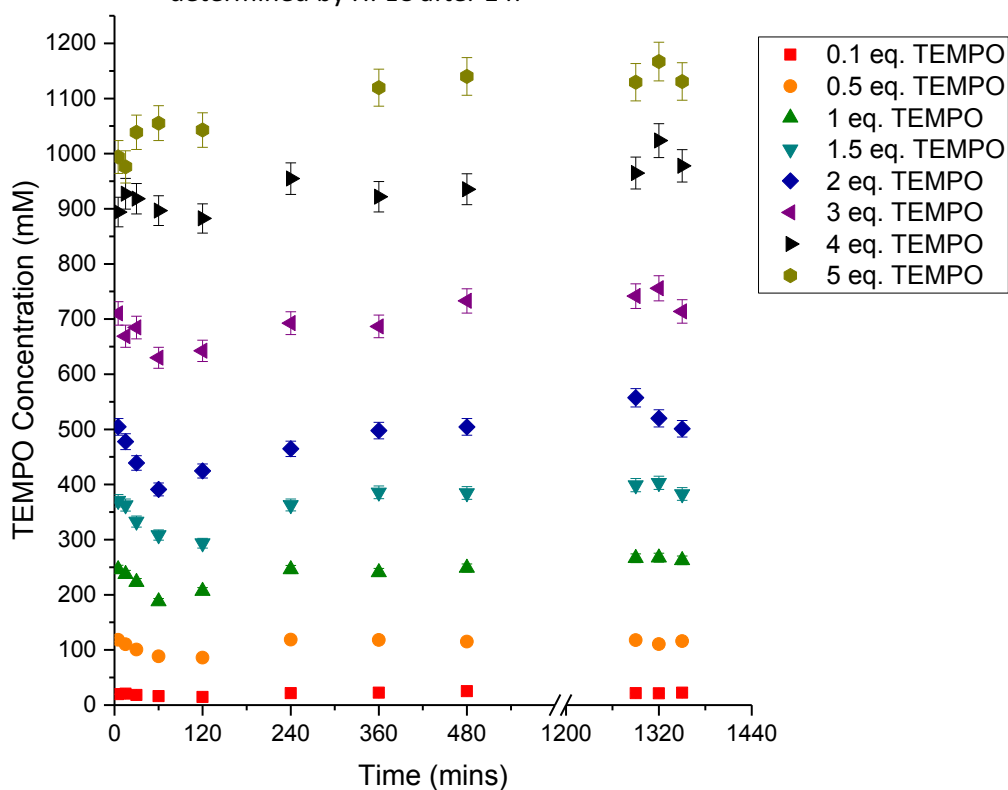


Figure 4-5. TEMPO concentration profile during the Au/γ-Al₂O₃ catalysed oxidation amidation reaction, accelerated by the addition of between 0.1 and 5 equivalents of TEMPO (Scheme 4-34)

For each reaction performed with between 0.1 and 3 equivalents of TEMPO, the initial rates of benzaldehyde conversion (up to 1 hour) fit approximately to a linear trend. However, it was noted that increasing the starting concentration of TEMPO appeared to increase the reaction order of benzaldehyde, as evident by the changing trend in the rate of change of benzaldehyde concentration (Figure 4-6).

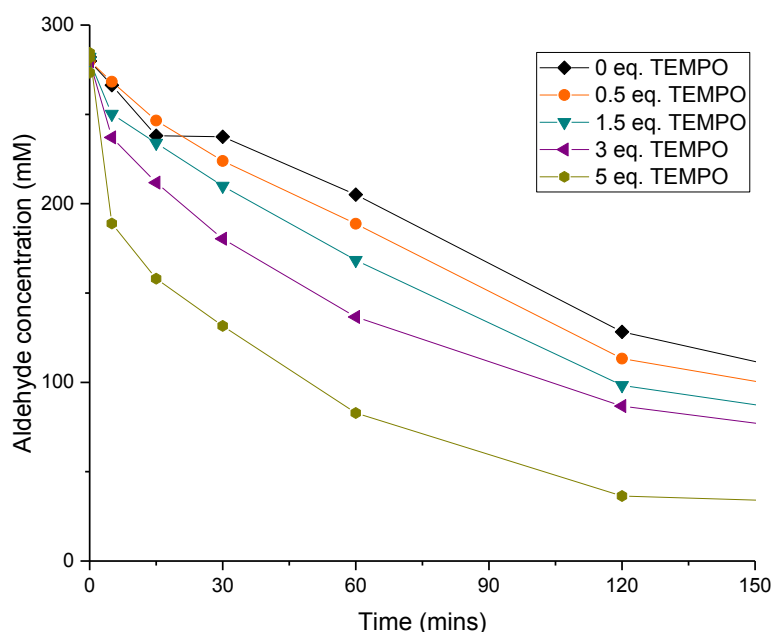


Figure 4-6. Concentration of **1-99** for Au/ γ -Al₂O₃ catalysed oxidative amidation reaction with the addition of increasing equivalents of TEMPO (alternate data sets omitted for clarity)

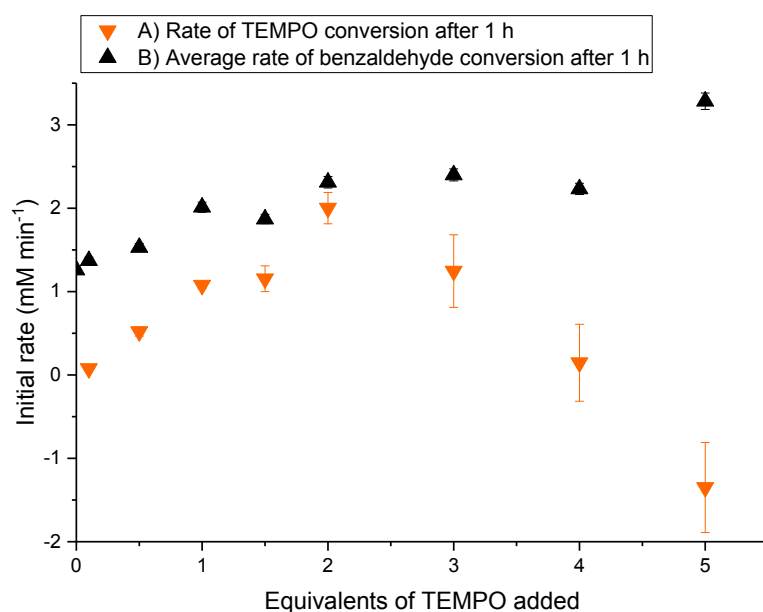


Figure 4-7. Rates calculated at 1 hour for the Au catalysed oxidative amidation reaction (Scheme 36) plotted against the equivalents of TEMPO A) Rate of TEMPO conversion B) Average benzaldehyde conversion after 1 hour (**1-99** conversion (mM)/60 mins)

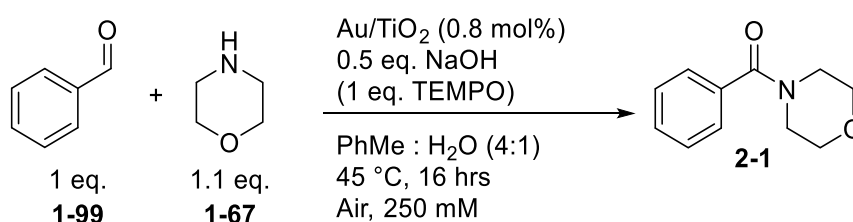
Under the specified conditions for oxidative amidation (Scheme 4-34), the change in TEMPO concentration for each reaction was found to follow a similar trend. In reactions where catalytic or slight excesses (1 to 2 equivalents) of TEMPO were employed the magnitude of the rate of TEMPO conversion increased proportionally to the initial concentration of TEMPO. However, there was an observed reduction in the initial rate of TEMPO conversion when larger excesses (3 or 4 equivalents) of TEMPO were employed (Figure 4-7).

The increasing rate of both aldehyde and TEMPO conversion is expected, the observed reduction in TEMPO conversion rate is due to the TEMPO regeneration proceeding faster than TEMPO conversion as the oxidative amidation reaction nears completion.

4.4.6 TEMPO Effect in Oxidative Amidation Catalysed by a Commercial Au/TiO₂

Thus far investigations into Au catalysed oxidative amidation have been limited to supported AuNP catalysts prepared via a sol immobilisation method. To explore the generality of the developed method, a commercially available Au/TiO₂ (1 wt% AUROLite®, prepared using a deposition-precipitation technique) was employed for the oxidative amidation reaction between benzaldehyde **1-99** and morpholine **1-67**. The average AuNP size is 2 – 3 nm, which is comparable with the sol-immobilised AuNP catalysts prepared in our laboratory.

Two oxidative amidation experiments using Au/TiO₂ were performed, one without TEMPO and one with the addition of 1 equivalent of TEMPO (Scheme 4-35). The oxidative amidation reactions were performed at the 1 mmol scale using an identical procedure described for the oxidative amidation reactions catalysed by Au/γ-Al₂O₃.



Scheme 4-35. Oxidative amidation reaction of benzaldehyde and morpholine catalysed by Au/TiO₂ with the addition of 1 equivalent of TEMPO

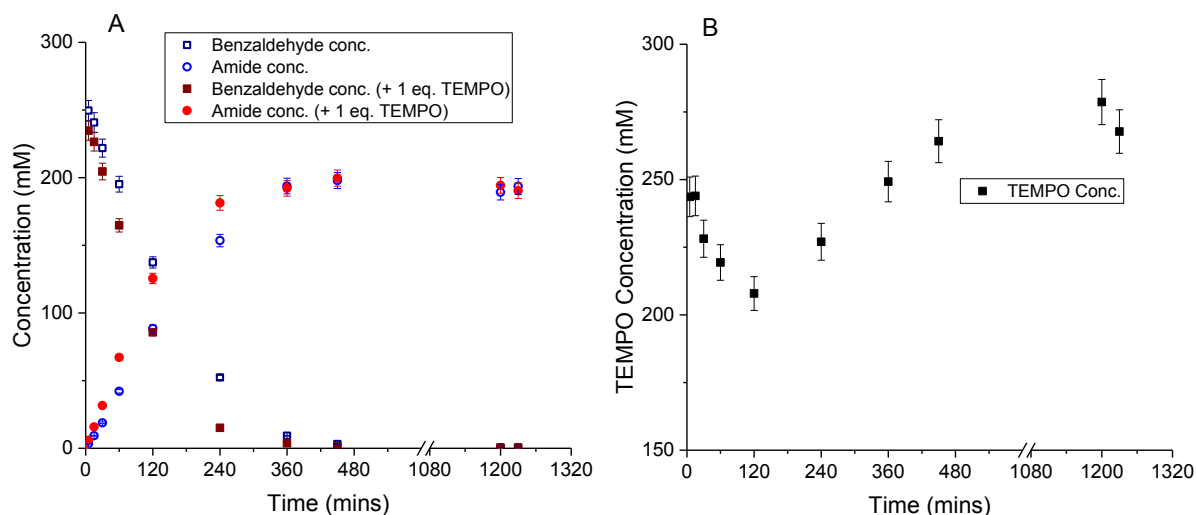


Figure 4-8. Comparing the Au/TiO₂ catalysed oxidative amidation reaction of **1-99** and **1-67** with and without the addition of 1 equivalent of TEMPO (Scheme 4-35) A) Concentration profiles of **1-99** and amide **2-1** B) Concentration profile of TEMPO

The addition of 1 equivalent of TEMPO to the Au/TiO₂ catalysed reaction resulted in an increased rate of **1-99** conversion. The selectivity of the reaction and the magnitude of the accelerating effect of TEMPO was similar to that observed in Au/γ-Al₂O₃ catalysed reaction (Table 4-5).

Table 4-5. Comparing the initial rates of benzaldehyde conversion in the Au catalysed oxidative amidation reaction with and without the addition of TEMPO

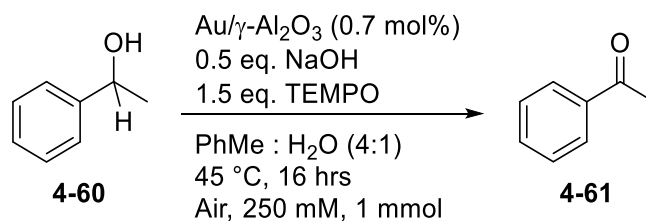
Entry	Catalyst	Initial rate of 1-99 conversion without TEMPO ^b (mM min ⁻¹)	Initial rate of 1-99 conversion. with 1 eq. TEMPO ^b (mM min ⁻¹)
1	Au/γ-Al ₂ O ₃	1.296 ± 0.068	1.613 ± 0.117
2	Au/TiO ₂	1.021 ± 0.024	1.482 ± 0.076

^aReaction conditions: Benzaldehyde (1 mmol), morpholine (1.1 mmol), PhMe (4 mL). ^bRates of benzaldehyde conversion were determined by HPLC using a linear fit of the concentration values obtained for the first 2 h of the oxidative amidation reaction. ^cErrors presented are the standard errors calculated for the linear fit to the aldehyde conversions.

The results confirm that the accelerating effect of TEMPO is not unique to Au catalysts prepared via sol-immobilisation. This would also suggest that the mechanism for Au catalysed oxidative amidation proceeds via common intermediates and therefore the reactivity is not unique to a specific AuNP size or geometry.

4.4.7 TEMPO Additive in Secondary Alcohol Oxidation

Continuing the investigation into the accelerating effect of TEMPO in other AuNP catalysed systems, the effect of TEMPO was assessed in the AuNP catalysed oxidation of a secondary alcohol. The aerobic oxidation of 1-phenylethanol **4-60** to acetophenone **4-61**, catalysed by Au/ γ -Al₂O₃, was examined under identical conditions to those employed in the oxidative amidation reaction (Scheme 4-36). The reaction was performed at the 1 mmol scale and the concentrations of **4-60**, **4-61**, and TEMPO were monitored by HPLC.



*Scheme 4-36. Au/ γ -Al₂O₃ catalysed oxidation of **4-60***

TEMPO could be converted into an oxoammonium salt via a Au catalysed reaction employing O₂ as the terminal oxidant. Oxoammonium salts can then be employed as oxidants for the conversion of secondary alcohols to ketones.^{217,233} One of our proposed hypotheses, though less likely, was that the reaction of TEMPO with the AuNP catalyst could facilitate the formation of an oxoammonium salt. Therefore, the addition of TEMPO should accelerate the oxidation of a secondary alcohol.

The addition of TEMPO resulted in no significant change in the rate of oxidation of **4-60**, although TEMPO is consumed during the reaction (Figure 4-9). This result suggests that either TEMPO does not accelerate AuNP oxidations via the catalysed formation of an oxoammonium salt or is not involved in the rate limiting step of alcohol oxidation.

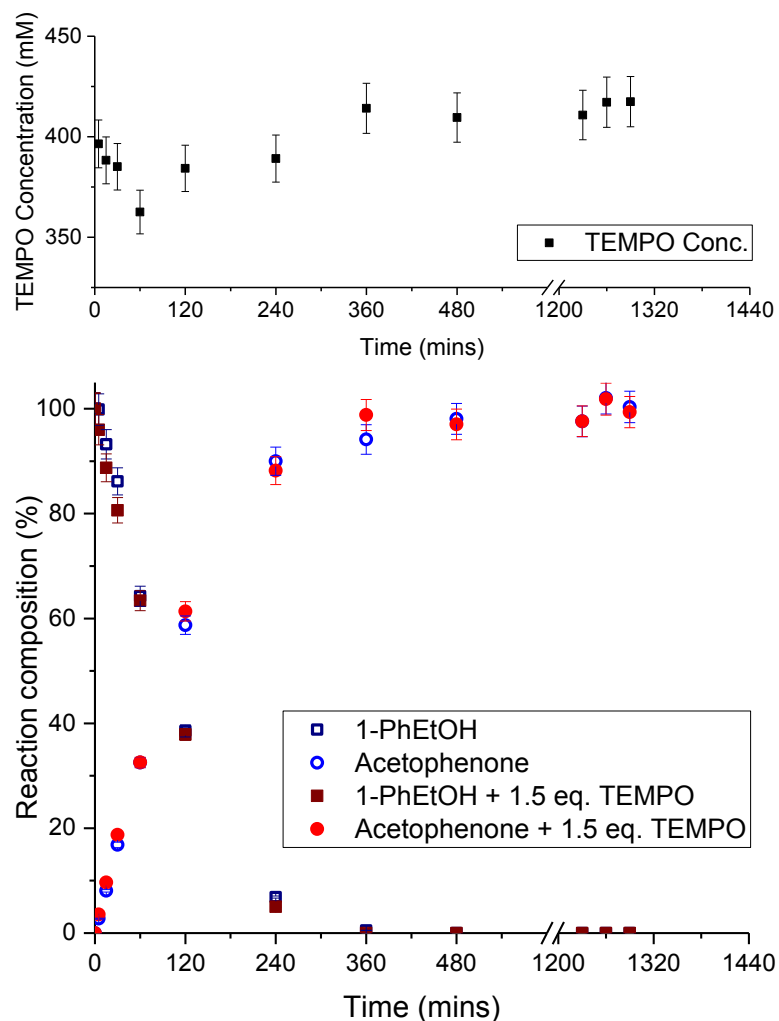


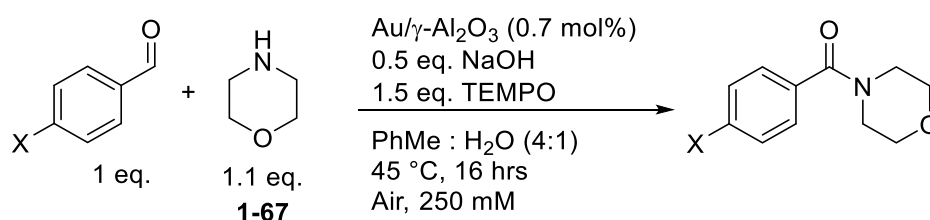
Figure 4-9. **4-60**, **4-61**, and TEMPO concentration profiles for the Au/ γ -Al₂O₃ catalysed oxidation of **4-60** (Scheme 4-36)

Chechik and co-workers reported that addition of TEMPO to the Au/CeO₂ catalysed oxidation of 3-octanol resulted in the formation of TEMPOH, via the abstraction of hydride species regenerating the AuNP surface.²⁰⁹ The authors observed no increase in the oxidation rate and various radical spin traps have been used to abstract surface bound Au-H species. This most likely scenario based on previous reports, is the reduction in TEMPO concentration can be rationalised by an Au-H abstraction, following hydride elimination of a surface bound alcohol.

4.4.8 Hammett Relationship with TEMPO

Previous experiments reported in this chapter have primarily attempted to identify the role and fate of TEMPO when employed in the Au catalysed oxidative amidation of aldehydes. It seems likely that TEMPO is converted to TEMPOH, while regenerating catalytically active sites. The addition of TEMPO appears to result in an increased order in aldehyde, based on the change in benzaldehyde concentration profile at high equivalents of TEMPO. The increasing substrate order suggests that the rate-limiting step changes when excess TEMPO is added to the reaction. However, studies into the mechanism by which TEMPO accelerates the Au catalysed oxidative amidation are thus far inconclusive.

In this part of the work, a Hammett analysis of the Au catalysed oxidative amidation reaction was performed, with the addition of 1.5 equivalents of TEMPO (Scheme 4-37), to reassess the relationship between the rate of aldehyde oxidation and the electronic effects at the carbonyl position. The results of the TEMPO accelerated Hammett analysis are then compared to the earlier study without the addition of TEMPO (Figure 4-10).



Scheme 4-37. Au/γ-Al₂O₃ catalysed oxidative amidation reaction of para-substituted benzaldehydes accelerated by the addition of 1.5 eq. TEMPO

The rates of conversion for each para-substituted benzaldehyde employed in the TEMPO accelerated amidation (Figure 4-10A), were determined as previously described for the Hammett analysis of the Au catalysed oxidative amidation reaction conducted without TEMPO (Control) (Figure 4-10B, section 2.6.1). The same batch of Au/γ-Al₂O₃ was used to facilitate a direct comparison between the ‘control’ and TEMPO accelerated rates.

The reaction of each para-substituted benzaldehyde employed was performed independently and monitored over 6 hours by HPLC analysis. The rates were calculated by fitting a linear curve to the aldehyde concentration data collected over the first hour of the reaction.

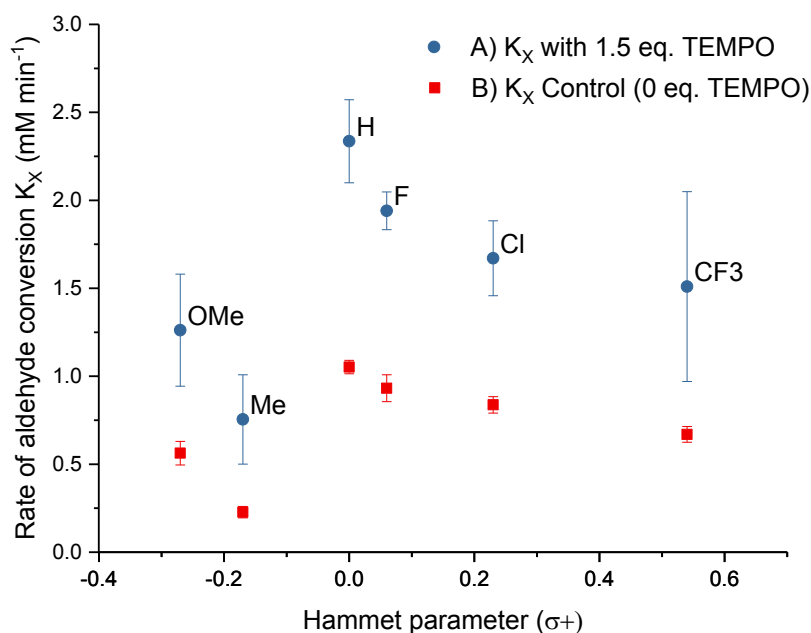


Figure 4-10. Plot of Hammett (σ^+) parameters¹⁴¹ against the rates of aldehyde conversion (K_X) for the oxidative amidation reaction of para-substituted benzaldehydes A) for the first hour with 1.5 eq. TEMPO (Scheme 4-37) and B) for the first 2 h without TEMPO (section 2.6.1). Error bars display the standard error associated with the correlation of the aldehyde concentrations to the linear fit.

Addition of TEMPO increased the rate of conversion of all para-substituted benzaldehydes, irrespective of electronic effect of the substituent, and the selectivity toward amide formation was not affected by the addition of TEMPO for any of the para-substituted benzaldehydes studied. The accelerating effect of TEMPO on aldehyde conversion in each oxidative amidation reaction was of a similar magnitude of between 2.0 and 2.3 when assuming the aldehyde was zero-order, with the exception of para-methyl benzaldehyde, where the addition of TEMPO resulted in a 4-fold increase in the rate of aldehyde conversion.

In the previous Hammett analysis, initial rates were calculated by fitting a linear curve to concentration data collected for the first 2 hours of the standard Au/ γ -Al₂O₃ catalysed oxidative amidation. However, the addition of TEMPO to the Au catalysed oxidative amidation reaction appears to increase the order of aldehyde. Approximating the rate of aldehyde conversion necessitated reducing the number of concentration points fitted to the linear curve. The rate value obtained is substantially less accurate, as evidenced by the large error associated with the determined rate values (Figure 4-10A), compared with the 'control' Hammett analysis (Figure 4-10B), due to the poorer on average fit and larger relative effects of data points that deviate from the linear trend.

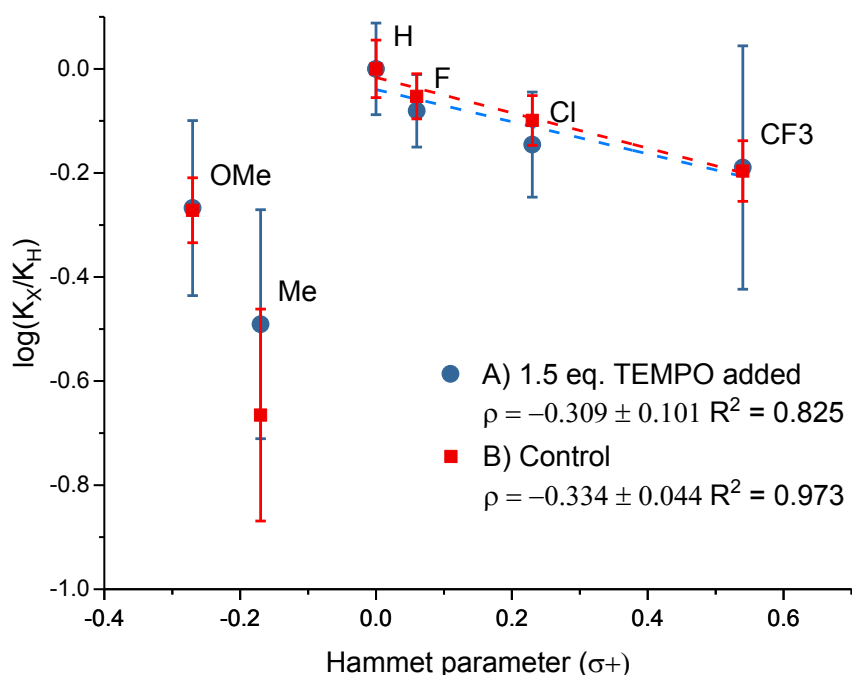


Figure 4-11. Plot of Hammett (σ_p) parameters¹⁴¹ against the log of the ratio of rates of aldehyde conversion (K_x/K_H) A) with 1.5 eq. TEMPO (Scheme 39) and B) without TEMPO (section 2.6.1). Error bars display the standard error associated with the correlation of the aldehyde concentrations to the linear fit.

Plotting the Hammett analysis of the rate data presented in Figure 4-10 showed no linear correlation between the rate of aldehyde conversion and the electronic effects of the para-substituents (Figure 4-11), but the large error in the rate values are still apparent. The Hammett analysis revealed the TEMPO accelerated Au catalysed oxidative amidation reactions (Figure 4-11A) follows the same trend as the 'control' Au catalysed oxidative amidation reaction (Figure 4-11B). The lack of correlation between the rate of aldehyde conversion and the electronic effects around the carbonyl position in both Hammett plots suggests that our original hypothesis that the rate of aldehyde conversion is determined by the net molecular properties of the para-substituted aldehydes.¹⁴²

Initially aldehyde conversion rate was calculated from the concentration to facilitate a direct comparison with the 'control' reaction. However, considering the observed increase in the order of aldehyde with the addition of TEMPO the Hammett analysis was repeated assuming the reaction is first-order in aldehyde. The rate constants for different para-substituted benzaldehydes were estimated using a linear fit for the natural logarithm of benzaldehyde concentration against time, where the gradient of the curve is the observed rate constant (Figure 4-12).

$$\text{Rate} = \frac{-d[\text{Ald}]}{dt} = k_{\text{obs}}[\text{Ald}]_t \quad (1)$$

$$\ln\left(\frac{[\text{Ald}]_t}{[\text{Ald}]_0}\right) = -k_{\text{obs}}t \quad (2)$$

$$\ln[\text{Ald}]_t = -k_{\text{obs}}t + \ln[\text{Ald}]_0 \quad (3)$$

Figure 4-12. (1) First-order rate equation (2) Integrated rate law for first-order rate equation (3) Integrated rate law in the form $y = mx + c$

Despite the large errors associated with the determined assuming the aldehyde is zero-order (e.g. Figure 4-13A), there is a reasonable correlation ($R^2 > 0.90$) for most of the para-substituted benzaldehyde concentrations to the respective linear fit (Table 4-6, entries **1**, **3** to **5**). However, the results obtained assuming the aldehyde is first-order were more accurate (reduced errors) and showed better correlation (greater R^2 values) to the linear curve fitted for the natural logarithm of benzaldehyde vs. time plot (e.g. Figure 4-13B) (Table 4-6).

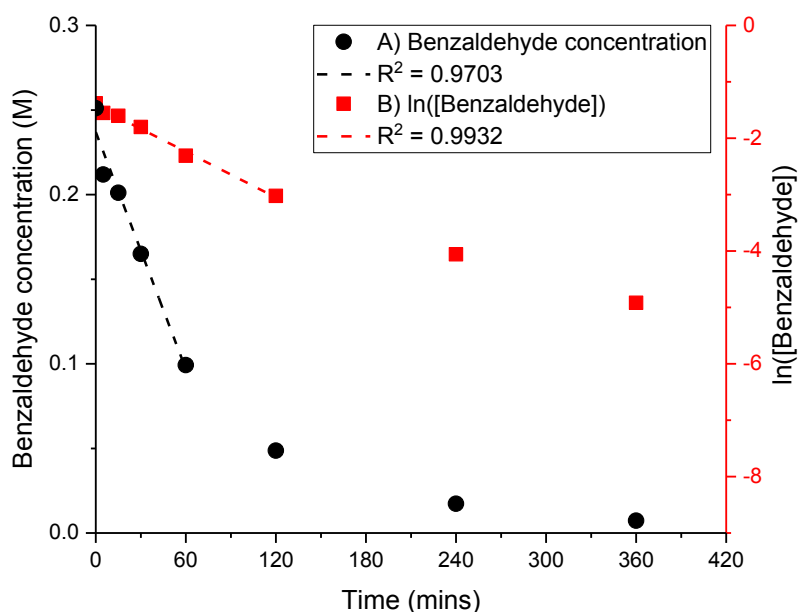


Figure 4-13. Comparing the linear fit of A) benzaldehyde concentration plotted against time B) natural logarithm of benzaldehyde concentration against time

Table 4-6. Rates of para-substituted benzaldehyde conversion in the TEMPO accelerated oxidative amidation, errors, and R-squared values for zero-order and first-order aldehyde approximations

Entry	X =	σ^+	Zero-order rate ^b (mM min ⁻¹)	Zero-order fit R ²	First-order rate constant ^c (* 10 ⁻² min ⁻¹)	First-order fit R ²
1	OMe	-0.27	1.26 ± 0.32	0.905	0.53 ± 0.06	0.958
2	Me	-0.17	0.75 ± 0.10	0.746	0.42 ± 0.05	0.948
3	H	0.00	2.34 ± 0.24	0.970	1.35 ± 0.06	0.993
4	F	0.06	1.94 ± 0.11	0.991	1.17 ± 0.05	0.995
5	Cl	0.23	1.67 ± 0.21	0.954	0.93 ± 0.08	0.978
6	CF ₃	0.54	1.51 ± 0.54	0.723	0.73 ± 0.05	0.927

^aReaction conditions: Au/ γ -Al₂O₃ (150 mg, 0.7 mol%), aldehyde (1 mmol), morpholine (1.1 mmol), PhMe (4 mL), 0.5 M NaOH (1 mL), Au/ γ -Al₂O₃ (150 mg), TEMPO (1.5 mmol) ^bZero-order rates calculated from a linear fit to the aldehyde concentrations plotted against time after 1 hour ^cFirst-order rates calculated from a linear fit to the natural log of aldehyde concentrations plotted against time after 1 hour

Replotting the Hammett analysis for the TEMPO accelerated oxidative amidation reaction using the rate constants obtained assuming a first-order aldehyde conversion (Figure 4-14) unsurprisingly shows the same trend as the Hammett plots obtained previously (Figure 4-11) and the standard ‘control’ Au catalysed oxidative amidation without TEMPO.

However, when assuming a first-order aldehyde concentration, there is a slight increase in the magnitude of the negative correlation observed for the rate of conversion for para-substituted aldehydes bearing electron withdrawing groups against the substituent’s Hammett parameters. Returning to the hypothesis presented in section 2.6.1, the negative correlation of the rate of para-substituted benzaldehyde conversion to the electronic effects of the substituent suggests an accumulation of positive charge at the benzylic carbon of a reaction intermediate. Therefore, the increased magnitude of the negative correlation would support our proposal that the addition of TEMPO to the Au catalysed oxidative amidation reaction increases the rate of active site regeneration, hence making the formation of amide via a hydride elimination the rate limiting step.

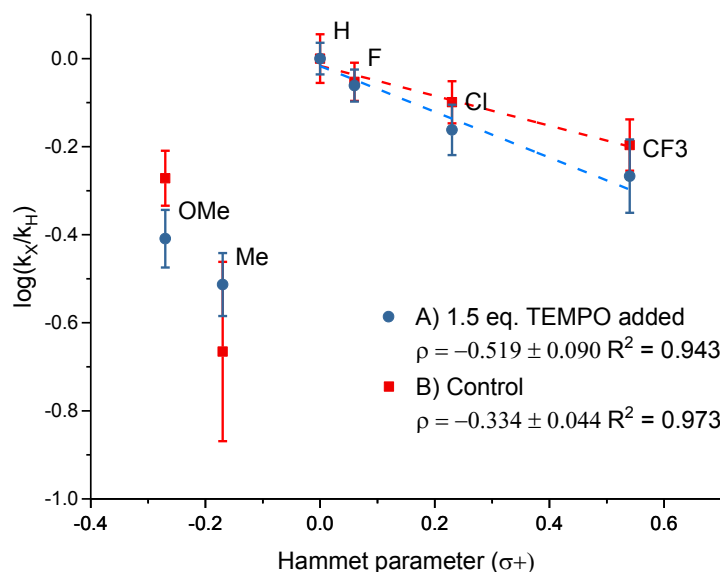


Figure 4-14. Plot of Hammett (σ_p) parameters¹⁴¹ against the log of the ratio between A) initial rate constants (k_X/k_H) with 1.5 eq. TEMPO (Scheme 39) and B) initial rates without TEMPO (section 2.6.1). Error bars display the standard error associated with the correlation of the aldehyde concentrations to the linear fit.

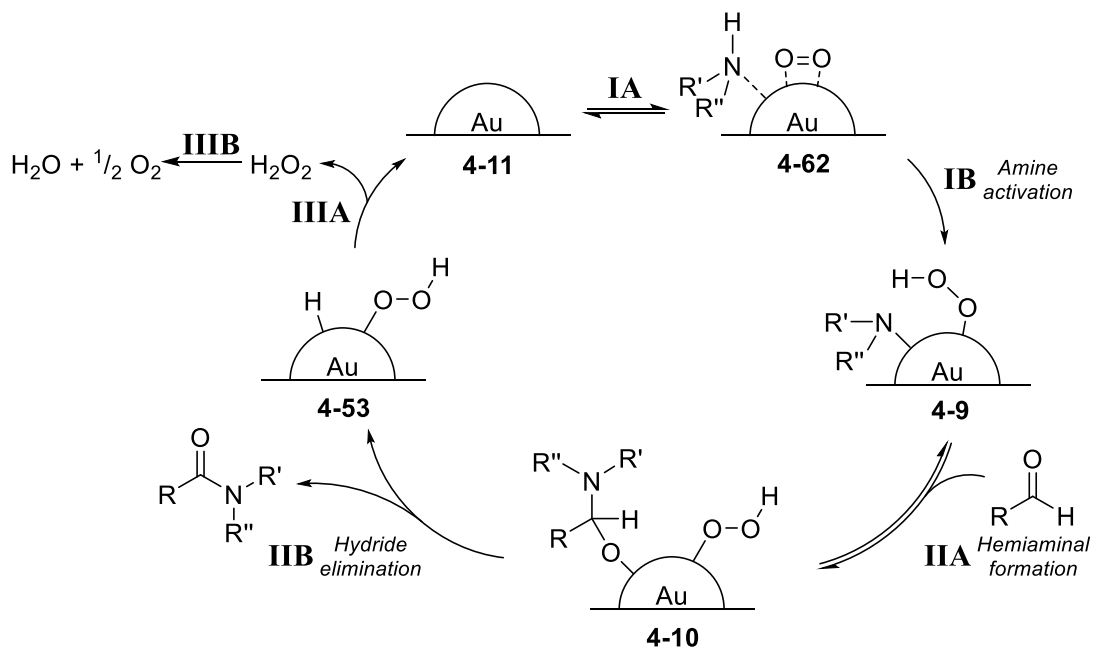
To summarise, the Hammett analysis did not conclusively demonstrate that the addition of 1.5 equivalents of TEMPO induces a change of the rate limiting step in the Au/ γ -Al₂O₃ catalysed oxidative amidation reaction. The addition of TEMPO to the oxidative amidation resulted in an increased rate of aldehyde conversion for all para-substituted benzaldehydes studied.

However two observations warranted a further investigation to understand how the Au catalysed oxidative amidation mechanism changes with the addition of TEMPO. Firstly, the negative correlation between the substituent Hammett parameters and the aldehyde conversion rates observed for para-substituted benzaldehydes bearing electron withdrawing groups suggests that there is an accumulation of positive charge at the reactive benzylic carbon centre. If the build-up of positive charge is due to a hydride elimination type mechanism, in a similar manner to findings reported for Au catalysed alcohol oxidation,¹⁴⁰ then it should be possible to observe a kinetic isotope effect for the breaking of the aldehydic C-H bond.

Secondly, the greater correlation and reduced errors associated when assuming aldehyde concentration is first-order strongly supports the earlier observation that the addition of TEMPO increases the order in aldehyde concentration. However, the exact order in aldehyde remains ambiguous as reasonable correlations assuming either a zero- or first-order relationship suggest that the exact order may not be trivial. The orders of catalyst and the substrates, benzaldehyde and morpholine, in the Au catalysed oxidative amidation reaction and how the reaction orders change with the inclusion of TEMPO are discussed in more detail in a section 4.6.

4.4.9 Revised Reaction Mechanism for the Au Catalysed Oxidative Amidation

Based on the known reactivity of AuNP's outlined in the introduction to this chapter and the results presented in this investigation into the effects of TEMPO on the Au catalysed oxidative amidation, a revised catalytic cycle can be proposed that addresses many of the mechanistic steps in explicit detail (Scheme 4-38).



Scheme 4-38. Revised AuNP catalysed oxidative amidation catalytic cycle

IA. Physisorption of O₂ and amine to AuNP surface **4-11**

IB. Oxygen assisted chemisorption of amine to the AuNP surface

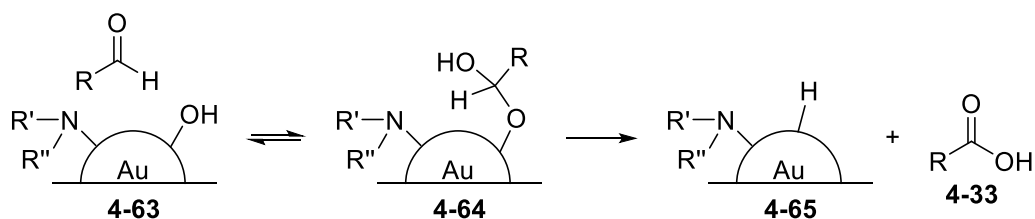
The absence of any amide formation in the Au catalysed reaction performed under an inert atmosphere, even with the addition of TEMPO, would suggest that O₂ adsorbed on the Au surface is required for oxidative amidation.

Our proposal contradicts the base-assisted amine adsorption suggested by Kobayashi and co-workers (section 4.1.1).¹⁰¹ There are multiple examples demonstrating hydroxide is not essential to the chemisorption of an amine to the AuNP surface.^{109,137,234} However, both base-free and base-assisted amine adsorptions may be occurring at the Au/ γ -Al₂O₃ surface.

IIA. Physisorption of aldehyde to the catalyst surface followed by reaction with a surface-bound amide species **4-9**.

IIB. Elimination of a hydride species from a surface bound hemiaminal (**4-10**) to yield the amide. The elimination of a hydride species from a surface-bound hemiaminal has so far not been unambiguously established. But a hydride elimination seems the most likely pathway, based on previous literature reports for the oxidation of secondary alcohols and the results obtained with the addition of TEMPO to the Au/ γ -Al₂O₃ catalysed oxidative amidation.

Hemiaminal formation and hydride elimination steps likely determine the selectivity of this Au catalysed oxidative amidation system. It has been demonstrated previously that the background rate of aldehyde autoxidation under these oxidative amidation conditions is insignificant. Acyl radical formation is an unlikely reaction pathway and carboxylic acid formation most likely occurs via an analogous catalytic pathway to the oxidative amidation reaction (Scheme 4-39).



Scheme 4-39. Alternative reaction pathway resulting in the formation of a carboxylic acid

Carboxylic acid formation is preceded by the reaction of an aldehyde with a surface bound oxygen species to form acetal **4-64** that subsequently undergoes a hydride elimination to yield carboxylic acid **4-33** and Au hydride species **4-65**. Our hypothesis is consistent with the lower selectivity observed with greater concentrations of hydroxide, which would result in a greater proportion of hydroxide species on the Au surface.

Both higher O₂ and hydroxide concentrations could feasibly lead to a greater number of oxygen species on the Au surface, hence a lower selectivity toward amide formation. However, higher O₂ concentrations may also facilitate the Au initiated radical chain oxidation pathway proposed by Chechik and co-workers.²¹³

IIIA. Regeneration of the AuNP active site and formation of H₂O₂ by-product

IIIB. Decomposition of H₂O₂ to form H₂O and ½ O₂

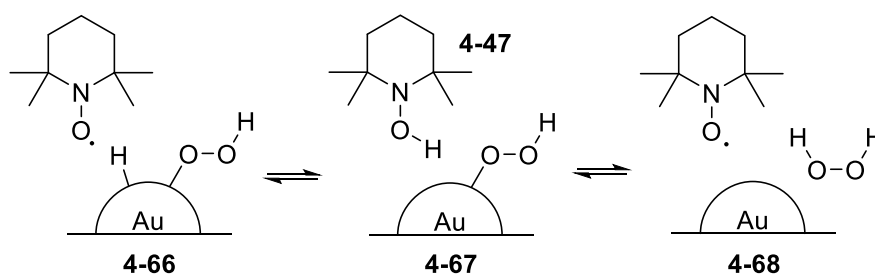
As stated previously in this chapter, the application of Au catalysis in H₂O₂ synthesis and decomposition is well studied.^{201–205} However, it is also possible that the regeneration of the AuNP active site is a non-trivial sequence of reaction steps that involve the reaction of proposed Au-H species with other reactive oxygen species adsorbed to the AuNP surface.²³⁵

Possibly the most counter-intuitive point, given the empirical optimisation of reaction conditions presented in chapter 2, is that base is not explicitly involved in any step of the proposed oxidative amidation mechanism (Scheme 4-38). In addition to the reasons for base outlined in chapter 2: preventing imine/aminal formation and neutralising carboxylic acid by-products, the addition of base is also likely to facilitate the formation and adsorption of hemiaminal species to the AuNP surface (4-10, III).

4.4.10 Effect of TEMPO on the Au Catalysed Oxidative Amidation

Previous reports have found the addition of TEMPO to Au initiated radical processes results in inhibition of the radical oxidation pathway.²¹³ Whereas, under the conditions adopted in this study, there is no evidence to suggest the involvement of acyl radicals in either the oxidative amidation or carboxylic acid formation.

With this in mind, it was proposed that the oxidative amidation reaction is likely to proceed via the formation of Au-H species, which is extracted by TEMPO to form TEMPOH 4-47. The accelerating effect of TEMPO under these Au catalysed oxidative amidation conditions could therefore be explained by TEMPO acting as a mediator in the regeneration of the active catalyst site (Scheme 4-40).



Scheme 4-40. Proposed TEMPO mediated catalyst regeneration pathway

The abstraction of Au-H species, regenerating the catalyst surface has precedent and is the simplest explanation for the accelerating effect of TEMPO. Other proposed hypotheses for the accelerating effect of TEMPO, namely the formation of either hydroxylamine esters or the oxoammonium salt, seem less likely based on the results discussed in this chapter.

4.5 Kinetic Isotope Effects in Au Catalysed Oxidative Amidation

4.5.1 Background

Kinetic isotope effect (KIE) experiments provide valuable information that can be used to postulate the rate-limiting step of a reaction mechanism.²³⁶ The value of a KIE is expressed as the ratio of the reaction rates (k_H/k_D) between two isotopomers under identical reaction conditions. The difference in reaction rate usually derives from a difference in bond dissociation energies for isotopic atoms. Chemical bonds to heavier isotopes result in lower zero-point energies, and thus higher activation energies, than the corresponding bond to lighter isotopes.

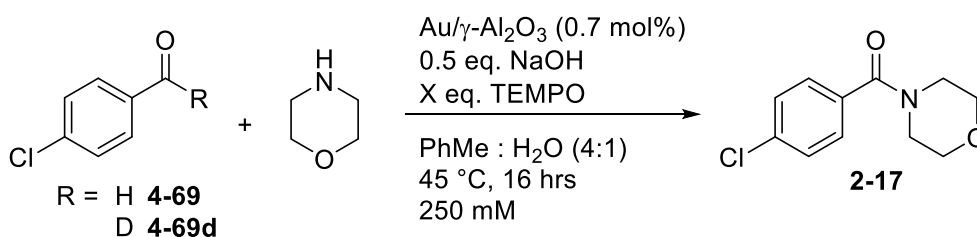
The magnitude of a KIE is dependent on the relative difference in mass between the isomers employed; hence reactions investigating H^1 vs D^2 tend to give large KIE as D^2 is twice the mass of H^1 . Secondly, the magnitude of a KIE is dependent on the role the isotopic centre has in the reaction mechanism. Reactions where the C-H/C-D bond is either broken or formed in the rate-limiting step result in a 'primary' KIE. 'Secondary KIE' typically have a much lower magnitude and result from interactions that do not involve the breaking of the C-H/C-D bond, usually arising from the energy difference between bending modes of C-H and C-D bonds. KIE of greater than 1 are referred to as 'normal KIE' ($k_H/k_D > 1$) and react as expected where the lower activation energy results in a faster reaction for the lighter isotope. Whereas reactions where the KIE is less than 1 are referred to as 'inverse KIE' ($k_H/k_D < 1$), and the heavier isotope reacts faster.

KIE values of between $k_H/k_D = 1.4 - 2.0$ have been reported for the Au catalysed oxidation of benzylic alcohols to aldehydes performed employing O_2 as the terminal oxidant.^{122,140} The observation points to the hydride elimination as the rate-limiting step, although there is no direct spectroscopic evidence for the formation of surface-bound alkoxylate intermediate or the resulting hydride species.

To date there have been no reported studies on KIEs in the AuNP catalysed oxidative amidation of either alcohols or aldehydes.

4.5.2 AuNP Catalysed Oxidation Amidation

The Au/ γ -Al₂O₃ catalysed oxidative amidation reactions of para-chlorobenzaldehyde **4-69** and *d*¹-para-chlorobenzaldehyde **4-69d** with morpholine **1-67** were performed under the conditions described in Chapter 2 (Scheme 4-41, Figure 4-15). Each reaction was repeated with the addition of either 1 or 3 equivalents of TEMPO (Scheme 4-41, Figure 4-16). The progress of each reaction was monitored by HPLC over 8 hours. Deuterated **4-69d** was selected for the KIE studies as deuterated benzaldehyde rapidly oxidised to benzoic acid.



Scheme 4-41. Au/ γ -Al₂O₃ catalysed oxidative amidation of **4-69** and **4-69d** for KIE experiment

Because the catalytic pathway for carboxylic acid formation remains unclear, KIE values were determined by comparing the ratio between the rates of amide formation in each reaction employing **4-69** and **4-69d**. The same amide selectivity was observed for the Au-catalysed reaction with both **4-69** or **4-69d**.

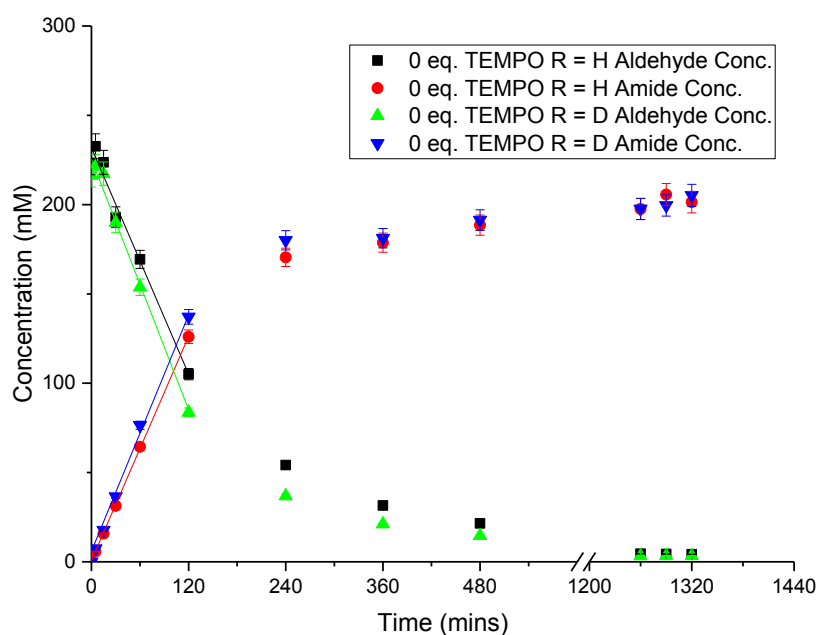


Figure 4-15. Concentration profile for the Au/ γ -Al₂O₃ catalysed oxidative amidation reaction of **4-69** and **4-69d**

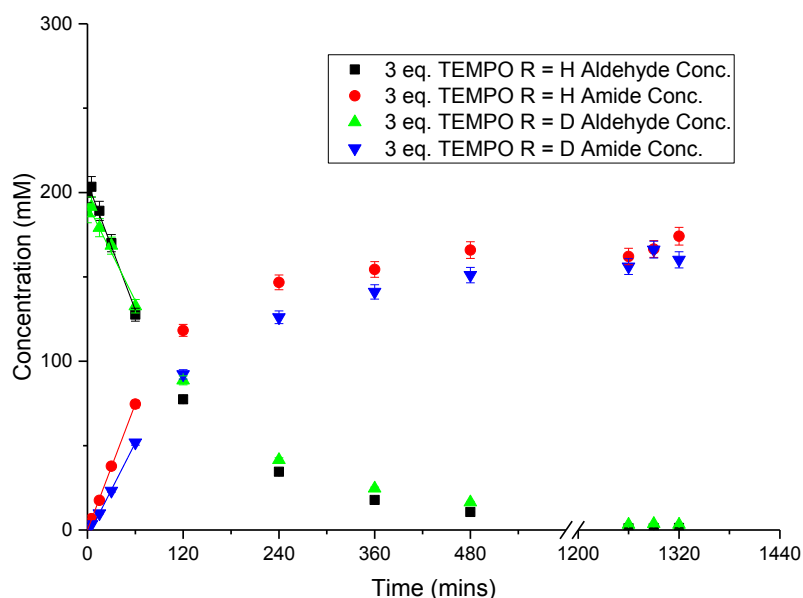


Figure 4-16. Concentration profile for the Au/ γ -Al₂O₃ catalysed oxidative amidation reaction of **4-69** and **4-69d** accelerated by the addition of 3 equivalents of TEMPO

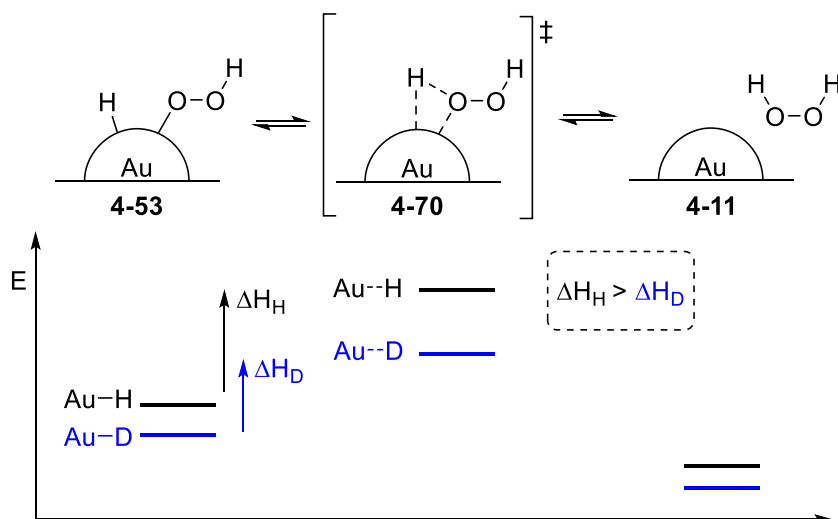
Table 4-7. Table summarising initial rates of amide formation and observed KIE found for the Au/ γ -Al₂O₃ catalysed oxidative amidation reaction of para-chlorobenzaldehyde and morpholine

Entry	TEMPO eq.	Initial rate of amide formation (mM min ⁻¹)		Observed KIE
		4-69 R = H	4-69d R = D	
1	0	1.068 ± 0.048	1.265 ± 0.216	0.85 ± 0.18
2	1	1.307 ± 0.255	1.215 ± 0.089	1.08 ± 0.27
3	3	1.245 ± 0.048	0.870 ± 0.194	1.43 ± 0.48

Rate of amide formation after 1 hour using a linear curve for **Scheme 4-41**. Errors are calculated from the standard error associated with the linear fit. All reported values are the average of 2 values obtained from reactions performed in parallel.

The rates of amide formation for each isotopomer were determined independently and the values are summarised in Table 4-7. The initial rate of amide formation was determined over the first hour of the reaction. Errors associated with the observed KIEs are calculated as the average of two experiments, using the standard errors associated with the fit of the linear curve to the concentration profiles. Unexpectedly, the standard Au catalysed oxidative amidation reaction employing the para-chlorobenzaldehyde appears to result in an inverse kinetic isotope effect (entry 1), i.e. the reaction was faster with the deuterated analogue ($K_H/K_D < 1$). Inverse KIE have been reported for other heterogeneously catalysed process, particularly hydrogenation reactions.^{237,238} To the best of our knowledge, this is the first observation of such an effect in a Au-catalysed oxidation reaction.

The inverse KIE effect is unlikely to be a result of a hydride elimination step, given the observations in previously reported Au catalysed oxidations. An inverse KIE observed for the regeneration of the AuNP surface, via the oxidation of a Au-H/D species, could be possible if there is a greater difference in zero-point energies of the transition state, the reaction of Au-H/D with an adsorbed reactive oxygen species (Scheme 4-42), than the Au-H/D species resulting from a hydride elimination.



Scheme 4-42. Proposed example transition state for the reaction of a Au-H/D species with a reactive oxygen species adsorbed to the AuNP surface and energy diagram

The addition of TEMPO to the oxidative amidation of the para-chlorobenzaldehyde isotopomers results in an incremental increase in the observed KIE (entries 2 and 3) and is consistent a change in the rate-limiting step. Despite the large errors associated with the KIE values, the mean observed KIE of 1.43 with the addition of 3 equivalents of TEMPO (entry 3) is similar to the values reported for the KIE investigations of Au catalysed alcohol oxidation, where the effect is attributed to a hydride elimination step. This hypothesis is consistent with the increased influence of substituent electronic effects observed in the Hammett analysis including TEMPO.

The errors in the KIE measurements are too large to make conclusive arguments. Retrospectively, calculating the KIE via a competition experiment would increase the reliability of the results and probably alleviate many sources of error as the ratio of reaction rates would be independent of mass transfer effects of O₂ in the multiphasic system.

4.6 Reaction Orders and Time Normalisation Analysis

Thus far in the investigation of the TEMPO accelerated Au catalysed oxidative amidation the rate of reaction has been approximated using the initial rate. Yet it is apparent from the shape of the aldehyde concentration profiles obtained that the order of aldehyde increases when high concentrations of TEMPO are employed (Figure 4-17).

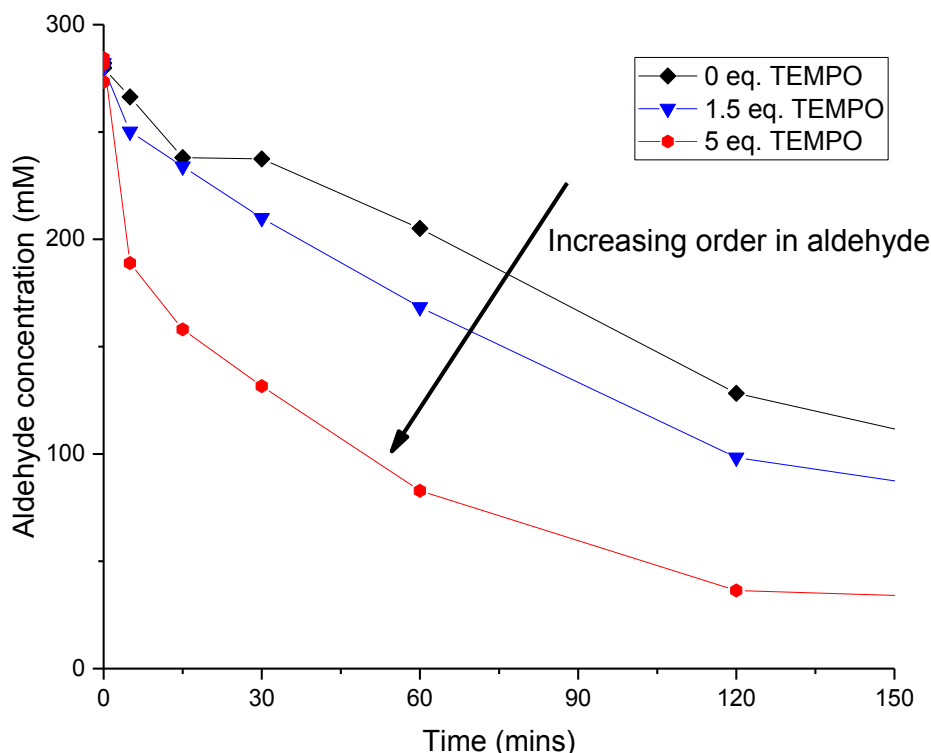


Figure 4-17. Change in aldehyde concentration profile in the oxidative amidation reaction as the starting concentration of TEMPO is increased

Comparing initial rates is arguably the simplest approach to kinetic analysis; whereby the order of a specified substrate is determined by observing the effect on the initial stages of the reaction. While conceptually simple, multiple data sets are required for accuracy and assume a constant conversion of substrates at low conversions.

A common alternative approach is to attempt to fit a mathematical function (curve) to a plot of the reaction rate against the concentration of a specified substrate. Fitting curves to reaction rate profiles is more versatile than comparing initial rates and can be effective for the confirmation of hypothesised mechanisms derived by other experiments. However, the subjective selection of a curve(s) to fit the data set inherently biases the outcome toward the pool of mathematical functions investigated. Accurate fitting of kinetic curves to reaction rate plots usually requires high-density data sets such as reaction rate derived from *in situ* spectroscopic methods or calorimetric analysis. However, the

complex multiphasic nature of this reaction mixture makes continuous spectroscopic analysis impractical and the multiple complex interactions and potential side reactions make curve fitting an overly-complex solution. Because of the complexities of this multiphasic Au catalysed oxidative amidation reaction neither of the two common approaches were employed in this study.

Instead, the orders for the Au catalyst and substrates were calculated using a 'Time Normalisation' method described by Bures.^{239,240} Time normalisation is a graphical approach to reaction order analysis, that manipulates datasets to plot curves that can be visually compared to determine the orders of catalyst and multiple substrates. Time normalisation is a complementary technique to reaction progress kinetic analysis (RPKA), a methodology reported by Blackmond that outlines several graphical manipulations that can be used to perform a 'graphical interrogation' of continuous rate data, such as calorimetric analysis.²⁴¹ Graphical interrogation involves plotting functions of the rate of a reaction against substrate concentrations to make visual comparisons, which can elucidate possible deactivation processes and determine the order in substrates.

'Time Normalisation' analysis can be applied directly to the substrate/product concentration profiles of a reaction, allowing a quick analysis of average reaction orders. A mathematical manipulation of the time scale normalises the time duration between each data point to the average concentration of a reaction component in that segment of the reaction profile. For example, species where the concentration can be assumed to be constant, i.e. catalytic components, time normalisation is achieved by plotting concentration of a substrate or product against time multiplied by catalyst concentration raised to the desired order. Multiple catalyst (c) and substrate orders (n) can be calculated by performing $c + n + 1$ reactions, providing the starting concentration of each species of interest is varied in at least one experiment. Hence, multiple reaction orders can be calculated reliably from relatively few experiments compared to an initial rate investigation of the same reaction.

4.6.1 Catalyst Reaction Order

Reaction orders of catalyst, aldehyde, and amine were calculated using the time normalisation analysis method for the Au/ γ -Al₂O₃ catalysed oxidative amidation of benzaldehyde and morpholine. Aldehyde and amide concentrations are determined using HPLC, but morpholine **1-97** is not detectable by UV-Vis analysis. Therefore, the concentration of morpholine is estimated by subtracting the amide concentration from the known starting amine concentration, this assumes morpholine reacts to yield only the amide, which has been demonstrated to be the case when aqueous base is added to the reaction.

Values for the catalyst and substrate orders were determined using a spreadsheet constructed using Microsoft Excel (Figure 4-18). The catalyst and substrate orders reported were determined by finding the point at which the initial gradients of the time normalised plots for each excess reaction were equivalent and R^2 values were >0.98 .

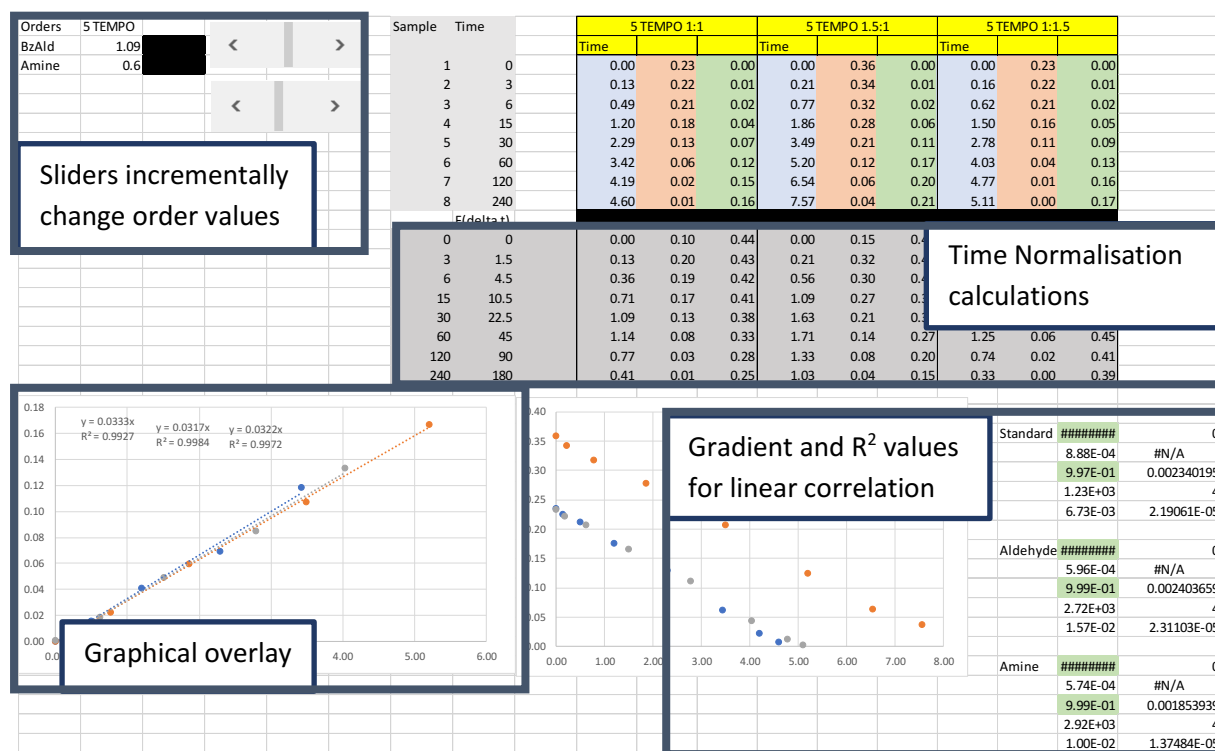
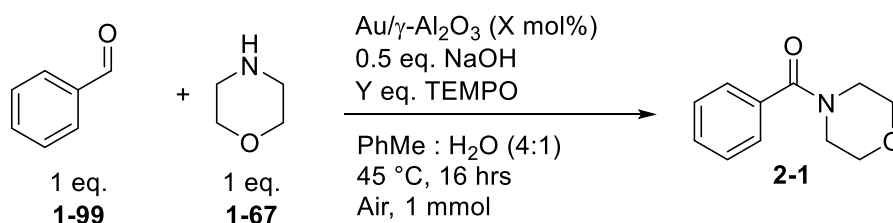


Figure 4-18. Spreadsheet to determine reaction orders using Time Normalisation analysis

Reactions to determine the catalyst order for the standard $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ catalysed oxidative amidation and the TEMPO accelerated variant were performed in parallel employing catalyst loadings of 0.35, 0.70, and 1.05 mol% (Scheme 4-43). The relationship between reaction rate, catalyst loading, and starting TEMPO concentration was investigated in an array format, four reactions at each catalyst loading were performed, each reaction was performed either under the standard oxidative amidation conditions or with the addition of 1, 3, or 5 equivalents of TEMPO.



Scheme 4-43. $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ catalysed oxidative amidation of benzaldehyde and morpholine varying the loading of $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ ($X = 0.35, 0.70, 1.05$ mol%) and starting concentration of TEMPO ($Y = 0, 1, 3, 5$)

Table 4-8. Summarised results table for catalyst order experiment

Entry	TEMPO Y eq.	1-99 conversion at 1 h ^a (%)			Observed Catalyst order
		0.35 mol%	0.70 mol%	1.05 mol%	
1	0	38 (74)	41 (80)	52 (77)	0.30
2	1	49 (59)	70 (70)	68 (69)	0.44
3	3	63 (60)	81 (66)	88 (67)	0.90
4	5	66 (63)	83 (58)	85 (60)	1.00

^aBenzaldehyde conversion determined by HPLC after 1 h, number in parenthesis is selectivity of amide with respect to benzaldehyde conversion

Table 4-8 summarises the observed catalyst orders determined using Time Normalisation analysis of the standard Au/ γ -Al₂O₃ catalysed oxidative amidation (entry **1**) and the TEMPO accelerated variant (entries **2** to **4**). **1-99** conversion after 1 hour increased as either the catalyst loading or starting TEMPO concentration was increased. Amide **2-1** selectivity after 1 hour of reaction time remained constant with each catalyst loading, supporting our hypothesis that acid formation is a AuNP catalysed side reaction. Under the specified reaction conditions the selectivity of **2-1** reduced as the starting concentration of TEMPO was increased. However, the observed catalyst order determined from the Time Normalisation of the amide concentration profiles increased from 0.30 to 1.00 when 5 equivalents of TEMPO was added to the oxidative amidation (entries **1** and **4**, Figure 4-19 and Figure 4-20).

Because of the complex multiphasic reaction mixture and unknown nature of the surface-catalysed mechanism, it is not possible to make a quantitative assessment of the effect of TEMPO on the catalyst reaction order. Nevertheless, the unusually low catalyst order observed for the standard oxidative amidation reaction (entry **1**) suggests the reaction is limited by mass transfer effects of O₂ in solution. The apparent increase in reaction order with the addition of TEMPO (entries **2** to **4**) is consistent with our hypothesis that TEMPO can alleviate the O₂ mass transfer limitations

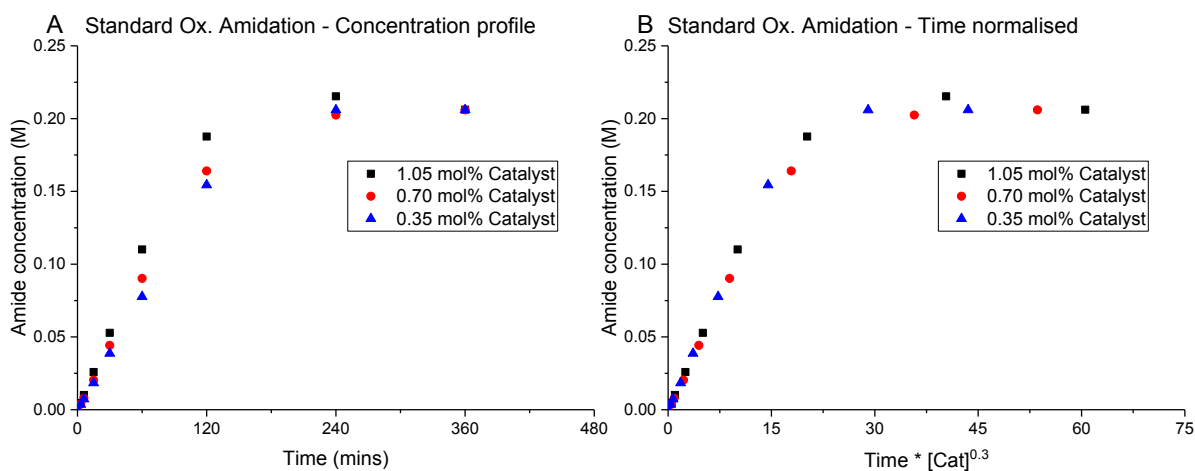


Figure 4-19. Amide **2-1** concentration profile for Au/γ-Al₂O₃ catalysed oxidative amidation reaction at 3 different catalyst loadings plotted against A) reaction time B) time scale normalised to concentration of Au/γ-Al₂O₃

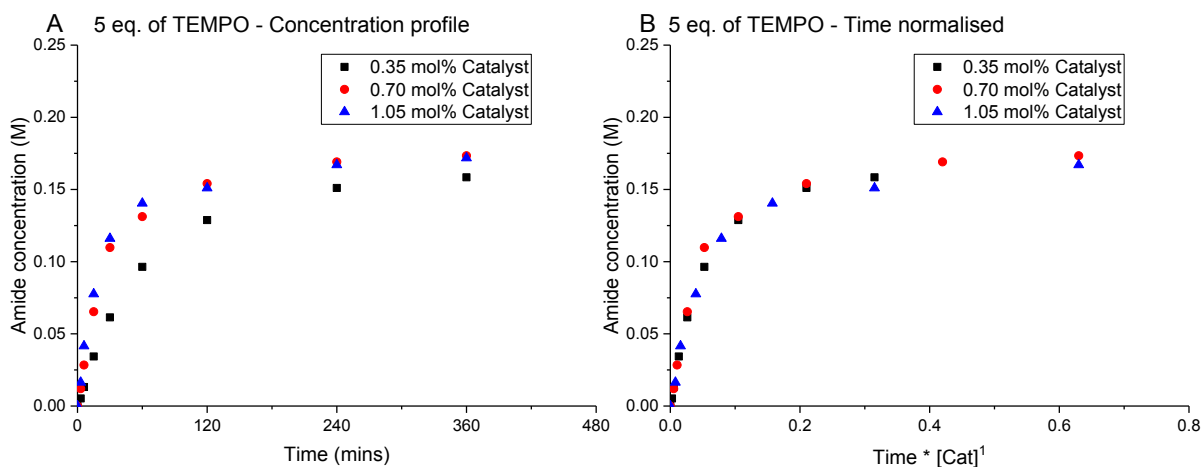
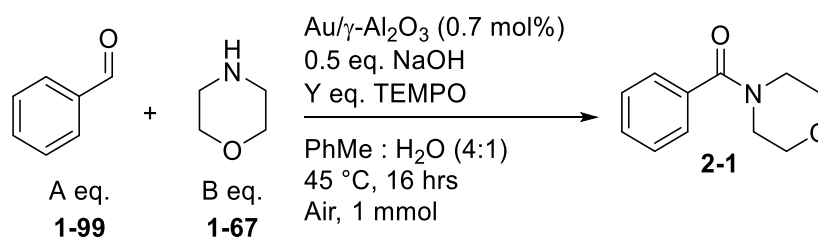


Figure 4-20. Amide **2-1** concentration profile for TEMPO accelerated Au/γ-Al₂O₃ catalysed oxidative amidation reaction at 3 different catalyst loadings plotted against A) reaction time B) time scale normalised to concentration of Au/γ-Al₂O₃

4.6.2 Substrate Reaction Orders

Reactions to determine the order in aldehyde and infer the order in amine for the standard oxidative system and each TEMPO accelerated system were performed in parallel. Substrate orders were determined by comparing a control reaction (1:1 ratio of **1-99** – **1-67**) to reactions employing a 1.5 equivalent excess of either **1-99** or **1-67** (Scheme 4-44). Time Normalisation analysis of the amide concentration profile was performed to reveal the orders of both **1-99** and **1-67** simultaneously.



Scheme 4-44. Au/γ-Al₂O₃ catalysed oxidative amidation of benzaldehyde and morpholine varying the ratio of substrates (A:B = 1:1, 1.5:1, 1:1.5) and starting concentration of TEMPO (Y = 0, 1, 3, 5)

Table 4-9. Summarised results table for substrate orders experiment

Entry	TEMPO Y eq.	1-99 conversion at 1 h ^a (mM)			Observed substrate orders	
		Control	Excess 1-99	Excess 1-67	1-99	1-67
1	0	108 (66)	130 (65)	110 (69)	0.39	0.08
2	1	132 (79)	174 (72)	141 (72)	0.40	0.03
3	3	159 (74)	240 (74)	167 (74)	0.70	0.05
4	5	172 (69)	229 (73)	188 (70)	1.09	0.60

^aBenzaldehyde conversion determined by HPLC after 1 h, number in parenthesis is the selectivity (%) of amide with respect to benzaldehyde conversion.

Table 4-9 summarises the reaction results and observed substrate orders determined using Time Normalisation analysis for the standard oxidative amidation reaction (entry **1**) and the TEMPO accelerated variant (entries **2** to **4**). All reactions employing an excess of aldehyde resulted in a significant increase in **1-99** conversion after 1 hour, whereas there was only a slight increase in **1-99** conversion when an excess of amine was employed. Under these conditions, amide selectivity of the Au/γ-Al₂O₃ catalysed oxidative amidation was not significantly affected by an excess of either aldehyde or amine.

Figure 4-21 presents a summary of the observed average reaction orders determined for the Au/γ-Al₂O₃ oxidative amidation reaction.

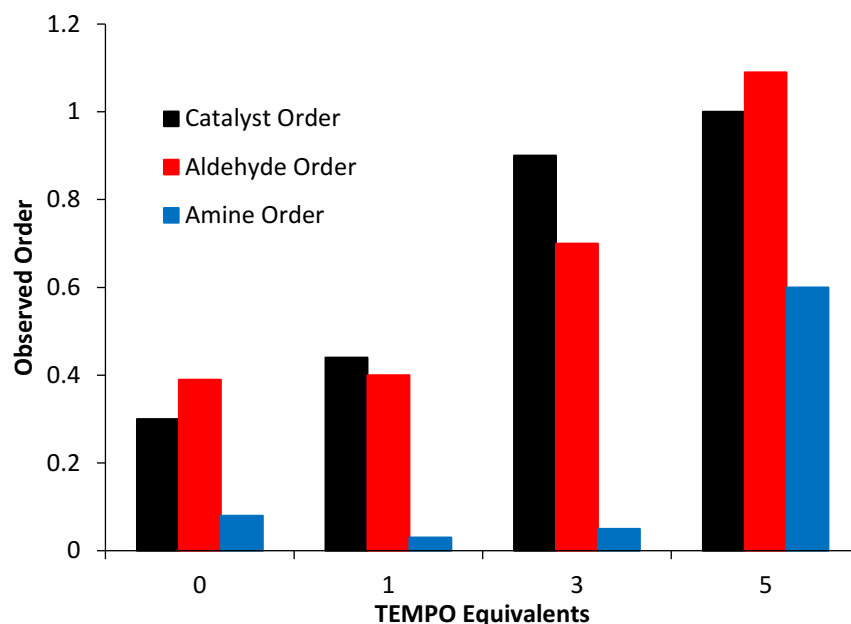


Figure 4-21. Summary plot of the reaction orders determined using Time Normalisation analysis

The observed reaction order in **1-99** increased from 0.39 to 1.09 as the starting TEMPO concentration was increased from 0 to 5 equivalents. The increasing order of **1-99** further supports our hypothesis that the addition of TEMPO causes a change in the rate-limiting step from a mass transfer effect to a substrate-dependent step, such as a hydride elimination.

The observed reaction order in **1-67** for the standard oxidative amidation reaction (Table 4-9, entry **1**) was found to be 0.08, and no significant change in the order when reactions were performed with 1 or 3 equivalents of TEMPO (entries **2** and **3**). However, the addition of a five-fold excess of TEMPO resulted in an apparent order of 0.60 (entry **4**). The individual values for each reaction order in amine are unreliable, as such the order of 0.60 obtained for amine in large excess of TEMPO may be inaccurate.

The concentration plots for the standard oxidative amidation reaction (entry **1**, Figure 4-22) and oxidative amidation reaction with 5 equivalents of TEMPO (entry **4**, Figure 4-23) are presented below, plotted against time and the Time Normalised x-axes.

When Time Normalisation is applied to the substrate orders x-axis (Figure 4-22B and Figure 4-23B) the overlaid curves are linear. A linear relationship between the product concentration and normalised time axis indicates that the reaction rate does not contain any terms which change in concentration. Hence, under the specified conditions neither TEMPO nor hydroxide contribute the observed rate.

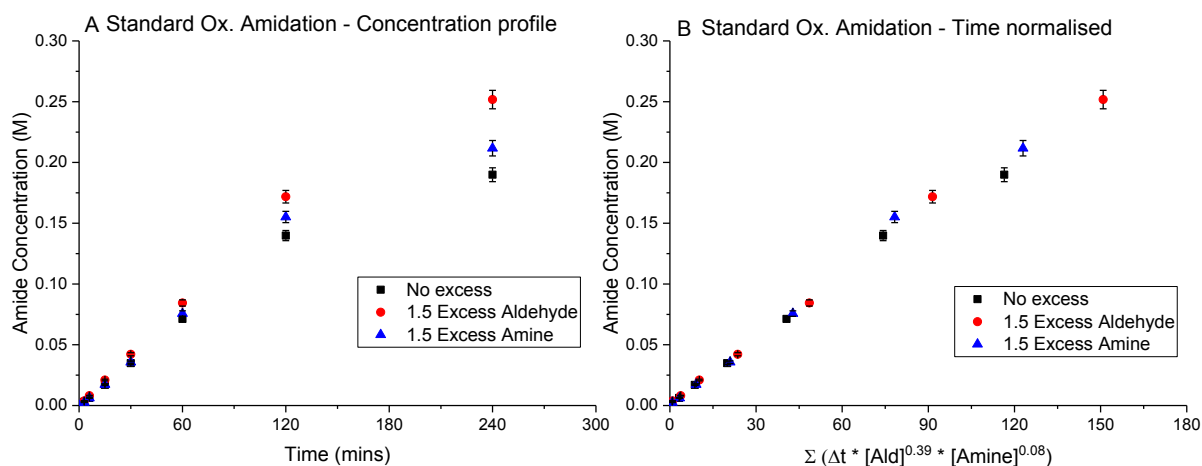


Figure 4-22. Amide **2-1** concentration profiles for the standard $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ catalysed oxidative amidation performed to investigate the substrate reaction orders plotted against A) reaction time B) time scale normalised to the concentrations of **1-99** and **1-67**

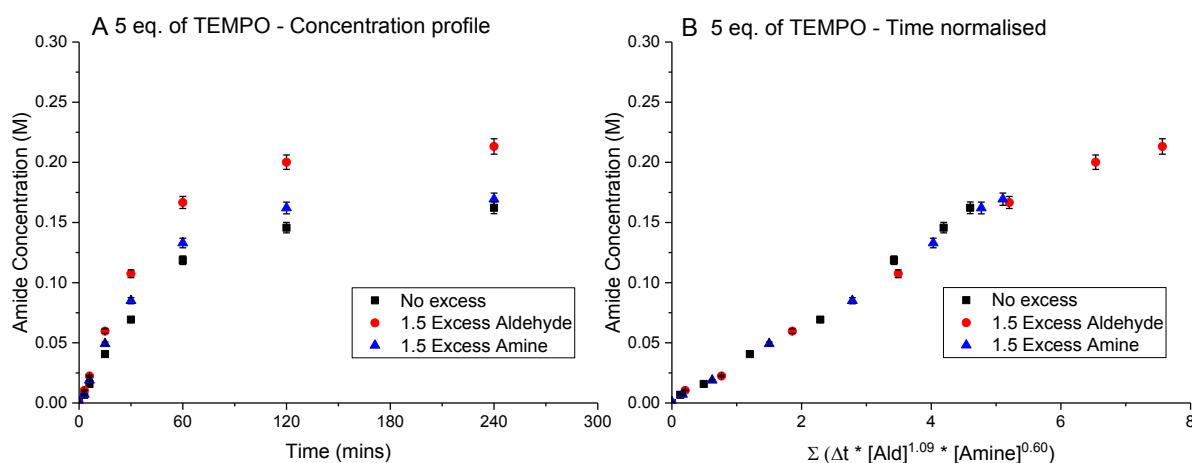


Figure 4-23. Amide **2-1** concentration profiles for the TEMPO accelerated $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ catalysed oxidative amidation performed to investigate the substrate reaction orders plotted against A) reaction time B) time scale normalised to the concentrations of **1-99** and **1-67**

An interesting observation that can be made for the results in Figure 4-21 is the disparity between the reaction orders for **1-99** and **1-67**. Initial thoughts would suggest the absence of a significant morpholine order would discredit the proposed rate-limiting step of a hydride elimination from a surface-bound hemiaminal intermediate. However, Kobayashi and co-workers¹⁰¹ reported that strongly adsorbed amines on AuNPs can prevent the adsorption of O_2 . Amine adsorption preventing the adsorption of O_2 and subsequent activation of the amine group is a reversible inhibition process and could explain the observed reduction in the order relative to the catalyst and aldehyde.

4.7 Conclusions

Experiments initially performed to eliminate possible radical reactions have revealed a much greater insight into the mechanistic pathway of the AuNP catalysed oxidative amidation. The addition of TEMPO, a stable free radical species, has been shown to accelerate the rate of oxidative amidation by enhancing the AuNP catalysed pathway. Various mechanistic proposals for the beneficial effect of TEMPO have been presented. It was concluded that TEMPO most likely increases the rate of oxidative amidation by regeneration of the AuNP surface via the abstraction of a surface hydride species. However, the mechanistic steps leading to the formation of surface hydrides are yet to be identified.

From the experiments detailed in this chapter this work presents these key observations to construct a proposed mechanistic cycle (Scheme 4-38) and highlight the effect of TEMPO:

- O_2 is required for Au catalysed oxidative amide formation, but not solely for regeneration of the catalyst active site – as evident by the successful oxidative amidation reaction with TEMPO in limited O_2 atmospheres
- Addition of excess TEMPO appears to change the rate-limiting step of the oxidative amidation reaction, as evidenced by a possible increased dependence on both the electronic nature of the aldehyde and increased orders in both catalyst and substrates
- The disparity between the increasing order of aldehyde and amine with the addition of TEMPO, assuming TEMPO does not react with the aldehyde, would suggest that excess amine could also have an inhibitory effect on the oxidative amidation reaction

The inhibitory effect of amine adsorption on the AuNP surface would also support the lower amide yield obtained when employing large excesses (3 equivalents) of amine reported in the optimisation of reaction conditions.

Experiments were performed under controlled atmospheres to demonstrate the necessity of O_2 in the oxidative amidation reaction, even with an external oxidant capable of regeneration the catalyst surface. The relationship between O_2 concentration and reaction outcome is highly complex. O_2 is essential for oxidative amidation, starting the cycle via the activation of amines on the Au surface and then the regeneration of active sites. However, greater O_2 concentrations result in a lower selectivity due to a surface catalysed carboxylic acid formation. Catalyst deactivation occurs when the carboxylic acid neutralises the added base and adsorbs to the Au surface. The use of stable free radicals to accelerate the regeneration of AuNP active sites could facilitate rapid oxidative amidation with a high selectivity at low O_2 concentrations. Although this use of TEMPO in Au-catalysed oxidative amidation is yet to be explored.

5 Slurry Bubble Column for Multiphasic Flow Chemistry

5.1 Introduction

Many industrial scale catalytic processes are operated under continuous flow conditions due to their practicality in large-scale synthesis. While flow reactors may incur additional start-up costs, there are numerous benefits to reaction safety, efficiency, and homogeneity; that result from the smaller reactor volumes. Hazardous reagents and intermediates can be carefully controlled or generated in flow without the need for isolation. Heat and mass transfer are inherently more efficient due to the smaller reactors required and larger external surface areas relative to the vessel size.

Broadly speaking there are two extremes of continuous flow reactors; namely continuously stirred tank reactors (CSTR) and plug flow reactors (PFR), which can be described by their mixing profile.

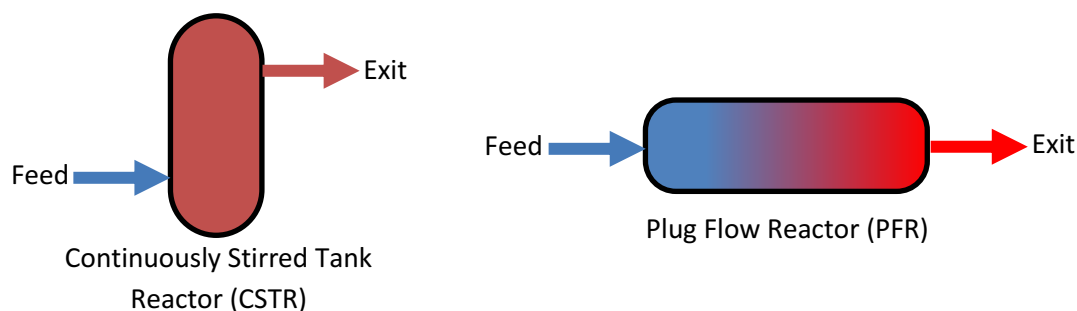


Figure 5-1. Schematic representation of a CSTR and a PFR

CSTR's are essentially batch reactors fitted with an inlet(s) and an outlet(s). A CSTR assumes that mixing is turbulent, and the contents of the vessel are homogeneous, and therefore the chemical composition of the fluid is constant and exit concentration is equivalent to the concentration inside the vessel. On the other hand, PFR's assume the flow is laminar and the fluid mixes radially not laterally, therefore the residence times are well defined.

The use of flow chemistry has many potential benefits when applied to certain reaction systems and is particularly advantageous when applied to multiphasic reactions.^{242,243} The reactor types available will depend on the phases employed in the reaction and how to ensure adequate mixing between them. The mixing of phases and distribution of chemical concentration and heat throughout a reactor is known as the macromixing of the reactor.¹³³

The oxidative amidation reaction described in this work utilises four distinct phases: a solid catalyst, a biphasic liquid of an organic substrate solution and an aqueous base solution, and air (gas) as the terminal source of O₂. Initial experiments performed using a commercial plug flow reactor (X-cube)

failed as the reactor blocked due to attrition of the solid catalyst particles. Further investigation found that the catalyst particles would slowly disperse when suspended in the aqueous base solution.

Rather than stabilising the $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ using chemical binders, which can introduce additional complexity and change the catalyst's properties,^{244–246} it was decided to perform the oxidative amidation as a sparged CSTR, operating as a slurry bubble column reactor (SBCR). A SBCR consists of fine solid catalyst particles suspended in a liquid reaction medium which is sparged by a constant gas feed (Figure 5-2).²⁴⁷

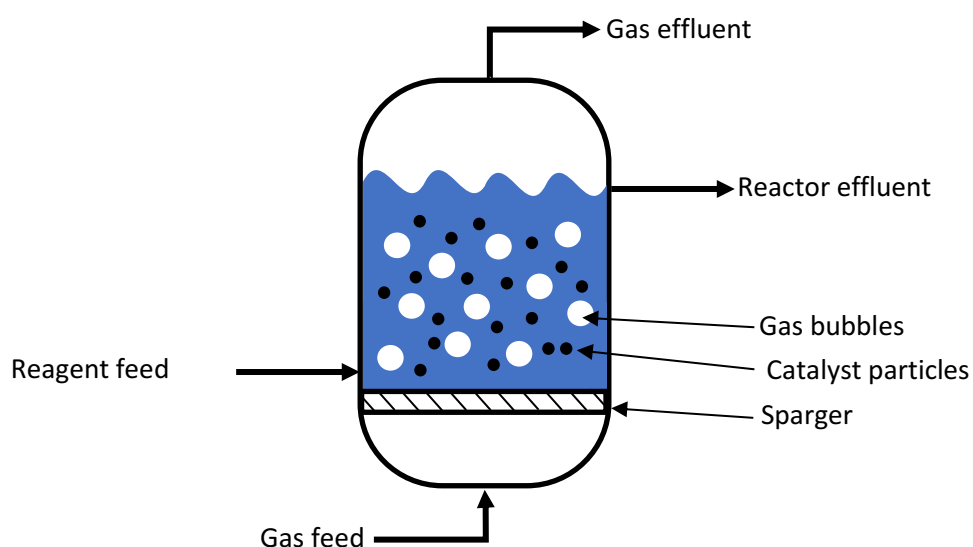


Figure 5-2. Slurry bubble column reactor

Like other flow reactors, sparged CSTRs can be operated under different flow regimes;²⁴⁸ but can be broadly described as either SBCRs or fluidised bed reactors (FBRs). The significant difference between these two regimes is the distribution of catalyst particles in the reactor chamber. SBCRs are typically operated by fluidising fine catalyst particles forming a pseudo-homogeneous liquid phase, whereas FBRs can be visualised as an expanded catalyst bed, in which catalyst particles settle quickly creating an uneven distribution of solid through the reactor column.²⁴⁹

SBCRs are commonly used in many industrial processes, including bioreactors for chemical production and gas to liquid manufacturing such as the Fischer–Tropsch process for hydrocarbon synthesis.^{250,251}

There are many factors to consider when designing an SCBR which can critically impact the mixing of the slurry bed and thus the reaction outcome. Gas flow velocities will control both the fluidisation and depth of the slurry bed, but also influence the bubble size, hence the gas-liquid contact area and thus the rate of gas diffusion, and the gas hold-up (the void volume of the slurry) will contribute to the total volume of the reactor. The gas flow velocity and bubble size affects the macro-mixing and bubble

columns can operate under a range of flow regimes; which can be dispersed and size controlled at low gas velocities, or turbulent at high gas velocities.²⁴⁸

Other reactor configurations were considered, such as oscillating flow reactors,²⁵² however CSTRs can achieve near ideal macro-mixing and is more streamlined with respect to the reaction conditions. NaOH is catalytic in the oxidative amidation reaction; consumption of the base occurs due to the formation of carboxylic acid by-products. Theoretically, to operate the reaction under continuous conditions only the organic phase needs to be circulated. The Au/ γ -Al₂O₃ catalyst material is naturally suspended in the aqueous layer and separates from the organic phase upon standing. Hence the organic effluent stream can be removed under gravity separation, removing the need for a subsequent separation and recycling of the aqueous catalyst layer.

5.2 Aims

To date there are no examples of continuous oxidative amidation from aldehydes and amines that utilise O₂ as the terminal oxidant. Previous attempts have been conducted using tubular PFRs and H₂O₂ as the terminal oxidant.^{253–256} The use of H₂O₂ as an oxidant can be problematic, as the reagent tends to degrade in storage and can be incompatible with many function groups. Each reported reaction for the oxidative amidation in flow required elevated temperatures (80 °C) and required excess amounts of the amine coupling partner, likely due oxidative degradation which was observed during previous work conducted by the Hii research group.²⁵⁷

The aim of this chapter is to present the development of a proof-of-concept SBCR for the Au catalysed oxidative amidation reaction; utilising the conditions and the Au/ γ -Al₂O₃ catalyst determined in Chapter 2. One advantage of the SBCR is that the concentration of O₂ can be controlled by varying the ratio of feed gases without changing the flow rate, thus allowing O₂ concentration to be investigated independently of the reactor mixing. Finally, the effectiveness of the SBCR design and controlled O₂ concentration will be investigated for the oxidative amidation reaction employing different substrates and in continuous operation.

5.3 Reactor Design

The core of the SBCR system (Figure 5-3 and Figure 5-4) consisted of A) two needle valves used to control the flow of N_2 and O_2 B) a peristaltic pump for both the feed and product streams, and C) a custom-made glass slurry column reactor (GSCR) and stagnant separating chamber (SSC).

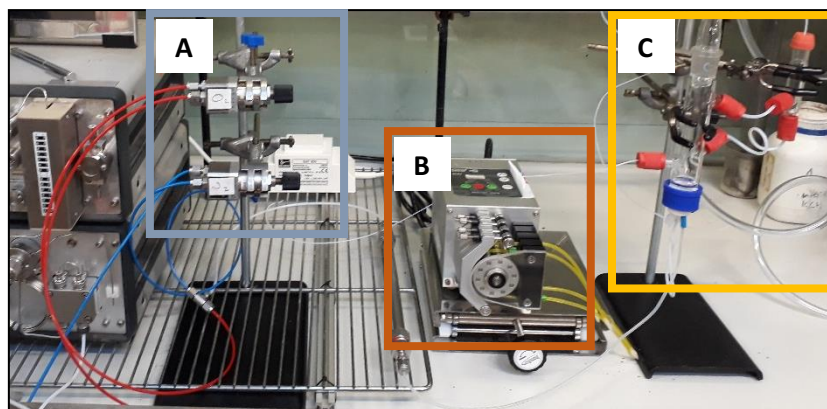


Figure 5-3. Core components of Slurry-Bubble Column Reactor

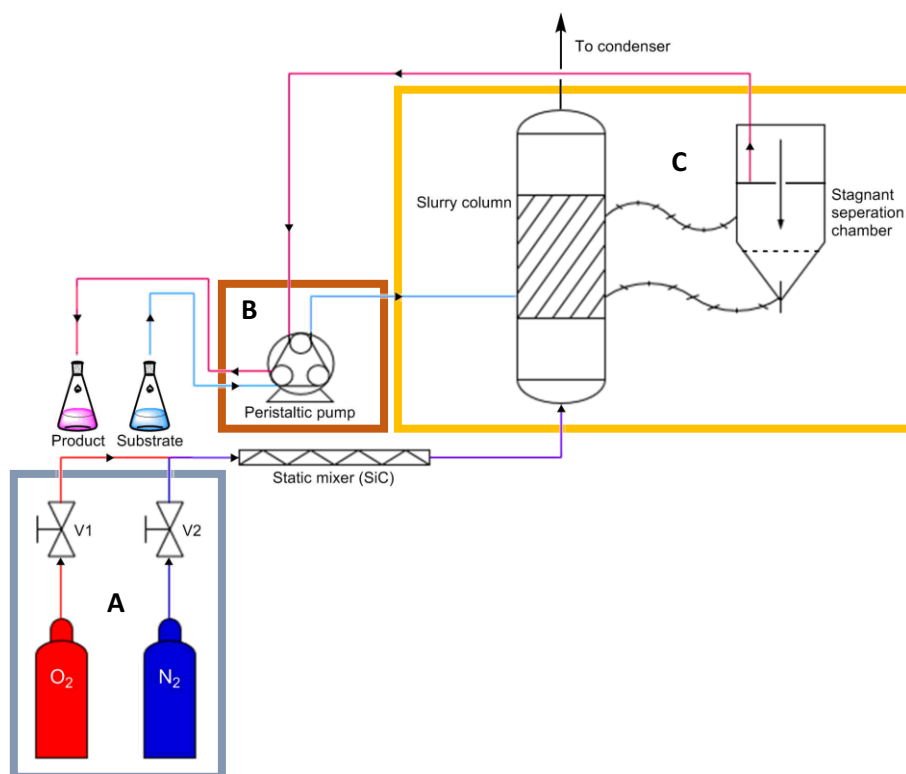


Figure 5-4. Schematic of the Slurry-Bubble Column Reactor core components

Gas was fed through the base of the GSCR to fluidise the catalyst bed and facilitate mixing of the aqueous catalyst slurry and the organic phase containing the reagents. The gas feed was composed of N_2 and O_2 from cylinders and supplied at a constant pressure of between 3 and 4 bar. The flow rates of N_2 and O_2 were controlled using individual needle valves (Figure 5-5). For each experiment the

volumetric flow rate of N_2 was maintained between 300 and 350 mL/min to ensure homogeneity and turbulent mixing of the reactor contents. The volumetric flow rate of O_2 was set using a graduated needle valve. The flow rate at each graduation was calibrated and for operation the flow rate of O_2 was set between 15 and 30 mL/min, nominally 4 – 10%.

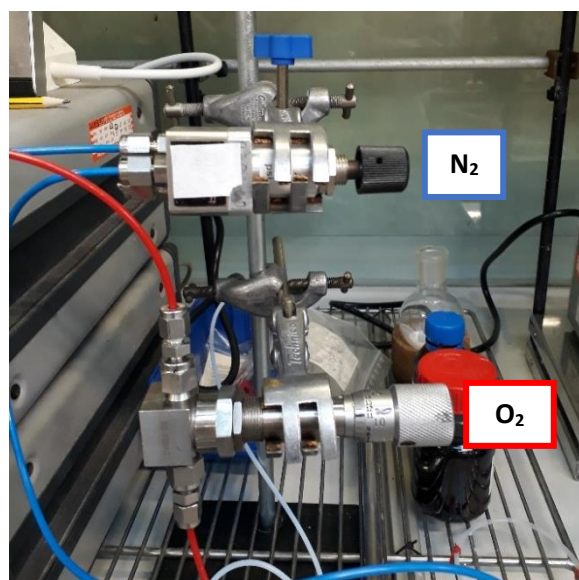


Figure 5-5. Gas flow control using needle valves at constant pressure

Needle valves were employed as a simple and low-cost measure of gas control. Gas was introduced into the GSCR using a 2 μ m stainless steel frit (15 mm diameter) and sparged through a small layer ($\sim$ 20 mm) of glass beads (4 mm diameter) to prevent both the blocking of the frit and to assist in the even distribution of the bubbles across the reactor. The SBCR was operated open to the atmosphere and a minimum pressure of $\sim$ 3 bar was required for the continuous formation of small sized bubbles. The minimum pressure was due to the bubble point of the stainless-steel frit, the pressure of the gas supply was set slightly above this value and the volumetric rate of gas flow was used to ensure homogeneous mixing of the reactor contents. Given the small-scale and preliminary nature of this investigation neither gas hold-up nor the pressure-drop across the reactor vessel were measured.

A peristaltic pump (Watson Marlow Sci-Q403U/WM4) equipped with solvent resistant manifold tubing (Watson Marlow, #984.0185.000, i.d. 1.85 mm) was employed for both the feed and product streams (Figure 5-6). The rationale for choosing a peristaltic pump was to ensure that the flow rate of the organic feed and product streams remained constant, therefore the reactor would neither empty nor overflow.



Figure 5-6. 4-Channel Peristaltic pump

Initial attempts to employ the $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ catalyst using the multiphasic conditions in a commercial plug-flow style reactor failed. Significant mechanical difficulties were encountered when attempting to pump the biphasic liquid mixture through a packed catalyst bed. Despite the chemical and physical robustness of the $\gamma\text{-Al}_2\text{O}_3$ support material, it was observed that 125 – 250 μm pellets of the $\text{Au}/\gamma\text{-Al}_2\text{O}_3$ catalyst gradually dispersed in an alkaline aqueous solution even without active mixing. The gradual dispersion of fine solid catalytic material invariably led to blockages under flow conditions.

The SBCR reactor is centred around the custom-made GSCR and SSC (Figure 5-7). The SBCR reactor operates under CSTR conditions. The principle behind the 2-column design was to suspend a fine catalyst powder as a recyclable aqueous slurry that is contained within the GSCR and SSC, thus avoiding the possibility of blockages when the reactor is operated continuously. The total volume of the GSCR is approximately 75 mL, with a maximum fill level of 50 mL, and the SCC has a maximum volume of approximately 20 mL and the fill is controlled by changing the height of the SCC relative to the GSCR, using the connection between the 2 vessels as a weir.

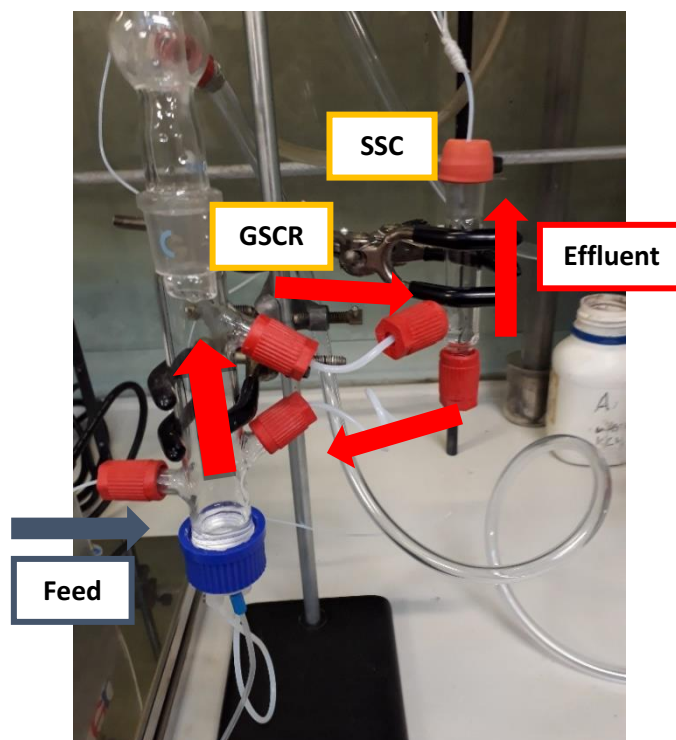


Figure 5-7. Custom Glass Slurry Column Reactor and Stagnant Separating Chamber

Figure 5-8 depicts the custom reactor setup in operation. An organic solution of reagents is continuously added to the GSCR containing the aqueous Au/ γ -Al₂O₃ catalyst slurry and the mixture is raised to reaction temperature using an electrical contact heater made from a flexible polymer. The reaction mixture is perturbed using a high gas flow rate and continuously transferred into the SSC via a short section of PTFE tubing acting as a weir. The difference in density between the two liquid phases is exploited to facilitate the separation of the organic effluent stream and aqueous catalyst slurry.

When toluene was employed as the organic reaction solvent, separation of the liquid phases occurred quickly, however the organic layer remained turbid suggesting that H₂O remained in the organic phase as a slow separating micro-emulsion. Upon standing a sample of the cloudy reactor effluent became clear and an aqueous layer formed in the sample vial. Effective separation of the organic and aqueous phases requires either a longer SSC, allowing more time for a greater separation of the liquid phases, or alternatively the use of sequential separation apparatus.

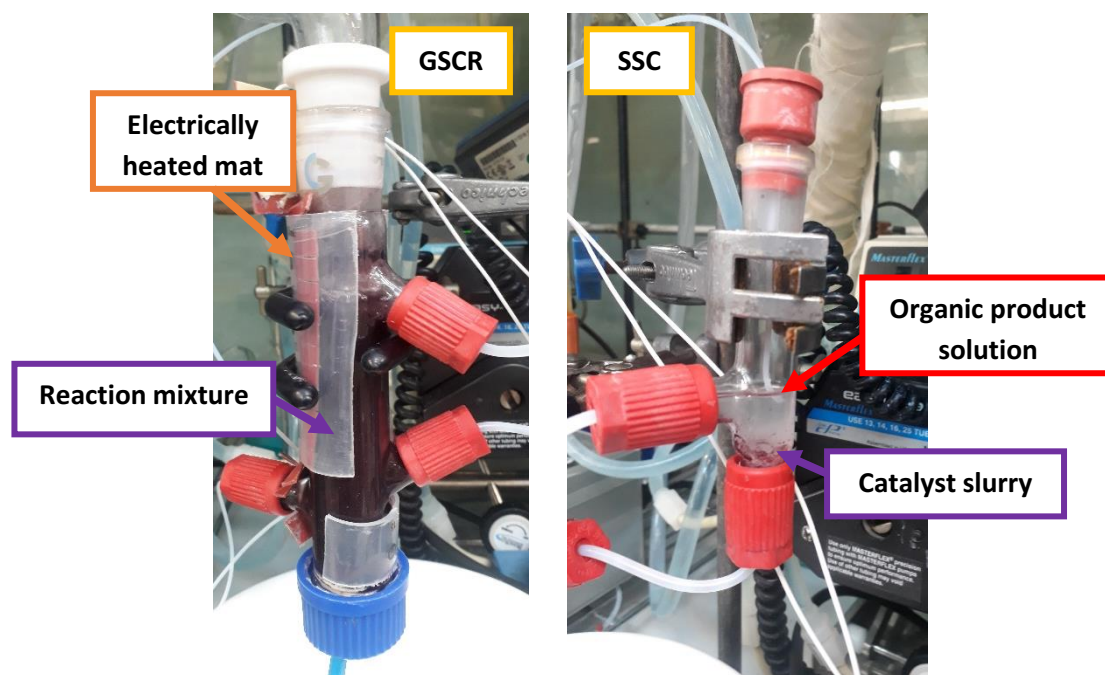


Figure 5-8. Custom GSCR and SSC in operation

Figure 5-9 depicts the SBCR in continuous operation, additional components to support the functions of the core components: A) needle valves, B) peristaltic pump, and C) the GSCR/SSC.

- A) As stated above, N_2 and O_2 were fed from cylinders at a pressure of between 3 and 4 bar and the pressure supplied to the needle valves was monitored via individual digital pressure gauges. After the needle valves the combined O_2/N_2 gas flow was passed through a static mixing column (300 mm x 20 mm i.d.) filled with silicon carbide to homogenise the gas mixture being fed into the reactor. The flow rate of O_2/N_2 through the GSCR was calculated at regular intervals using a manual volumetric (bubble) meter averaging the time taken for 3 measurements.
- B) In addition to the peristaltic pump and manifold tubing, 1/16" PTFE tubing was employed to transfer the feed/effluent solutions between the reagent/product vessels and the pump and 1/8" PTFE tubing was used to transfer the reaction mixture between the GSCR and SSC. A larger bore of tubing was chosen to link the GSCR and SSC to avoid fouling or catalyst blockages, however it was demonstrated that a catalyst slurry containing $Au/\gamma-Al_2O_3$ particles <125 μm could pass through 1/16" PTFE tubing unimpeded.
- C) As stated above, the GSCR was fitted with an electrical contact heater made from a flexible polymer, the temperature of the reactor was recorded manually at regular intervals and controlled by changing the voltage supplied to the heater by an adjustable DC power supply. Finally, a double coil condenser, chiller/coolant setup, and second peristaltic pump were

required to condense the solvent from the effluent vapour. Due to the high flow rate of gas through the reactor, less than 4 hours was required to evaporate 50 mL of a toluene-H₂O (4:1) mixture at 45 °C, even when a typical single coil condenser was employed using cooling water at ambient temperatures.

Hence, a double coil condenser with a high surface area using a continuous circulated mixture of water-glycol (1:1) chilled to between 5 – 10 °C was utilised. Biphenyl was added to all reactions performed in the SBCR set up to monitor the rate of evaporation. Despite the improved condenser apparatus, over a typical 4-hour reaction there is a 30% loss of organic solvent volume. The ratio between organic solvent and water has been shown previously to have a significant effect on the outcome of the oxidative amidation reactions. However, for the development of this proof-of-concept technology and in the interest of time limitations the condensing apparatus described above was used and any losses of solvent were recorded however no additional reagents or solvents were added once a reaction had commenced.

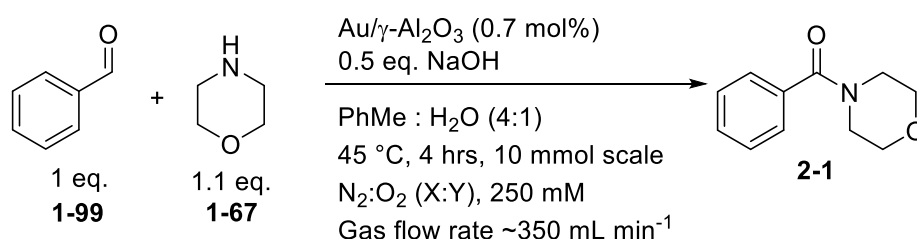
Initial investigations and substrate screening reactions were performed while operating the SBCR as a batch reactor to simplify the procedure, omitting the use of both the peristaltic pump and SCC. Without the continuous circulation of the organic liquid phase there is no driving force hence the contents of the SSC remain stagnant.



Figure 5-9. Slurry-Bubble Column Reactor set-up in continuous operation

5.4 Effect of Reactor O₂ Concentration

The first investigation, following successful commissioning of the SBCR system, was to use the variable gas feed capabilities to observe the effect of changing the concentration of O₂ in Au catalysed oxidative amidation. Three reactions between benzaldehyde **1-99** and morpholine **1-67** were performed at the 10 mmol scale under the conditions determined previously in Chapter 2 (Scheme 5-1). The SBCR was operated under batch conditions, and reactions were conducted for 4 hours. The reaction composition was monitored by HPLC and the concentrations of **1-99** and **2-1** were determined via UV-Vis analysis as in previous studies (Figure 5-10).



Scheme 5-1. Oxidative amidation reaction between 1-99 and 1-67 performed using the SBCR varying the concentration of O₂ in the feed gas

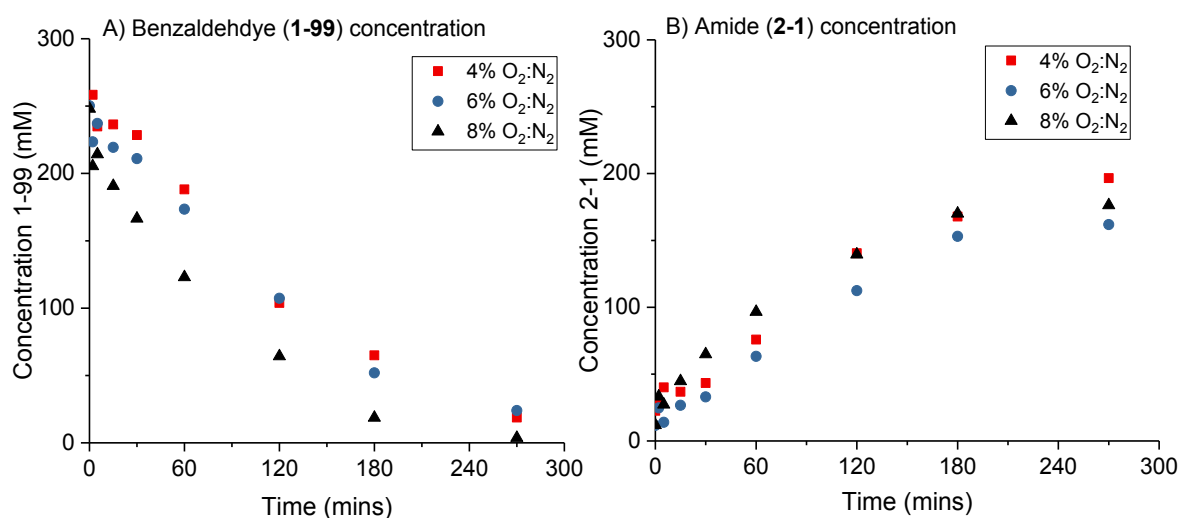


Figure 5-10. Concentration profiles for 1-99 and 2-1 in the oxidative amidation performed using the SBCR varying the concentration of O₂ in the feed gas

From the data presented in Figure 5-10 the initial rates of **1-99** conversion and **2-1** formation were calculated using a linear fit to the concentration profile of each reagent up to 1-hour reaction time. The calculated rates of were plotted against the % concentration of O₂ in the gas feed and the selectivity for **2-1** was calculated from the ratio between the rates of **2-1** formation and **1-99** conversion (Figure 5-11).

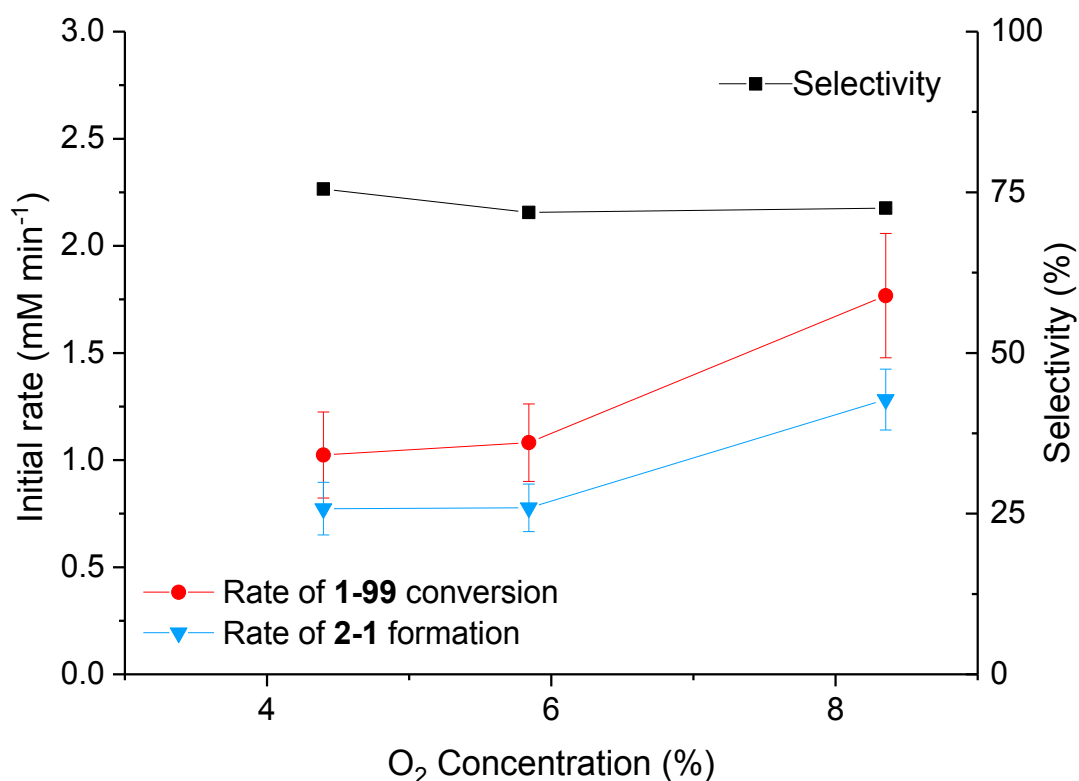


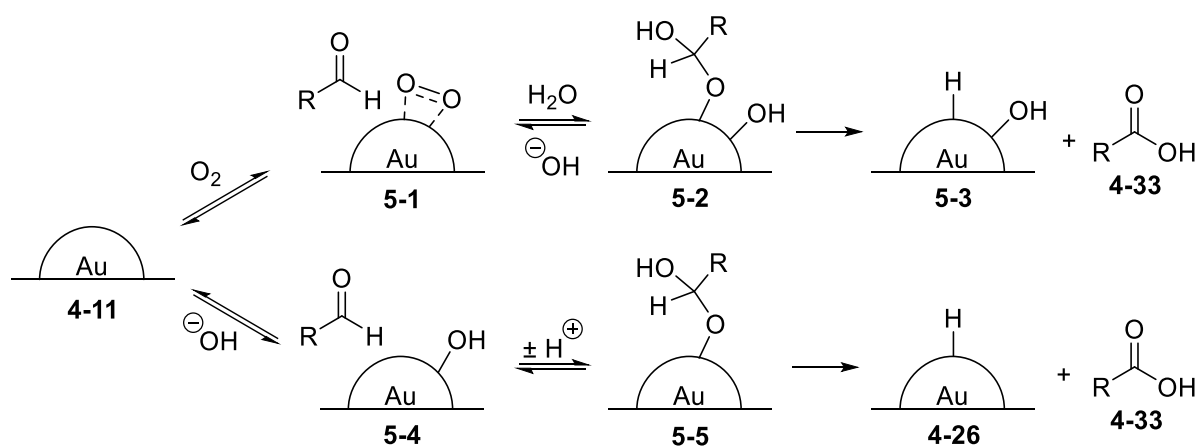
Figure 5-11. Initial rates of aldehyde **1-99** conversion and amide **2-1** (calculated from concentration profiles for the first hour of reaction time) and selectivity of **2-1** formation

As expected, increasing the concentration of O₂ in the feed gas resulted in an increase in the rate of benzaldehyde conversion and amide **2-1** formation. Referring to the proposed mechanism in the previous chapter (Section 4.4.9), the most likely hypothesis is that O₂ fulfils a dual function in Au catalysed oxidative amidation. However, under the specified conditions determined in Chapter 2 and those that have been adapted for implementation in the SBCR, it appears that an increased O₂ concentration increases the rate of reaction but also leads to a reduction in amide selectivity.

The observed increase in the rate of reaction due to greater O₂ concentration is consistent with the hypothesis that O₂ is required for the regeneration of the Au catalyst active site. Additionally, the increased reaction rate is consistent with the observed results for the effect of stirring speed on the rate of Au catalysed oxidative amidation. Greater stirring speeds increase the contact surface area between the liquid and vapour phases. Whereas, in this experiment the concentration of O₂ is varied demonstrating that the increased rate when stirring is increased is likely also due to greater rate of O₂ dissolution.

The slight decrease in selectivity as the concentration of O₂ is increased from 4% to 8% is also consistent with experiments that have investigated the effect stirring speed and that of atmosphere on the oxidative amidation reaction. But, using the SBCR it is still not possible to differentiate between

the catalysed acid formation and background autoxidation pathways for the formation of carboxylic acids. As asserted previously, the catalysed carboxylic acid formation, via the formation of an acetal species, probably proceeds faster than the background autoxidation pathway. Acetal species can form as the result of a reaction between an aldehyde and surface bound reactive oxygen species, which appear to result either from the adsorption of either O_2 or hydroxide. This hypothesis is evidenced by the reduced selectivity observed with a higher concentration of both O_2 and hydroxide.



Scheme 5-2. Selectivity of amide formation

5.5 Oxidative Amidation Scope in SBCR

To demonstrate the synthetic applications of the SBCR towards amide formation the scope of the Au/ γ -Al₂O₃ catalysed oxidative amidation reaction was investigated. Reactions between various aldehydes and amines were performed using the SBCR in batch operation and a gas feed comprising of a nominal 4% O₂ in N₂ at a gas flow rate of 350 mL min⁻¹ (Table 5-1).

Table 5-1. Scope of Au/ γ -Al₂O₃ catalysed oxidative amidation reaction performed using the SBCR operating under batch conditions

$ \begin{array}{c} \text{R}-\text{CHO} + \text{R}'-\text{NH}-\text{R}'' \xrightarrow[\text{0.5 eq. NaOH}]{\text{Au}/\gamma\text{-Al}_2\text{O}_3 \text{ (0.7 mol\%)}} \text{R}-\text{C}(=\text{O})-\text{N}(\text{R}')\text{R}'' \\ \text{1 eq.} \qquad \qquad \text{1.1 eq.} \end{array} $ PhMe : H₂O (4:1) 45 °C, 4 hrs, 7.5 mmol scale N₂:O₂ (4%), 250 mM Gas flow rate ~350 mL min⁻¹			
Entry	Substrate	Yield obtained in batch ^b (%)	Yield obtained in SBCR ^b (%)
1		85	76
2		53	62
3		64	66
4		81	64
5		63	76
6		0	24

^aReaction conditions: Au/ γ -Al₂O₃ (1.13 g, 0.7 mol%), aldehyde (7.5 mmol), amine (8.25 mmol), PhMe (30 mL), and aqueous 0.5 M NaOH (7.5 mL) ^bIsolated amide yields

Reactions in the SBCR were conducted at the 7.5 mmol scale for 4 hours due to the evaporation of the organic solvent. The isolated yields obtained using the SBCR are compared to the isolated yields obtained when performing the oxidative amidation reaction at the 1 mmol scale under air using a Radleys carousel reactor, as previously reported in Chapter 2.

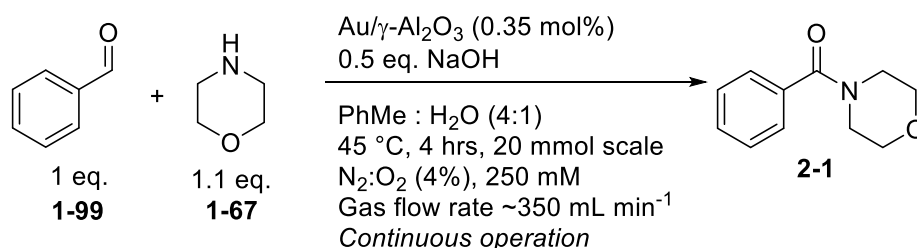
Reactions were performed using para-substituted benzaldehydes to examine the effect of electron withdrawing and electron donating functionalities (entries **2** and **3**). Para-methyl benzaldehyde was examined (entry **4**) due to the unusually slow rate of reaction noted when performing the Hammett analysis of the oxidative amidation reaction. The oxidative amidation reaction of hexanal with morpholine (entry **5**) performed marginally better in the SBCR confirming that the alternative reactor set-up allows greater efficiency to be obtained with substrates that are typically more challenging.

As expected, reactions between morpholine and benzaldehyde derivatives (entries **1** to **4**) resulted in comparable isolated yields as when the same reaction was performed in Radleys reaction tubes. While there is no significant enhancement in the yield of each reaction, these results demonstrate the application of the new reactor design to multiple substrates and consistency in the mixing of the aqueous catalyst slurry and organic reagent phase. It is worth highlighting that this result cannot be used to draw conclusions on the nature of carboxylic acid formation in the Au catalysed oxidative amidation reaction. Despite the concentration of O₂ being much lower than compared to atmospheric conditions, the fast gas flow rate required to effectively mix the two liquid phases means there is an abundance of O₂ available in solution for both the catalysed and autoxidation processes. The same observations can be made for the amidation reaction between hexanal and morpholine (entry **5**).

Finally, the reaction of benzaldehyde and aniline (entry **6**) was performed to assess the effect of SBCR conditions on an oxidative amidation reaction shown to be challenging when performed using Radleys reaction tubes due to the rapid formation of imine. Employing electron deficient amines in Radleys reaction vessels failed due to the formation of carboxylic acids or imines. Either a greater effective concentration of O₂ or increased homogeneity of the reaction mixture afforded by the SBCR resulted in formation of amide, although in poor yield. These results suggest that the amidation yields obtained using the SBCR could be optimised by controlling the O₂ concentration; which can potentially be determined on-the-fly when the SBCR is operated continuously.

5.6 Oxidative Amidation in Continuous Flow

Having demonstrated the use of the SBCR in batch operation the reactor was configured to perform the continuous Au catalysed oxidative amidation reaction between benzaldehyde **1-99** and morpholine **1-67** (Scheme 5-3).



Scheme 5-3. Continuous Au/ γ -Al₂O₃ catalysed oxidative amidation

The GSCR was charged with toluene and an aqueous slurry of Au/ γ -Al₂O₃ in 0.5 M NaOH solution before being heated to 45 °C. After reaching the specified reaction temperature the GSCR vessel was charged with benzaldehyde and morpholine, and sparged using a gas feed comprising of 4% O₂ in N₂. For the first 3 hours the SBCR was operated under batch conditions, after 3 hours the peristaltic pump was engaged and the SBCR was operated continuously at a flow rate of 0.1 mL min⁻¹. The effluent stream of the SBCR was collected over 7 hours in 1 mL aliquots (every 10 minutes) for a total reaction time of 10 hours. The composition of the reactor and each fraction was determined by HPLC and the concentrations of benzaldehyde and amide **2-1** were determined via UV-Vis analysis (Figure 5-12).

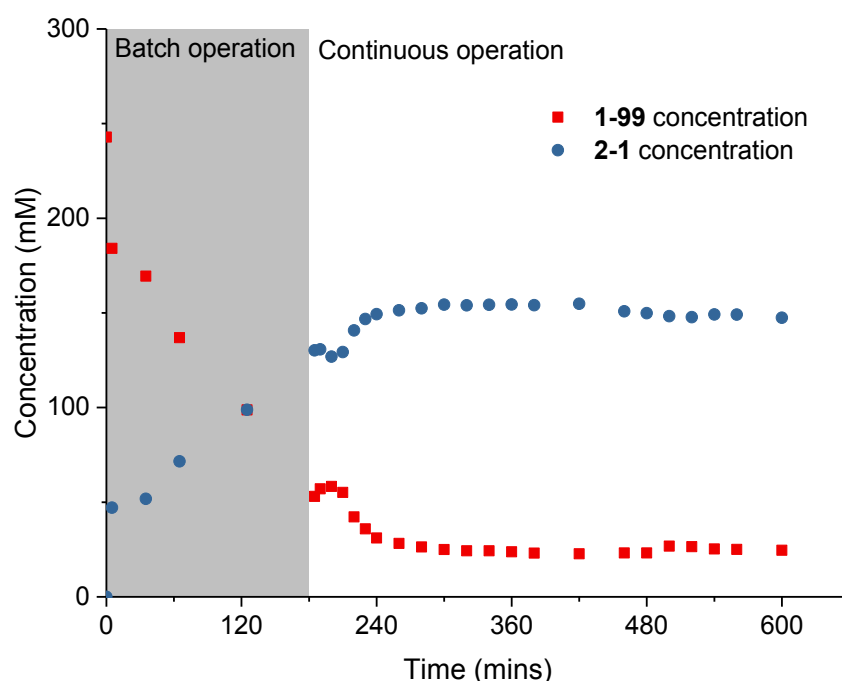


Figure 5-12. Composition of A) GSCR for first 3 hours B) Effluent stream

Plotting the cumulative benzaldehyde conversion and amide yield against reaction time results in a linear correlation (Figure 5-13). This observation would suggest that reaction is O₂ limited under the reaction conditions employed for the continuous process. Catalyst turnover continued for 10 hours after which point the manifold tubing failed and the reactor was deemed not safe enough to operate unattended. The total mass deficit observed for the continuous reaction was 5.1 mmol, which is less than the 10 mmol of NaOH charged at the start of the reaction, therefore based on the current plot it can be assumed the reactor could be operated for 20 hours before requiring a recharge of the aqueous catalyst slurry.

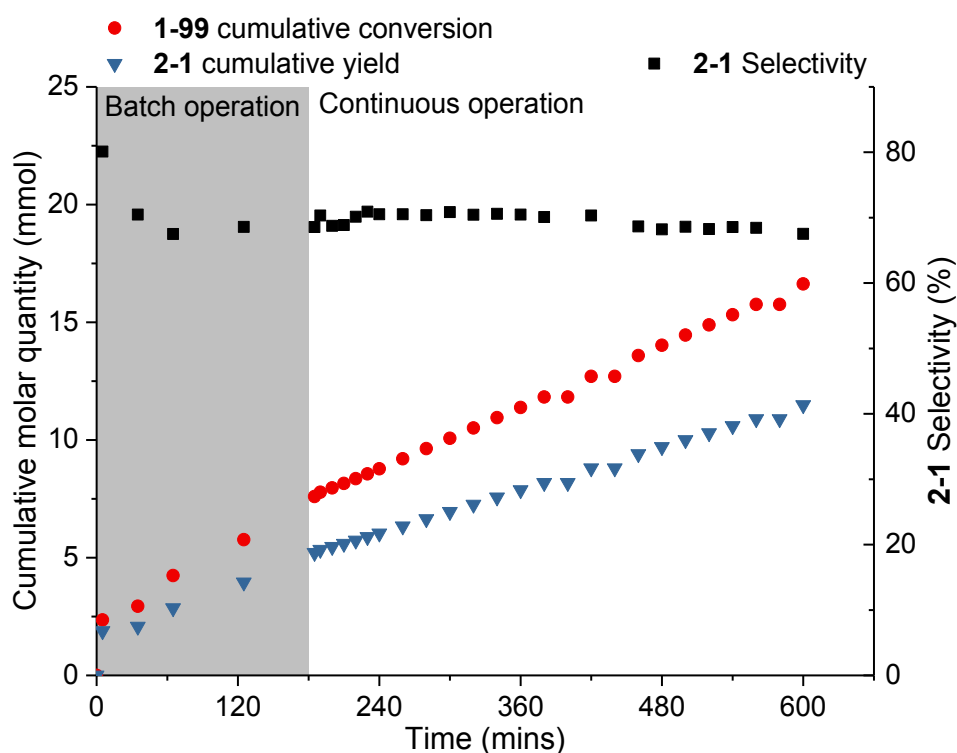


Figure 5-13. LHS) Cumulative benzaldehyde conversion and amide yield observed during the continuous oxidative amidation reaction RHS) Selectivity observed in each aliquot collected

Plotting the selectivity obtained at each point of the reaction revealed that after an initial sharp decrease, the selectivity remained approximately constant before decreasing after extended reaction times (>6 hours). The initial decrease would be explained by an increase in the concentration of oxygenated Au atoms, followed by a gradual deactivation of the catalyst surface, presumably due to reversible inhibition by the sodium benzoate by product as increases in AuNP size typically lead to a reduced reaction rate but an increased selectivity (section 3.3.3).

5.7 Conclusions

This chapter describes the first example of a lab scale SBCR for oxidative amidation chemistry, the reactor was constructed from a custom designed bubble column (GSCR) and stagnant separation chamber (SSC) that allowed the reaction to be conducted as a homogeneous slurry without the need for additional work-up/purification. O₂ concentration was confirmed to directly affect the selectivity of the oxidative amidation reaction, independent of mixing of the organic substrates and aqueous base. Greater yields were obtained using the SBCR compared to the batch reaction, supporting the hypothesis that yields for the oxidative amidation can be optimised by controlling the O₂ concentration.

More broadly, this thesis has described the development of AuNP catalysed oxidative amidation of aldehydes using an iterative approach to understand the complex equilibria present in this multiphasic process. Firstly, the often simplified role of base, has been investigated and expanded to identify the role it plays in catalyst turnover and controlling the equilibrium between reagents and undesired side products, namely in amination formation. These observations are further supported by the excesses of reagents and base often employed in previous examples of Au catalysed alcohol amidation, as discussed in section 1.5.3.

The design of the SBCR reactor has been driven by the necessity of a multiphasic system and the observation that mass transfer effects are critical in controlling the reaction outcome. Efficient macromixing of the biphasic liquid is required to ensure adequate availability of substrates and base at the catalyst surface. Whereas, the concentration of O₂ must be appropriately controlled to maintain catalyst turnover but preventing the formation of the carboxylic acid side product. This critical parameter can be controlled by defining the composition and flow rate of the gas sparge.

The use of TEMPO to accelerate the rate of AuNP oxidative amidation may not be practical from a synthetic perspective. However, identifying the multiple roles of O₂ in Au catalysed aldehyde amidation is a novel mechanistic insight, which further evidences the complex mass transfer effects that necessitate a more creative approach to synthesis and the application of novel technologies.

6 Future Work

6.1 AuNP Catalysed Amidation of Aldehydes and Amines

This work has explored and developed the mechanism and reaction conditions associated with AuNP catalysed oxidative amidation, however the of the process is still in the early stages of scoping the synthetic utility of AuNP catalysts in amide formation. One of the key observations during the identification of a suitable catalyst was that the addition of an aqueous base substantially increased the effectiveness of many AuNP catalysts (section 2.3).

Metal support interactions (MSI) are known to affect the outcome of supported AuNP catalysed oxidations,^{173–175} it is reasonable to suggest that the optimal catalyst support for a desired amidation reaction would vary depending on the substrates employed. Likewise, the reaction conditions for given sets of substrates can be optimised to provide greater yields and access to a wider substrate scope. While not undertaken in this work, design of experiments (DOE) could offer greater insight into the complex interaction in the multiphasic oxidative amidation reaction. Particularly the relationship between phase composition, base concentration, stirring speed (O_2 concentration), and catalyst loading.

6.2 Catalyst Synthesis and AuNP Properties

Sol-immobilisation proved to be an efficient means of synthesising small batches of AuNP catalysts for development work. Thermal treatment of these catalysts afforded AuNP catalysts with various diameters and size distributions, which were shown to directly affect the turnover frequency and selectivity of the oxidative amidation reaction. Firstly, the origin of this effect remains unknown and likely relates to the relative adsorption enthalpies of O_2 , the amine substrate, and amide product;¹⁰¹ however, this hypothesis is currently unproven. Secondly, the thermal treatment of resulted in an apparent change in the morphology of the deposited nanoparticles.^{193,194} A more detailed understanding of the morphology of the AuNP catalysts, using adsorption or X-ray based techniques, could be used to improve catalyst design and identify the most reactive sites.

6.3 SBCR Design

The SBCR presented in this work is a proof-of-concept demonstration. Firstly, time constraints restricted the amount of design and development work undertaken; a number of refinements can be made to the reactor design to improve usability and reproducibility of the results.

The most significant improvement required is the re-design of the gas inlet. Firstly, substituting the manually controlled needle valves with digitally controlled mass flow controllers will allow a precision measurement of the O₂ concentration being fed into the reactor. Additionally, this set-up will allow for precise changes to the O₂ concentration *in operando* allowing optimisation of the reaction conditions 'on the fly'. Secondly, the sparging set up employed in this initial design performed poorly, and a better design sparging system should allow for a uniform bubble stream that encourages a more turbulent mixing regime.

Likewise, a redesigned GSCR and SSC would include a longer column to create both a better phase separation and improve the recycling of the catalyst solution. A greater degree of baffling around the return to the GSCR would restrict and diminish the possibility of 'back-flow' of the catalyst solution into the SSC. Other more mechanical problems to be addressed, include the suitability of materials used in the peristaltic pump system and heating of the GSCR.

Finally, at the outset of this project it was envisaged that the oxidative amidation of alcohols and amines would be conducted in continuous operation as two distinct chemical steps. The first being the selective oxidation of an alcohol to an aldehyde which is subsequently transformed into an amide using the SBCR reactor. Both steps have now been demonstrated in principle by the Hii group and coupling the processes is now the next significant step forward to be taken in this research program.

Experimental

7.1 General Experimental

HAuCl₄·3H₂O was commercially sourced from Alfa Aesar. The metal oxide supports in this work were generously provided free-of-charge by Sasol. All solvents and organic reagents were obtained from commercial sources and used as received unless specified otherwise. Benzaldehyde was purified by vacuum distillation over MgSO₄ (b.p. 62 °C at 0.01 bar) and stored at -20 °C as 1 mL samples.

NMR spectra were recorded on AV400 Bruker spectrometer, chemical shifts are reported in ppm and peak are reported as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), broad singlet (bs), or multiplet (m). Infrared spectra were recorded using a Perkin Elmer ATR-IR. Mass spectra were recorded using a Micromass Autospec Premier by Imperial College Chemistry Mass-Spec service.

All kinetic and Hammett studies were followed using a HP series 1100 HPLC equipped with a C18 column, using a reverse phase gradient method eluting MeOH and H₂O with 0.1% TFA. All peaks were manually integrated and corrected against an internal standard.

7.2 Standard Oxidative Amidation Procedure

A reaction tube was charged with Au/γ-Al₂O₃ (150 mg) and a 16.5 mm rare-earth cross stir bar. An aqueous solution of 0.5 M NaOH (1 mL, 0.5 equiv.) was added and reaction was heated to 45 °C in a Radley's 12 reaction carousel, followed by addition of a solution of 250 mM benzaldehyde (4 mL, 1 equiv.) in toluene followed rapidly by the addition of morpholine (97 μL, 1.1 mmol, 1.1 equiv.). The reaction mixture was kept at 45 °C and stirred at 550 RPM.

For reaction optimisation deviations were made from the standard procedure as required. Aliquots of the reaction mixture were extracted after 16 hours; conversions and yields were calculated by HPLC analysis.

Kinetic plots were obtained from 8 extracted aliquots, typically over a working day (8-hour period). The reactions were left overnight, before a further 3 samples were taken the following day at 30 min intervals. The mixture was allowed to separate, a 50 μL aliquot was taken from the organic phase, which was diluted to 0.5 mL using a 2.5 mM solution of biphenyl in MeOH.

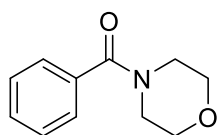
7.3 Oxidative Aldehyde Amidation Scope

AuNP Oxidative Amidation Procedure

A reaction tube was charged with Au/ γ -Al₂O₃ (150 mg) and a 16.5 mm rare-earth cross stir bar. An aqueous solution of 0.5 M NaOH (1 mL, 0.5 equiv.) was added and reaction was heated to 45 °C in a Radley's carousel, followed by addition of a 250 mM solution of aldehyde (4 mL, 1 mmol, 1 equiv.) in dibutyl ether or toluene, followed rapidly by the addition of amine (1.1 mmol, 1.1 equiv.). The reaction mixture was kept at 45 °C and stirred at 550 RPM overnight in air.

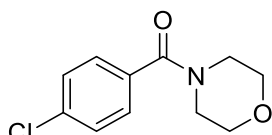
The catalyst was removed by filtration and washed with EtOAc (3 x 10 mL). The combined filtrate was washed with water (10 mL) and brine (10 mL) and dried over MgSO₄. The organic fractions were concentrated and passed through a plug of Celite. The remaining solvent was removed to afford the crude product, which was purified by recrystallisation or column chromatography.

Morpholino(phenyl)methanone²⁵⁸ (2-1)



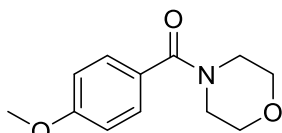
Description: White solid (137 mg, 72%) **m.p.** 75 – 77 °C (lit.²⁵⁸ 73 – 74 °C) **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 3055, 2963, 2853, 1629, 1426, 1362, 1277, 1113, 1015, 841, 788, 709 **¹H NMR** (400 MHz, CDCl₃) δ 7.43 – 7.39 (m, 5H, Ar), 3.76 – 3.45 (m, 8H, CH₂); **¹³C NMR** (101 MHz, CDCl₃) δ 170.6 (C=O), 135.4 (Ar), 130.0 (Ar), 128.7 (Ar), 127.2 (Ar), 67.1 (OCH₂), 48.4 (NCH₂), 42.8 (NCH₂); **ES⁺MS** m/z 192 [M + H⁺, 100]

(4-Chlorophenyl)(morpholino)methanone²⁵⁹ (2-17)



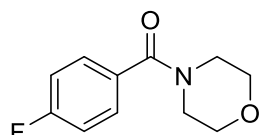
Description: White solid (145 mg, 64%) **m.p.** 81 – 84 °C (lit.²⁵⁹ 75 – 76 °C) **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2964, 2899, 2855, 1634, 1429, 1279, 1114, 1011, 838, 755; **¹H NMR** (400 MHz, CDCl₃) (*Rotameric*) δ 7.45 – 7.30 (m, 4H, Ar), 3.88 – 3.32 (m, 8H, CH₂); **¹³C NMR** (101 MHz, CDCl₃) δ 169.5 (C=O), 136.2 (Ar), 133.7 (Ar), 129.0 (Ar), 128.8 (Ar), 67.0 (OCH₂), 48.3 (NCH₂), 42.7 (NCH₂); **ES⁺MS** m/z 226 [M + H⁺, 100, Cl³⁵], 228 [M + H⁺, 35, Cl³⁷].

(4-Methoxyphenyl)(morpholino)methanone²⁶⁰ (2-18)



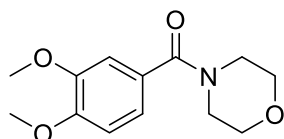
Description: Clear oil (117 mg, 53%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2962, 2851, 1683, 1602, 1512, 1424, 1245, 1111, 1020, 837, 762; **¹H NMR** (400 MHz, CDCl₃) δ 7.39 (dt, J = 10.4, 2.8 Hz, 2H, Ar), 6.92 (dt, J = 9.5, 2.8 Hz, 2H, Ar), 3.83 (s, 3H, CH₃), 3.70 – 3.58 (m, 8H, CH₂); **¹³C NMR** (101 MHz, CDCl₃) δ 170.6 (C=O), 161.1 (Ar), 129.4 (Ar), 127.4 (Ar), 113.9 (Ar), 67.0 (OCH₂), 55.5 (OCH₃) 49.2 (NCH₂), 43.2 (NCH₂); **ES⁺MS** m/z 222 [M + H⁺, 100].

(4-Fluorophenyl)(morpholino)methanone²⁶⁰ (1-68)



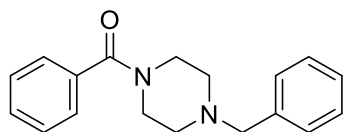
Description: White oil (163 mg, 78%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2858, 1633, 1511, 1431, 1279, 1224, 1115, 1023, 845; **¹H NMR** (400 MHz, CDCl_3) δ 7.48 – 7.35 (m, 2H, Ar), 7.19 – 7.04 (m, 2H, Ar), 4.14 – 3.15 (m, 8H, CH_2); **¹³C NMR** (101 MHz, CDCl_3) δ 169.7 (C=O), 129.6 (d, J = 8.6 Hz, Ar), 115.8 (d, J = 22.0 Hz, Ar), 67.0 (OCH_2), 49.0 (NCH_2), 42.7 (NCH_2); **¹⁹F NMR** (377 MHz, CDCl_3) δ 109.9 (tt, J = 8.4, 8.4, 5.6, 5.6 Hz); **ES⁺MS** m/z 210 [$\text{M} + \text{H}^+$, 100].

(3,4-Dimethoxyphenyl)(morpholino)methanone²⁶¹ (2-19)



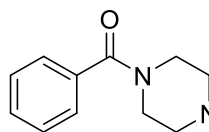
Description: Yellow oil (100 mg, 40%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2961, 2852, 1625, 1515, 1425, 1262, 1112, 1022; **¹H NMR** (400 MHz, CDCl_3) δ 7.00 – 6.96 (m, 2H, Ar), 6.86 (d, J = 8.2 Hz, 1H, Ar), 3.90 (m, 6H, OCH_3), 3.77 – 3.59 (m, 8H, CH_2); **¹³C NMR** (101 MHz, CDCl_3) δ 170.5 (C=O), 150.6 (Ar), 149.2 (Ar), 127.6 (Ar), 120.3 (Ar), 111.0 (Ar), 110.6 (Ar), 67.1 (OCH_2), 56.1 (ArOCH_3); **ES⁺MS** m/z 252 [$\text{M} + \text{H}^+$, 100].

(4-Benzylpiperazin-1-yl)(phenyl)methanone²⁶² (2-23)



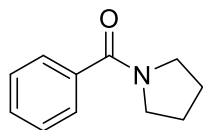
Description: Clear oil (179 mg, 64%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 3060, 2917, 2808, 1633, 1430, 1278, 1158, 1000, 699; **¹H NMR** (400 MHz, CDCl_3) δ 7.42 – 7.37 (m, 5H, Ar), 7.35 – 7.27 (m, 5H, Ar), 3.79 (bs, 2H, NCH_2CH_2), 3.54 (s, 2H, NCH_2Ar), 3.42 (bs, 2H, NCH_2CH_2), 2.46 (m, J = 62.0 Hz, 4H, NCH_2CH_2); **¹³C NMR** (101 MHz, CDCl_3) δ 170.3 (C=O), 137.5 (Ar), 129.6 (Ar), 129.1 (Ar), 128.5 (Ar), 128.3 (Ar), 127.3 (Ar), 127.0 (Ar), 62.9 (NCH_2Ar), 53.3 (NCH_2CH_2), 52.8 (NCH_2CH_2), 42.1 (NCH_2CH_2);

(4-Methylpiperazin-1-yl)(phenyl)methanone²⁶³ (2-22)



Description: Yellow oil (192 mg, 94%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2939, 2793, 1429, 1294, 1130, 1130, 1002, 785, 711; **¹H NMR** (400 MHz, CDCl_3) δ 7.40 (d, J = 2.0 Hz, 5H, Ar), 3.80 (s, 2H, NCH_2), 3.44 (s, 2H, NCH_2), 2.48 (s, 2H, NCH_2), 2.35 (s, 2H, NCH_2), 2.31 (s, 3H, NCH_3); **¹³C NMR** (101 MHz, CDCl_3) δ 170.4 (C=O), 135.8 (Ar), 129.7 (Ar), 128.5 (Ar), 127.0 (Ar), 55.3 (NCH_2), 54.7 (NCH_2), 47.6 (NCH_2), 46.0 (NCH_3), 42.0 (NCH_2); **ES⁺MS** m/z 205 [$\text{M} + \text{H}^+$, 100].

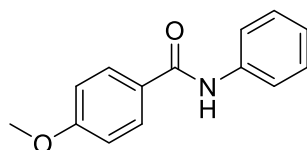
Phenyl(pyrrolidin-1-yl)methanone²⁶⁴ (2-29)



Description: Yellow oil (170 mg, 97%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2972, 2877, 1618, 1575, 1419, 1430, 792, 719; **¹H NMR** (400 MHz, CDCl_3) δ 7.55 – 7.46 (m, 2H, Ar), 7.44 – 7.34 (m, 3H, Ar), 3.64 (t, J = 7.0 Hz, 2H, NCH_2), 3.41 (t, J = 6.6 Hz, 2H, NCH_2), 1.99 – 1.82 (m, 4H, NCH_2CH_2); **¹³C NMR** (101

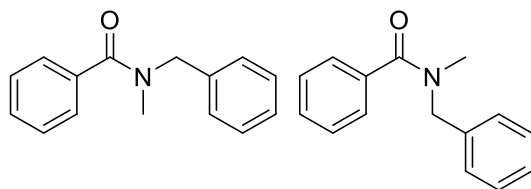
MHz, CDCl₃) δ 169.8 (C=O), 137.4 (Ar), 129.9 (Ar), 128.3 (Ar), 127.2 (Ar), 49.7 (NCH₂), 46.3 (NCH₂), 26.5 (CH₂), 24.6 (CH₂); **ES⁺MS** m/z 176 [M + H⁺, 100].

4-Methoxy-N-phenylbenzamide²⁶⁵ (2-20)



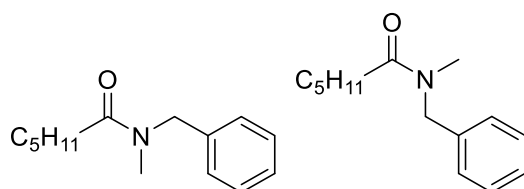
Description: White solid (82 mg, 36%); **m.p.** 177 – 180 °C (lit.²⁶⁵ 177 – 178 °C); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 3336, 1655, 1597, 1528, 1438, 1252, 1184, 752, 691; **¹H NMR** (400 MHz, CDCl₃) δ 7.85 (dt, 2H, J = 8.8, 3.0 Hz, Ar), 7.76 (bs, 1H, C(O)NH), 7.63 (d, 2H, J = 7.3 Hz, Ar), 7.36 (t, 2H, J = 7.3 Hz, Ar), 7.14 (t, 1H, J = 7.5, Ar), 6.98 (dt, 2H, J = 8.8, 3.1 Hz, Ar), 3.88 (s, 3H, OCH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 165.3 (C=O), 162.6 (Ar), 138.2 (Ar), 129.2 (Ar), 129.0 (Ar), 127.3 (Ar), 124.5 (Ar), 120.3 (Ar), 114.1 (Ar), 55.6 (OCH₃); **ES⁺MS** m/z 228 [M + H⁺, 100].

N-Benzyl-N-methylbenzamide²⁶⁶ (2-24)



Description: Clear oil (77 mg, 34%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 3061, 3029, 2926, 1630, 1497, 1447, 1399, 1264, 1069, 698; **¹H NMR** (400 MHz, CDCl₃) (*Rotameric*) δ 7.52 – 7.30 (m, 9H, Ar), 7.20 (d, J = 7.7 Hz, 1H, Ar), 4.79 (s, 2H, NCH₂Ar), 4.54 (s, 2H, NCH₂Ar), 3.06 (s, 2H, NCH₃), 2.89 (s, 2H, NCH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 184.8 (C=O), 129.8 (Ar), 129.0 (Ar), 128.9 (Ar), 128.6 (Ar), 128.6 (Ar), 128.3 (Ar), 127.7 (Ar), 127.7 (Ar), 127.1 (Ar), 126.9 (Ar), 51.5 (NCH₂Ar), 50.9 (NCH₂Ar), 37.2 (NCH₃), 33.3 (NCH₃); **ES⁺MS** m/z 226 [M + H⁺, 100].

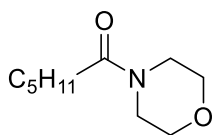
N-Benzyl-N-methylhexanamide (2-25)



Description: Brown oil (64 mg, 29%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2956, 2929, 2871, 1643, 1453, 1402, 1263, 1093, 732, 699; **¹H NMR** (400 MHz, CDCl₃) (*Rotameric*) δ 7.38 – 7.22 (m, 4H, Ar), 7.16 (d, J = 7.3 Hz, 1H, Ar), 4.59 (s, 2H, NCH₂Ar), 4.54 (s, 2H, NCH₂Ar), 2.94 (s, 3H, NCH₃), 2.91 (s, 3H, NCH₃), 2.37 (t*, J = 7.8 Hz, 2H, CH₂CH₂C(O)), 1.81 – 1.54 (m, 2H, CH₂CH₂CH₂), 1.45 – 1.18 (m, 4H, CH₂CH₂), 1.06 – 0.66 (m, 3H, CH₂CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 173.5 (C=O), 137.7 (Ar), 136.9 (Ar), 129.0 (Ar), 128.7 (Ar), 128.2 (Ar), 128.2 (Ar), 127.7 (Ar), 127.4 (Ar), 126.4 (Ar), (53.5, 50.9) (NCH₂Ar), (35.0, 34.0) (NCH₃), (33.7, 33.3) (CH₂) (31.8, 31.8) (CH₂), (25.3, 25.0) (CH₂), (22.7, 22.6) (CH₂), (14.1, 14.1) (CH₃); **ES⁺MS** m/z 220 [M + H⁺, 100].

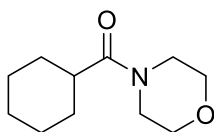
t* overlapping, but distinct, triplets from individual rotamers

1-Morpholinohexan-1-one²⁶⁷ (2-8)



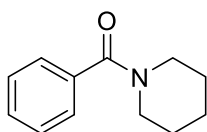
Description: Clear oil (117 mg, 63%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2957, 2928, 2857, 1644, 1431, 1272, 1116, 1029, 848; **¹H NMR** (400 MHz, CDCl_3) δ 3.66 (dd, $J = 5.7, 3.9$ Hz, 4H, OCH_2), 3.62 (bs, 2H, NCH_2), 3.46 (bs, 2H, NCH_2), 2.30 (dd, $J = 7.6$ Hz, 2H, $\text{CH}_2\text{C(O)}$), 1.65 – 1.61 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.39 – 1.27 (m, 4H, CH_2), 0.94 – 0.85 (m, 3H, CH_3); **¹³C NMR** (101 MHz, CDCl_3) δ 172.1 (C=O), (67.1, 66.9) (NCH_2), (46.2, 42.0) (OCH_2), 33.2 (CH_2), 31.8 (CH_2), 25.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3); **ES⁺MS** m/z 186 [$\text{M} + \text{H}^+$, 100].

Cyclohexyl(morpholino)methanone⁷¹ (2-9)



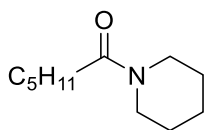
Description: White oil (128 mg, 65%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2928, 2853, 1641, 1441, 1434, 1249, 1217, 1117; **¹H NMR** (400 MHz, CDCl_3) δ 3.67 – 3.65 (m, 4H, OCH_2), 3.55 (bs, 4H, NCH_2), 2.43 (dt, 1H, $J = 11.5, 3.5$ Hz, $(\text{CH}_2)_2\text{CHC(O)}$), 1.82 – 1.78 (m, 2H, CH_2), 1.73 – 1.68 (m, 3H, CH_2), 1.58 – 1.54 (m, 2H, CH_2), 1.29 – 1.23 (m, 3H, CH_2); **¹³C NMR** (101 MHz, CDCl_3) δ 174.9 (C=O), 67.1 (OCH_2), 40.4 (CH), 29.5 (CH_2), 26.0 (CH_2), 26.0 (CH_2); **ES⁺MS** m/z 198 [$\text{M} + \text{H}^+$, 100].

Phenyl(piperidin-1-yl)methanone²⁵⁸ (1-62)



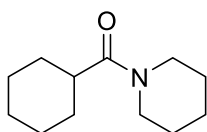
Description: Yellow oil (127 mg, 67%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2935, 2854, 1625, 1430, 1274, 1110, 1003, 707; **¹H NMR** (400 MHz, CDCl_3) δ 7.38 (s, 5H), 3.70 (s, 2H), 3.33 (s, 2H), 1.67 (bs, 4H), 1.51 (bs, 2H); **¹³C NMR** (101 MHz, CDCl_3) δ 170.4, 136.6, 129.5, 128.5, 126.9, (48.9, 43.2), (26.7, 25.8), 24.7; **ES⁺MS** m/z 190 [$\text{M} + \text{H}^+$, 35].

1-(Piperidin-1-yl)hexan-1-one²⁶⁸ (2-11)



Description: Yellow oil (147 mg, 87%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2932, 2856, 1639, 1434, 1254, 1140, 853; **¹H NMR** (400 MHz, CDCl_3) δ 3.59 (bt, $J = 5.0$ Hz, 2H, NCH_2), 3.54 (bt, $J = 5.0$ Hz, NCH_2), 2.35 – 2.26 (m, 2H, CH_2), 1.65 – 1.54 (m, 8H, CH_2), 1.38 – 1.26 (m, 4H, CH_2), 0.89 (m, 3H, CH_3); **¹³C NMR** (101 MHz, CDCl_3) δ 171.6 (C=O), 46.7 (CH_2), 42.6 (CH_2), 33.5 (CH_2), 31.7 (CH_2), 26.6 (CH_2), 25.6 (CH_2), 25.2 (CH_2), 24.6 (CH_2), 22.5 (CH_2), 14.0 (CH_3); **ES⁺MS** m/z 184 [$\text{M} + \text{H}^+$, 100].

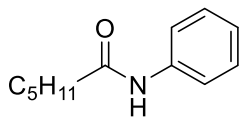
Cyclohexyl(piperidin-1-yl)methanone²⁶⁹ (2-12)



Description: Clear oil (115 mg, 59%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2927, 2852, 1631, 1442, 1252, 1213, 1118, 1003, 730; **¹H NMR** (400 MHz, CDCl_3) δ 3.48 (t, $J = 5.6$ Hz, 4H, CH_2), 2.47 (t, $J = 11.5, 3.4$ Hz, 1H, CH), 1.80 – 1.75 (m, 2H, CH_2), 1.72 – 1.61 (m, 5H, CH_2), 1.57 – 1.47 (m, 6H, CH_2), 1.31 – 1.22

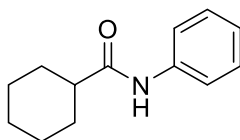
(m, 3H, CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 174.7 (C=O), 44.9 (CH), 40.6 (CH₂), 29.5 (CH₂), 26.4 (CH₂), 26.1 (CH₂), 26.0 (CH₂), 24.8 (CH₂); **ES⁺MS** *m/z* 196 [M + H⁺, 100].

N-Phenylhexanamide²⁷⁰ (2-14)



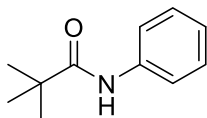
Description: Brown solid (111 mg 58%); **m.p.** 93 – 98 °C (lit.²⁷⁰ 94 – 95 °C); **IR** (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 3292, 3138, 2930, 2860, 1659, 1599, 1543, 1499, 1442, 1253, 754, 692; **¹H NMR** (400 MHz, CDCl₃) δ 7.51 (d, *J* = 7.7 Hz, 2H, Ar), 7.32 (t, *J* = 7.9 Hz, 2H, Ar), 7.14 (s, 1H, C(O)NH), 7.10 (t, *J* = 7.4 Hz, 1H, Ar), 2.35 (t, *J* = 7.7 Hz, 2H, CH₂), 1.73 (m, 2H, CH₂CH₂CH₂), 1.44 – 1.27 (m, 4H, CH₂), 0.98 – 0.86 (m, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 171.5 (C=O), 138.1 (Ar), 129.1 (Ar), 124.3 (Ar), 119.8 (Ar), 38.0 (CH₂), 31.6 (CH₂), 25.5 (CH₂), 22.6 (CH₂), 14.1 (CH₃); **ES⁺MS** *m/z* 192 [M + H⁺, 100].

N-Phenylcyclohexanecarboxamide¹⁰⁴ (2-15)



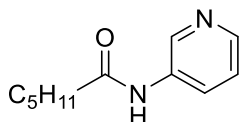
Description: White solid (108 mg, 53%); **m.p.** 144 – 149 °C (lit.¹⁰⁴ 144 – 146 °C); **IR** (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 3245, 3135, 3077, 2932, 2852, 1659, 1598, 1547, 1442, 757; **¹H NMR** (400 MHz, CDCl₃) δ 7.52 (bd, *J* = 8.2 Hz, 2H, Ar), 7.31 (dd, *J* = 8.5, 7.3 Hz, 2H, Ar), 7.15 (bs, 1H C(O)NH), 7.09 (t, *J* = 7.4 Hz, 1H), 2.22 (tt, *J* = 11.7, 3.5 Hz, 1H, (CH₂)₂CHC(O)), 1.96 (bd, *J* = 13.2 Hz, 2H, CH₂), 1.86 – 1.82 (m, 2H, CH₂), 1.72 – 1.65 (m, 1H, CH₂), 1.60 – 1.49 (m, 2H, CH₂), 1.37 – 1.23 (m, 3H, CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 174.4 (C=O), 138.2 (Ar), 129.1 (Ar), 124.2 (Ar), 119.9 (Ar), 46.8 (CH), 29.8 (CH₂), 25.8 (CH₂); **ES⁺MS** *m/z* 204 [M + H⁺, 100].

N-Phenylpivalamide (2-16)



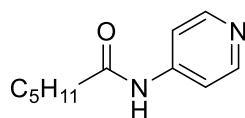
Description: Brown solid (45 mg, 27%); **m.p.** 133 – 137 °C (lit. 132 – 134 °C); **IR** (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 3311, 1655, 1598, 1535, 1438, 1318, 1242, 1170, 755; **¹H NMR** (400 MHz, CDCl₃) δ 7.55 (dd, *J* = 8.6, 1.1 Hz, 2H, Ar), 7.37 – 7.32 (m, 2H, Ar), 7.15 – 7.11 (m, 1H, Ar), 1.35 (s, 9H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 138.2 (C=O), 129.1 (Ar), 124.3 (Ar), 120.1 (Ar), 39.8 (Me₃CC(O)), 27.8 (CH₃); **ES⁺MS** *m/z* 178 [M + H⁺, 10].

N-(Pyridin-3-yl)hexanamide (2-28)



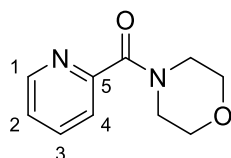
Description: Brown oil (40 mg, 21%); **IR** (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 3163, 2957, 2929, 2860, 1683, 1592, 1516, 1417, 1296, 1211, 1175, 829; **¹H NMR** (400 MHz, CDCl₃) δ 8.55 (bs, 1H, Ar), 8.35 (bd, *J* = 8.3 Hz, 1H, Ar), 8.30 (bd, *J* = 4.3 Hz, 1H, Ar), 8.23 (bs, 1H, C(O)NH), 7.33 (dd, *J* = 8.4, 4.8 Hz, 1H, Ar), 2.41 (t, *J* = 7.6 Hz, 2H, CH₂C(O)N), 1.86 (m, 2H, CH₂CH₂CH₂), 1.37 – 1.33 (m, 4H, CH₂), 0.98 – 0.85 (m, 3H, CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 172.5 (C=O), 143.6 (Ar), 140.0 (Ar), 135.9 (Ar), 128.3 (Ar), 124.3 (Ar), 37.6 (CH₂C(O)N), 31.5 (CH₂), 25.3 (CH₂), 22.5 (CH₂), 14.1 (CH₃); **ES⁺MS** *m/z* 193 [M + H⁺, 70].

N-(Pyridin-4-yl)hexanamide (2-29)



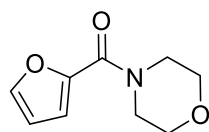
Description: Brown oil (19 mg, 10%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 3164, 2957, 2929, 2860, 1683, 1592, 1516, 1417, 1296, 1211, 1175, 828; **^1H NMR** (400 MHz, CDCl_3) δ 8.47 (d, J = 5.3 Hz, 2H, Ar), 8.02 (bs, 1H, C(O)NH), 7.51 (dd, J = 4.7, 1.7 Hz, 2H, Ar), 2.39 (t, J = 7.4 Hz, 2H, $\text{CH}_2\text{C(O)N}$), 1.76 – 1.68 (m, 2H, CH_2), 1.36 – 1.31 (m, 4H, CH_2), 0.92 – 0.87 (m, 3H, CH_3); **^{13}C NMR** (101 MHz, CDCl_3) δ 172.4 (C=O), 150.5 (Ar), 145.3 (Ar), 113.5 (Ar), 37.8 ($\text{CH}_2\text{C(O)N}$), 31.4 (CH_2), 25.0 (CH_2), 22.4 (CH_2), 13.9 (CH_2); **ES⁺MS** m/z 193 [$\text{M} + \text{H}^+$, 10].

Morpholino(pyridin-2-yl)methanone (2-26)



Description: Brown oil (102 mg, 53%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2853, 1634, 1588, 1567, 1424, 1284, 1114, 751; **^1H NMR** (400 MHz, CDCl_3) δ 8.59 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H, H-1), 7.81 (td, J = 7.7, 1.7 Hz, 1H, H-2), 7.68 (dt, J = 7.9, 1.2 Hz, 1H, H-3), 7.35 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H, H-4), 3.82 (bs, 4H, OCH_2), 3.71 – 3.64 (m, 4H, NCH_2); **^{13}C NMR** (101 MHz, CDCl_3) δ 166.9 (C=O), 153.1 (Ar), 147.7 (Ar), 138.2 (Ar), 125.0 (Ar), 124.5 (Ar), 67.1 (CH_2), 66.9 (CH_2), 47.9 (CH_2), 43.0 (CH_2); **ES⁺MS** m/z 193 [$\text{M} + \text{H}^+$, 100].

Furan-2-yl(morpholino)methanone²⁵⁴ (2-27)



Description: Brown oil (80 mg, 44%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 3117, 2902, 2857, 1623, 1571, 1486, 1431, 1281, 1183, 1115, 1026, 756; **^1H NMR** (400 MHz, CDCl_3) δ 7.48 (dd, J = 1.8, 1.0 Hz, 1H), 7.03 (dd, J = 3.6, 0.9 Hz, 1H), 6.49 (dd, J = 3.4, 1.8 Hz, 1H), 3.88 – 3.67 (m, 8H); **^{13}C NMR** (101 MHz, CDCl_3) δ 159.2 (C=O), 147.9 (Ar), 143.9 (Ar), 116.9 (Ar), 111.5 (Ar), 67.1 (OCH_2); **ES⁺MS** m/z 182 [$\text{M} + \text{H}^+$, 100].

7.4 Catalyst Synthesis and Characterisation

Au/ γ -Al₂O₃ Synthesis

Au/ γ -Al₂O₃ was prepared following a known sol-immobilisation procedure.¹²⁰ For 10 g catalyst, HAuCl₄·3H₂O (242 mg) was dissolved in 450 mL deionised water, followed by addition of PVA (MW 9,000 – 10,000, 80% hydrolysed, 121 mg). The yellow solution was stirred for 30 minutes to ensure complete dissolution of the PVA stabiliser. A freshly prepared aqueous solution of 0.1 M NaBH₄ (30 mL, 117 mg) was added in a single portion with vigorous stirring (1000 RPM) resulting in a rapid darkening of the solution to a red/brown sol and mild effervescence. After 2 hours of sol formation, γ -Al₂O₃ (Sasol Puralox TM100/150) (9.90 g) was added as a slurry in water (20 mL).

After AuNP deposition had complete, stirring was stopped and the brown solid was allowed to settle (to aid filtration). The brown AuNP supported material was collected by filtration and washed with deionised water (1 L).¹⁷⁹ The filter cake was dispersed in deionised water (500 mL) and heated to gentle reflux for 1 hour. The resulting brown suspension was filtered to collect the supported AuNP material. The resulting brown solid was dried at 80 °C overnight to yield a red/brown solid.

For synthetic purposes, the red/brown solid was calcined in a static oven: The red/brown solid was placed in an alumina crucible and heated at a rate of 10 °C min⁻¹ up to 500 °C and held isothermally for 3 hours. Thermal treatment resulted in the red/brown freshly deposited AuNP material changing colour to a deep purple. The purple supported AuNP catalyst was ground and sieved to a fine powder (<125 μ m).

Transmission Electron Microscopy (TEM)

TEM was used to determine the average nanoparticle size of the AuNP materials. A small amount (~1 mg) of catalyst was dispersed in pentane and deposited onto a holey carbon film on a copper support. TEM measurements were taken on a JEOL TEM 2100Plus located in the materials department at Imperial College London.

Brunauer–Emmett–Teller (BET)

The surface area of the catalytic materials was determined by BET analysis using a Micromeritics Tristar 3000. Between 100 – 200 mg of material degassed/dried at 120 °C under a flow of N₂ for at least 2 hours. BET surface area and approximate pore sizes were calculated by their low-temperature N₂ adsorption.

Ion Coupled Plasma – Atomic Emission Spectroscopy (ICP-AES)

Total metal content was calculated by ICP-AES using a Perkin Elmer Optima 2000DV. 20 mg of catalytic material was digested in aqua regia at 90 °C for 16 hours. After complete digestion, the solution was

diluted with water to 10 mL to make a stock solution. 1 mL of stock solution was diluted to 10 mL in water to prepare analysis samples.

Thermal Analysis

Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) measurements were conducted on Netzsch Jupiter simultaneous thermal analysis machines for TGA-DSC and TGA-MS. Approximately 20 mg of catalytic material was weighed into an alumina crucible. For TGA-DSC the sample is then heated at a computer controllable ramp rate under a flow of air while measuring the mass and heat changes. For TGA-MS the sample is heated at a computer controllable ramp rate under a flow of air while constantly measuring the gas outlet by mass spectrometry.

X-Ray Diffraction

XRD measurements were recorded using a PANalytical X'Pert-Pro MPD PW3040/60 XRD. X-rays were generated using a tungsten filament at 40 kV and a current of 20 mA. Data were collected over a range of 10 to 90 °2 θ using a step size of 0.1 °2 θ and a time per step of 0.5 s.

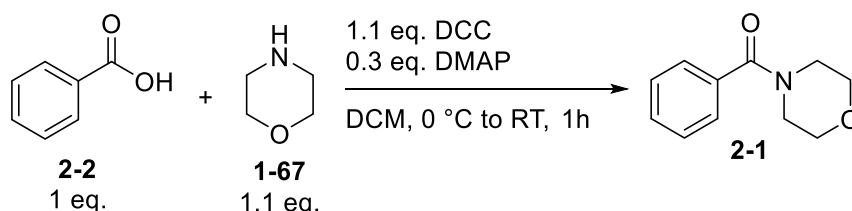
Point of Zero Charge

PZC was calculated using a pH titration technique. 100 mg of support or catalyst was shaken for 16 hours in 5 mL of sodium nitrate buffered solution of known pH between 2 and 11, adjusted by addition of weak solutions of NaOH and HNO₃. After shaking, samples were centrifuged to settle solids, and the final pH was measured. Plotting the final pH against the initial pH produces a linear correlation where the x-intercept is the PZC of the tested material.

7.5 Miscellaneous Synthesis

For the purposes of HPLC calibration, samples of amides **2-1** and **2-17** were synthesised independently using a DCC coupling method.

Morpholino(phenyl)methanone (**2-1**)

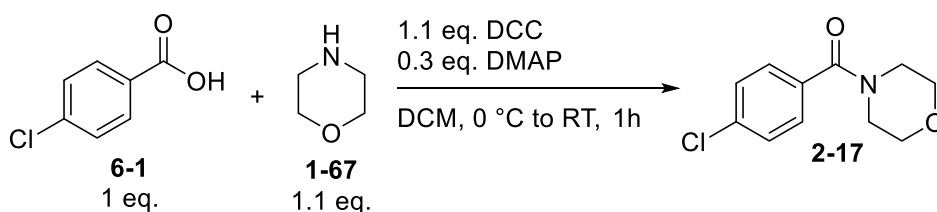


A solution of 4-dimethylaminopyridine (3.00 g, 24.6 mmol) in CH_2Cl_2 (25 mL) was added slowly to a solution of benzoic acid **2-2** (9.98 g, 81.7 mmol) and DCC (18.68 g, 90.5 mmol) and CH_2Cl_2 (175 mL). The solution was cooled to 0 $^\circ\text{C}$, and morpholine **1-67** (7.87 mL, 90.0 mmol) was added dropwise over 10 mins. After complete addition of morpholine, the reaction mixture was allowed to warm to room temperature and stirred for 1 hour, resulting in the formation of a cloudy suspension.

The crude reaction mixture was filtered to remove the white urea by-product, and the filtrate was concentrated to yield a yellow oil, which was dissolved in EtOAc (200 mL) and washed sequentially with 1 M HCl (150 mL) and H_2O (2 x 150 mL). The organic fraction was collected and concentrated to yield a yellow solid (9.35 g) that was recrystallised with EtOAc:Petroleum ether to yield the amide product as a white solid (8.57 g, 44.8 mmol, 55%).

m.p. 72 – 75 $^\circ\text{C}$ (lit.²⁵⁸ 73 – 74 $^\circ\text{C}$); **IR** (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 2967, 2854, 1627, 1424, 1276, 1255, 1111, 1012; **^1H NMR** (400 MHz, CDCl_3) δ 7.44 – 7.39 (m, 5H, Ar), 3.74 – 3.46 (m, 8H, CH_2); **^{13}C NMR** (101 MHz, CDCl_3) δ 170.6 (C=O), 135.4 (Ar), 130.0 (Ar), 128.7 (Ar), 127.2 (Ar), 67.0 (CH_2), 48.2 (CH_2), 42.8 (CH_2); **ES⁺MS** m/z 192 [$\text{M} + \text{H}^+$, 100]

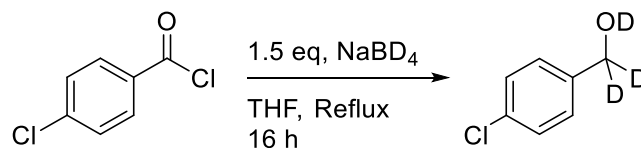
(4-Chlorophenyl)(morpholino)methanone²⁵⁹ (**2-17**)



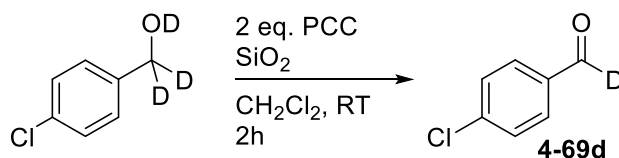
Amide **2-17** was prepared in following the same DCC procedure described for the preparation of amide **2-1**. Output: White solid (5.42 g, 24.1 mmol, 94%)

m.p. 79 – 82 $^\circ\text{C}$ (lit.²⁵⁹ 75 – 76 $^\circ\text{C}$) **IR** (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 2962, 2919, 2853, 1632, 1426, 1277, 1113, 1010, 837, 754; **^1H NMR** (400 MHz, CDCl_3) (*Rotameric*) δ 7.40 – 7.34 (m, 4H, Ar), 3.71 – 3.44 (m, 8H, CH_2); **^{13}C NMR** (101 MHz, CDCl_3) δ 169.4 (C=O), 136.0 (Ar), 133.6 (Ar), 128.9 (Ar), 128.7 (Ar), 66.8 (OCH_2), 48.2 (NCH_2), 42.7 (NCH_2); **ES⁺MS** m/z 226 [$\text{M} + \text{H}^+$, 100, Cl^{35}], 228 [$\text{M} + \text{H}^+$, 35, Cl^{37}].

d¹-*para*-Chlorobenzaldehyde (4-69d)



Sodium borodeuteride (600 mg, 14.3 mmol) was added in a single portion to a solution of *para*-chlorobenzoyl chloride (1.64 g, 9.4 mmol). The resulting suspension was warmed to 80 °C, and the heated reaction mixture was stirred for 16 h. After 16 h the reaction mixture was cooled to 0 °C and quenched by the dropwise addition of 4 M HCl. The resulting solution was extracted with CH₂Cl₂ (3 x 20 mL), and the combined organic fractions were dried and concentrated to yield the deuterated *para*-chlorobenzyl alcohol as a crude white solid (1.30 g, 8.9 mmol, 95%).



Crude deuterated *para*-chlorobenzyl alcohol (1.20 g, 8.2 mmol) was dissolved in CH₂Cl₂ (25 mL), and the solution was added to a suspension of pyridinium chlorochromate (4.08 g, 18.9 mmol) and SiO₂ (10 g) in CH₂Cl₂ (25 mL). The reaction mixture was stirred at room temperature for 2 h resulting in the formation of a dark brown suspension. The crude brown reaction mixture was passed through a short column of Celite to remove the SiO₂ and majority of the chromate salt by-products. Evaporation of the filtered reaction mixture resulted in a yellow/brown oil (2.40 g) that was further purified by flash chromatography (SiO₂, EtOAc:Petrol, 1:5) and recrystallised from EtOH yielding the deuterated *para*-chlorobenzaldehyde as a white solid (0.92 g, 6.5 mmol, 77%).

m.p. 40 – 43 °C (lit.²⁷¹ 38 – 40 °C); **IR** (neat) ν_{max} /cm⁻¹ 2957, 2926, 2857, 1720, 1680, 1593, 1488, 1400, 1270, 1119, 1092, 1014, 850, 759; **¹H NMR** (400 MHz, CDCl₃) δ 7.87 – 7.84 (m, 2H, Ar), 7.56 – 7.53 (m, 2H, Ar); **¹³C NMR** (101 MHz, CDCl₃) δ 130.9 (Ar), 129.5 (Ar); **EI⁺MS** m/z 141 [M, 100, Cl³⁵], 143 [M, 35, Cl³⁷]

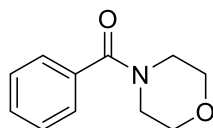
7.6 Slurry Column Bubble Reactor

Standard AuNP Oxidative Amidation Procedure Using SBCR

Each reaction investigating the effect of O₂ concentration and scope in the SBCR were performed following the same protocol, operating the glass slurry column reactor (GSCR) as a slurry batch reactor without the stagnant separating chamber (SSC). Each reaction was performed at ~1 g scale operating at approximately 75% capacity of the GSCR. A typical procedure for the oxidative amidation reaction is as follows:

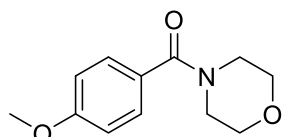
GSCR was charged with 4 mm diameter glass beads, toluene (30 mL), 0.5 M NaOH (7.5 mL), Au/ γ -Al₂O₃ (1.13 g) and heated to 45 °C sparging the reactor with a flow of N₂. When the GSCR reached 45 °C the feed rate of the gas was recorded and the desired aldehyde and amine were simultaneously charged to the reactor, making the charge as close as possible to the sparger. O₂ was introduced to the feed gas and the flow rate was recorded to determine the concentration of O₂ in the feed gas. Each reaction was conducted for approximately 4 hours, after which the contents of the reactor were decanted, and the organic layer was separated from the aqueous catalyst slurry. The aqueous catalyst slurry was washed with toluene (3 x 10 mL) and the combined organic layers were concentrated to yield the desired amide without additional purification.

Morpholino(phenyl)methanone²⁵⁸ (2-1)



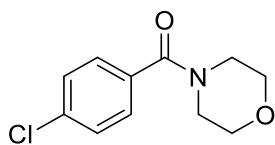
Description: White solid (1.09 g, 76%); **m.p.** 75 – 77 °C (lit.²⁵⁸ 73 – 74 °C); **IR** (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 3056, 2964, 2852, 1627, 1425, 1276, 1112, 1067, 1015, 841, 788, 709; **¹H NMR** (400 MHz, CDCl₃) δ 7.43 – 7.41 (m, 5H, Ar), 3.72 – 3.45 (m, 8H, CH₂); **¹³C NMR** (101 MHz, CDCl₃) δ 170.6 (C=O), 135.4 (Ar), 130.0 (Ar), 128.7 (Ar), 127.2 (Ar), 67.0 (OCH₂), 48.4 (NCH₂), 42.9 (NCH₂); **ES⁺MS** m/z 192 [M + H⁺, 100]

(4-Methoxyphenyl)(morpholino)methanone²⁶⁰ (2-18)



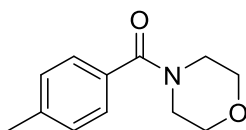
Description: Yellow oil (1.02 g, 62%); **IR** (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 2962, 2916, 2851, 1628, 1607, 1511, 1425, 1248, 1173, 1112, 1021, 839, 762, 703; **¹H NMR** (400 MHz, CDCl₃) δ 7.40 – 7.37 (m, 2H, Ar), 6.93 – 6.90 (m, 2H, Ar), 3.83 (s, 3H, OCH₃), 3.69 – 3.64 (m, 8H, CH₂); **¹³C NMR** (101 MHz, CDCl₃) δ 170.6 (C=O), 161.1 (Ar), 129.4 (Ar), 127.3 (Ar), 113.9 (Ar), 67.1 (OCH₂), 55.5 (OCH₃), 52.9 (NCH₂), 45.0 (NCH₂); **ES⁺MS** m/z 222 [M + H⁺, 100]

(4-Chlorophenyl)(morpholino)methanone²⁵⁹ (2-17)



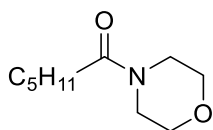
Description: Yellow oil/low m.p. solid (1.12 g, 66%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2963, 2918, 2853, 1630, 1591, 1426, 1277, 1255, 1112, 1010, 836, 755; **¹H NMR** (400 MHz, CDCl_3) δ 7.40 – 7.34 (m, 4H, Ar), 3.69 – 3.45 (m, 8H, CH_2); **¹³C NMR** (101 MHz, CDCl_3) δ 169.5 (C=O), 136.2 (Ar), 133.7 (Ar), 129.0 (Ar), 128.8 (Ar), 66.9 (OCH_2), 48.2 (NCH_2), 43.1 (NCH_2); **ES⁺MS** m/z 226 [M, 100, Cl^{35}], 228 [M, 35, Cl^{37}]

Morpholino(p-tolyl)methanone²⁷² (5-1)



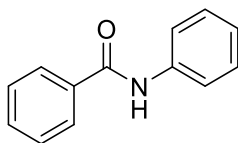
Description: Yellow oil (0.99 g, 64%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2955, 2927, 2855, 1642, 1456, 1429, 1244, 1115, 1029, 848, 740; **¹H NMR** (400 MHz, CDCl_3) δ 7.31 – 7.29 (m, 2H, Ar), 7.21 – 7.19 (m, 2H, Ar), 3.68 – 3.42 (m, 8H, CH_2) 2.37 (s, 3H, CH_3); **¹³C NMR** (101 MHz, CDCl_3) δ 170.8 (C=O), 140.2 (Ar), 132.4 (Ar), 129.3 (Ar), 127.3 (Ar), 67.0 (OCH_2), 47.6 (NCH_2), 42.2 (NCH_2), 21.5 (CH_3); **ES⁺MS** m/z 206 [M + H^+ , 100]

1-Morpholinohexan-1-one²⁶⁷ (2-8)



Description: Clear oil (1.05 g, 76%); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 2961, 2917, 2852, 1627, 1424, 1277, 1255, 1112, 1013, 830, 751; **¹H NMR** (400 MHz, CDCl_3) δ 3.66 (bt, J = 5.27 Hz, 4H, OCH_2), 3.54 (bs, 4H, NCH_2), 2.31 (bt, J = 7.6 Hz, 2H, $\text{CH}_2\text{C(O)}$), 1.66 – 1.59 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.33 – 1.31 (m, 4H), 0.91 – 0.87 (m, 3H, CH_3); **¹³C NMR** (101 MHz, CDCl_3) δ 172.2 (C=O), 66.9 (OCH_2), 45.8 (NCH_2), 40.8 (NCH_2), 33.1 (CH_2), 31.8 (CH_2), 25.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3); **ES⁺MS** m/z 186 [M + H^+ , 100]

N-Phenyl benzamide²⁷³ (1-42) 658



Description: Brown solid (0.35 g, 24%); **m.p.** 155 – 157 °C (lit.²⁷³ 160 – 162 °C); **IR** (neat) $\nu_{\max}/\text{cm}^{-1}$ 3337, 3208, 2955, 1603, 1508, 1329, 1214, 993, 821; **¹H NMR** (400 MHz, CDCl_3) δ 7.89 – 7.86 (m, 2H, Ar), 7.82 (bs, 1H, CONH), 7.65 (bd, J = 7.1 Hz, 2H, Ar), 7.56 (tt, J = 6.09, 1.27 Hz, 1H, Ar), 7.51 – 7.47 (m, 2 H, Ar), 7.40 – 7.36 (m, 2H, Ar), 7.16 (tt, J = 7.44, 1.27 Hz, 1H, Ar); **¹³C NMR** (101 MHz, CDCl_3) δ 164.5 (C=O), 138.0 (Ar), 135.1 (Ar), 132.0 (Ar), 219.3 (Ar), 129.0 (Ar), 127.1 (Ar), 124.7 (Ar), 120.3 (Ar); **ES⁺MS** m/z 198 [M + H^+ , 100]

Gas Flow Rate

The gas flow rate of the SBCR was determined using a bubble flow meter attached to the end of the bubble reactor. The flow rate was calculated as the average of three measurements of the time taken for 50 mL of gas to be evolved from the reactor (Figure 0-1).



Figure 0-1. Gas flow bubble meter

Each gas cylinder (N_2 and O_2) was operated at a constant pressure and the flow rates were controlled via needle valves. The flow rate of the graduated needle valve for O_2 was calibrated independently (Figure 0-2), but the O_2 concentration was calculated from the gas flow rates obtained for each reaction.

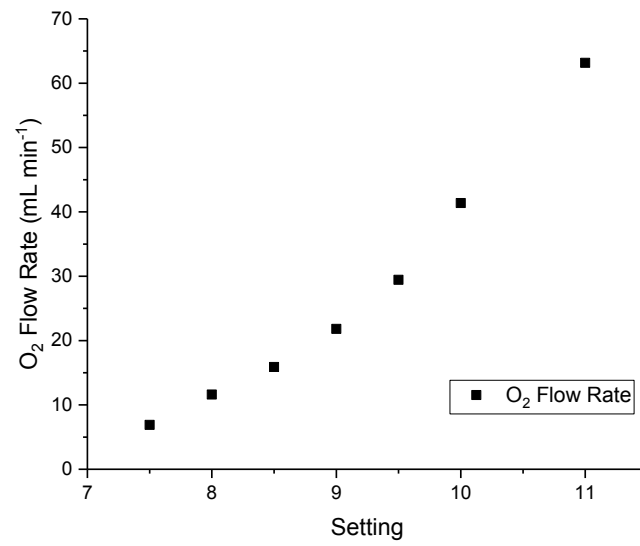


Figure 0-2. O₂ flow rate calibration

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