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Mechanistic Studies into Metal-Catalyzed Aldoxime to Amide Rearrangements

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Abstract: The metal-catalyzed rearrangement of aldoximes into primary amides is a completely atom economical synthetic method for the preparation of one of the most important functional groups in chemistry. There have been several reports of various metals successfully catalyzing this reaction, however, there are conflicting views as to the mechanism involved. Herein we report new experimental evidence to support the mechanism and whether this is universal to all catalysts reported or metal specific. We also describe our further studies into the mechanism of the nickel-catalyzed acylation of amines with aldoximes.

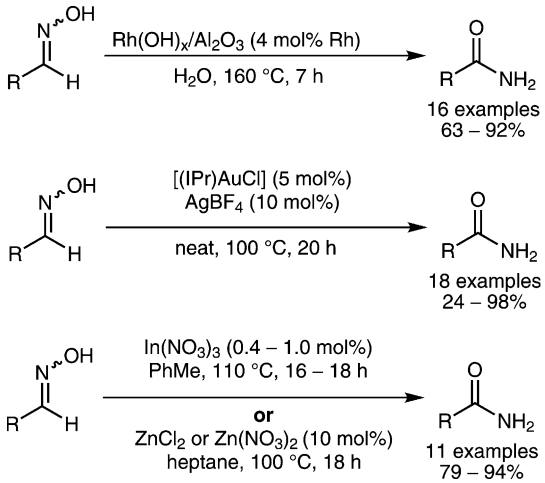
Keywords: aldoximes; amides; mechanism; rearrangement

The efficient synthesis of amide bonds is of great importance in both research and industrial chemistry due to the prevalence of this group in biologically active molecules, agrochemicals and polymer chemistry.[1] The metal-catalyzed rearrangement of aldoximes into primary amides offers a completely atom economical synthesis of this important chemical moiety. This reaction can also be run from the aldehyde oxidation level with the formation of the aldoxime occurring *in situ* when mixed with hydroxylamine.

The first catalytic conditions for this rearrangement were reported by Chang and co-workers in 2003.[2] They found that Wilkinson's complex (at a catalyst loading of 5 mol%) efficiently catalyzed the conversion of a range of aldoximes into their corresponding primary amides at a temperature of 150 °C. Following this initial publication, reports of iridium,[3] ruthenium[4] and palladium[5] catalysts performing the rearrangement appeared in the literature detailing procedures at lower temperatures.

Research efforts have more recently been focussed towards finding lower cost metal catalysts and procedures that can be run in the absence of undesirable organic solvents. This is highlighted in the work reported by Mizuno,[6] Nolan[7] and our own group[8,9] (Scheme 1). Mizuno and co-workers reported a reusable supported rhodium hydroxide catalyst to work in this reaction in aqueous conditions, followed later by Nolan and co-workers reporting a gold/silver co-catalyzed reaction proceeding under solvent-free conditions. We have shown that relatively inexpensive copper, zinc and indium salts are as effective as the precious transition metals at catalyzing aldoxime rearrangements.

It has been proposed that the mechanism for this metal-catalyzed rearrangement proceeds *via* a discrete nitrile intermediate which is formed through dehydration of a coordinated oxime species. This is supported by the frequent detection of a small quantity of nitrile by-product on analysis of the crude reaction



Scheme 1. Recently reported conditions for aldoxime rearrangements into primary amides.

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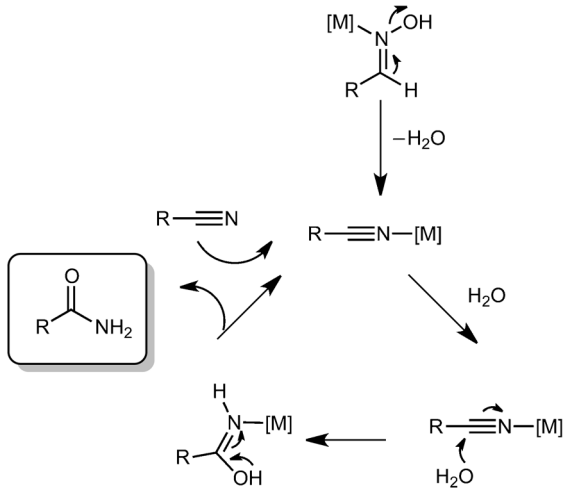
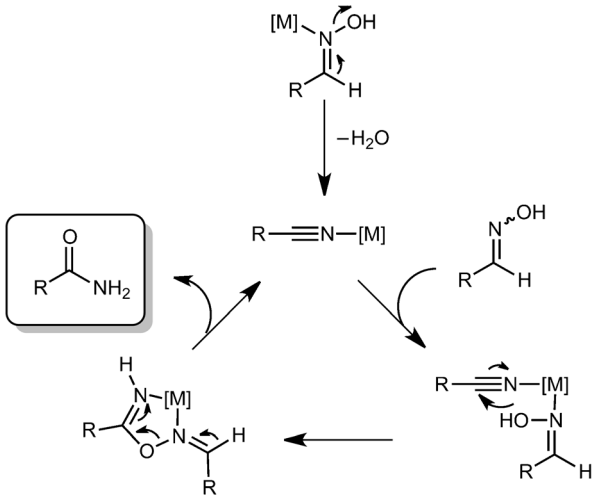


Scheme 2. Proposed mechanism A.



Scheme 3. Proposed mechanism B.

mixture and an observed increase in the rate of reaction when a catalytic amount of nitrile is added to the reaction. Specifically, in the rearrangement of benzaldoxime into benzamide using a supported rhodium catalyst, the reaction profile showed the initial formation of benzonitrile before subsequent formation of benzamide.[10] Additionally, the universal inertness of *O*-alkylated aldoximes and ketoximes towards rearrangement suggests that the transformation requires the presence of both a hydrogen and a hydroxy group.

The corresponding amide is thought to then be generated through hydration of this nitrile intermediate. The most commonly proposed mechanism involves nucleophilic attack by water (Scheme 2). Both individual metal-mediated steps for this dehydration/hydration process are independently reported within the literature to occur in the presence of a range of metal complexes.[11]

Whilst this dehydration/rehydration process has become the generally accepted mechanism for an oxime into amide rearrangement, inconsistencies have been reported which suggest that water may not be acting as the nucleophile in the hydration step, for example, we observe that, in completely anhydrous conditions, rearrangement into the amide still proceeded.

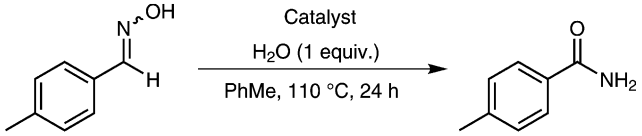
Additionally, many of the catalysts used to promote the oxime rearrangement were shown to not be active in the hydration of a nitrile with water.

A second proposed mechanism involves another molecule of aldoxime acting as the nucleophile to attack the metal-bound nitrile species instead of water (Scheme 3). This could generate a 5-membered cyclic intermediate, decomposition of which would yield the primary amide product and another metal-bound nitrile to continue the catalytic cycle.[12]

In an attempt to elucidate if one of these proposed mechanisms was operating, reactions involving ^{18}O-labelled substrates were carried out for a number of the metal complexes reported to catalyze the rearrangement.

(i) Experiments using ^{18}O-labelled water: Performing the rearrangement in the presence of one equivalent of $^{18}OH_2$ would determine whether water was acting as a nucleophile in the hydration of the nitrile intermediate. If water did indeed attack the nitrile intermediate, there would be ^{18}O incorporation into the amide product **2**. As most of the catalysts reported had been used under anhydrous conditions, it was first determined which of these catalysts were still active in the presence of water (Table 1).

Table 1. Catalyst screen in the presence of water.



1 **2**

Entry	Catalyst	Loading [mol%]	Conversion[a] [%]
1	$RhCl(PPh_3)_3$	5	100
2[b]	$Ru(PPh_3)_3(CO)H_2$	0.1	48
3	$[IrCp^*I_2]_2$	2.5	9
4	$Pd(OAc)_2$	5	100
5	$In(NO_3)_3$	1	18
6	$In(OTf)_3$	3	100
7	$ZnCl_2$	10	3
8	$NiCl_2 \cdot 6H_2O$	10	61
9	$Cu(OAc)_2$	2	100

[a] Determined by ^{1}H NMR.
[b] Catalytic system also consisted of dppe (0.1 mol%) and PTSA (0.4 mol%).

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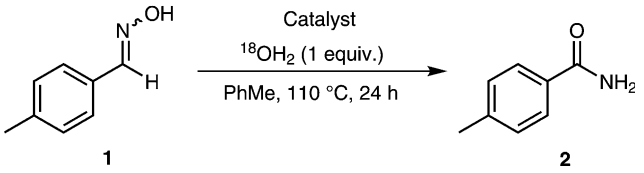
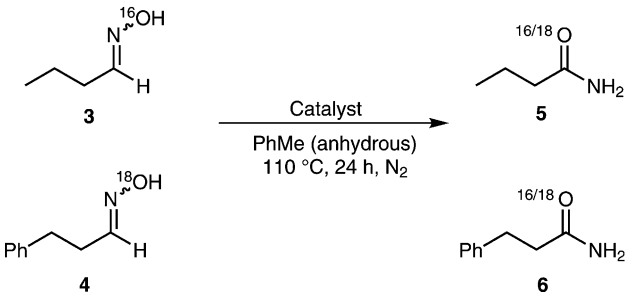


Scheme 4. Rearrangement in the presence of $^{18}OH_2$.



Scheme 5. Potential products from the reaction of unlabelled butyraldoxime in the presence of ^{18}O-labelled 3-phenylpropanaldoxime.

Table 1 entries 3, 5 and 7 show catalysts which were inhibited by the presence of water, hence they were not used in the $^{18}OH_2$ study. The other 6 catalysts were then used in the rearrangement of 4-methylbenzaldoxime **1** in the presence of one equivalent of $^{18}OH_2$ (Scheme 4).

Analysis of the mass spectral data for the crude reaction mixtures showed the presence of a peak with $m/z = 136.08$, corresponding to the unlabelled 4-methylbenzamide (conversion into amide was confirmed by ^{1}H NMR spectroscopy). However, a peak with an $m/z = 138.08$ was not observed for any of the catalytic systems, indicating that incorporation of ^{18}O into the amide product had not occurred, supporting an alternative hydration pathway where water is not acting as the nucleophile.

(ii) Experiments using ^{18}O-labelled aldoximes: In order to ascertain whether the aldoxime is acting as a nucleophile to attack a coordinated nitrile species, a second ^{18}O-labelling study was carried out using ^{18}O-labelled 3-phenylpropanaldoxime **4** (synthesized in accordance with literature procedures).[13] Two batches of ^{18}O-labelled 3-phenylpropanaldoxime were synthesized, with comparable levels of ^{18}O incorporation achieved within both: 67 and 63 atom%. The level of ^{18}O incorporation was determined by comparison of the intensity of the parent ions for ^{16}O and ^{18}O aldoxime in the mass spectra.

The rearrangement of the synthesized ^{18}O-labelled 3-phenylpropanaldoxime **4** was performed in the presence of an equimolar quantity of unlabelled butyraldoxime **3**. In all cases, conversion into amide was determined by ^{1}H and ^{13}C NMR spectroscopy. In the absence of any catalyst, no conversion into amide was seen and the level of ^{18}O label incorporation in 3-phenylpropanaldoxime remained the same.

Scrambling of the ^{18}O label between the two primary amide products **5** and **6** would be expected for a mechanism involving attack of the coordinated nitrile intermediate by an oxime. Following this mechanism (Scheme 3), there is the potential for nucleophilic attack onto a nitrile derived from unlabelled butyraldoxime by ^{18}O-labelled 3-phenylpropanaldoxime to afford ^{18}O-labelled butyramide and *vice versa* to afford ^{16}O 3-phenylpropanamide (Scheme 5).

As shown in Table 2, significantly lower ^{18}O label incorporation was observed for 3-phenylpropanamide relative to the starting oxime, indicating that scrambling of this label had occurred (Figure 1). Although butyramide did not ionize under the mass spectrometry conditions, it was possible to determine by ^{13}C NMR spectroscopy that partial incorporation of the ^{18}O label into this amide had occurred. Analysis of the peak attributed to the quaternary carbon showed two peaks due to the presence of both isotopic forms.

Table 2. Change in levels of ^{18}O incorporation upon rearrangement of ^{18}O-labelled 3-phenylpropanaldoxime.

Entry	Catalyst	Loading [mol%]	Oxime **4** atom% ^{18}O[a]	Amide **6** atom% ^{18}O[a]
1	$RhCl(PPh_3)_3$	5	63	37
2[b]	$Ru(PPh_3)_3(CO)H_2$	1	63	22
3	$Pd(OAc)_2$	5	67	39
4	$In(NO_3)_3$	1	63	30
5	$ZnCl_2$	10	63	28
6	$Cu(OAc)_2$	2	67	33

[a] Determined by mass spectroscopy.
[b] Catalytic system also consisted of dppe (0.1 mol%) and PTSA (0.4 mol%).

These results support proposed mechanism B, attack of another molecule of aldoxime on the coordinated nitrile species. This is consistent with previous results from our group for when the catalyst $NiCl_2$ was used in the same ^{18}O label crossover experiment. The results also show that this bimolecular mechanism is universal to all of the catalysts studied. However, it is possible, for some catalytic systems especially those which are competent for nitrile hydration with water, that the mechanism may depend on the catalyst being used.[6]

(iii) Improvements to the efficiency of the $Cu(OAc)_2$ catalyst in the rearrangement reaction: The standard reaction conditions developed within our lab for the copper-catalyzed rearrangement are shown below in Scheme 6.[8]

In order to examine the catalyst efficiency in the rearrangement, the conversion of 4-methylbenzaldox-

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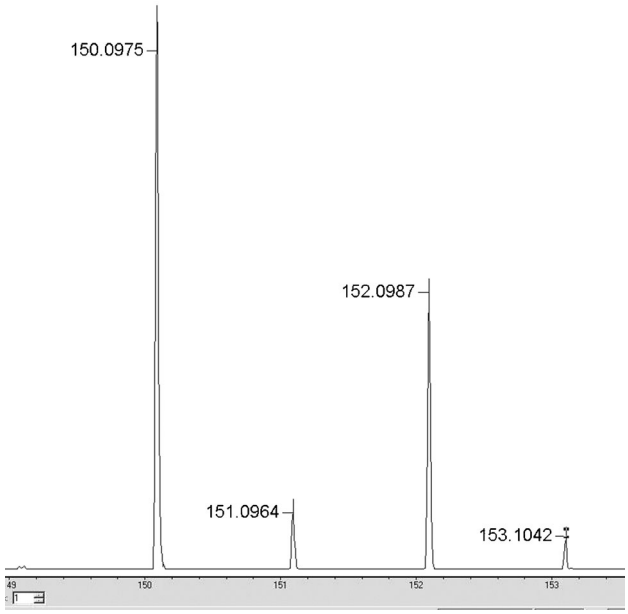
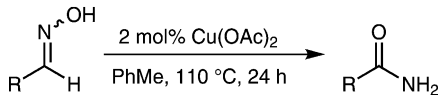


Figure 1. Mass spectrum of the products of the crossover reaction, showing the ratio of ^{16}O ([M+1]=150.0975) to ^{18}O ([M+1]=152.0987) within 3-phenylpropanamide.



Scheme 6. Standard reaction conditions using a copper catalyst.

ime into 4-methylbenzamide was followed over time by ^1H NMR spectroscopy (Table 3).

As shown in Table 3, complete conversion into 4-methylbenzamide can be achieved in the presence of 2 mol% $Cu(OAc)_2$ after 30 min at 110 °C and after 1 hour at the reduced temperature of 80 °C. Examination of the conversions achieved at 110 °C illustrate that there is a non-linear increase in conversion with time and that the initial rate of reaction is comparatively slow. This implies that there is an induction period for catalyst activation at the beginning of the reaction. If initiation of the catalytic cycle is the slow step, it is feasible that the rate-determining step would be initial dehydration of a coordinated aldoxime to the active metal-bound nitrile species whilst hydration of the nitrile species is relatively rapid.

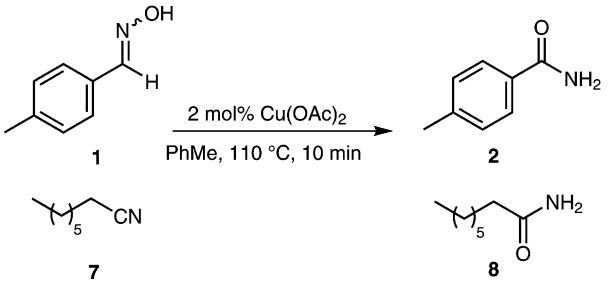
Evidence of this has been reported by Johnson and Miller who found that the reaction can be described by two consecutive pseudo-first order rate constants.[14] They report the first step to be cleavage of the aldoxime C–H bond, which is seen to be dependent on the concentration of the catalyst. This step is also assumed to be the rate-limiting step, as evidenced by the strong kinetic isotope effect seen when a deuterated oxime is used as a substrate. Chang et al. have reported that nitrile additives have a self-acceleration effect on aldoxime rearrangements.[10] Within Chang's study, reaction profiles were obtained for the rearrangement of benzaldoxime into benzamide, which indicated that the initial reaction rate was significantly increased in the presence of nitrile additives. Additionally, it was observed that the total concentration of nitrile remained almost constant throughout the reaction, with the amount of nitrile derived from the aldoxime increasing as the amount of nitrile additive decreased. However, even in the presence of a nitrile additive the rearrangements typically required 6 h to reach completion using a catalytic system of Rh(cod)(IMes)Cl in the presence of a Brønsted acid.

Based on these previous reports and our own findings we reasoned that, if the rate-determining step is initial dehydration of the aldoxime, then the rate of amide formation may be enhanced by performing the rearrangement in the presence of a nitrile additive. The reaction was carried out in the presence of varying amounts of octanonitrile **7** (Scheme 7) to see if any change in reaction rate could be observed (Table 4).

An increase in conversion of 4-methylbenzaldehyde oxime into 4-methylbenzamide was seen to accompany an increase in the mol% of nitrile additive (Table 4). Therefore, it may be concluded that octanonitrile is acting as a rate accelerant in this rearrangement reaction. Although a further nitrile species is generated in the hydration step to complete the catalytic cycle, octanonitrile is itself not regenerated and can therefore not be classified as a catalyst. For every

Table 3. Conversion of 4-methylbenzaldoxime into 4-methylbenzamide over time.

Entry	Time [min]	Temperature [°C]	Conversion [%]
1	30	110	100
2	15	110	34
3	10	110	17
4	240	80	100
5	60	80	100
6	30	80	43



Scheme 7. Copper-catalyzed rearrangement run in the presence of octanonitrile.

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Table 4. Variation of reaction rate with mol% nitrile additive.

Entry	Amount of nitrile [mol%]	Conversion into **2** [%]	Conversion into **8** [%]
1	0	9	–
2	5	14	100
3	10	27	100
4	25	70	100

molecule of octanamide **8** formed in this competing hydration reaction, one molecule of oxime cannot be rearranged to the corresponding amide but instead remains as the nitrile. Therefore, the highest potential conversion is reduced by an amount equivalent to the amount of nitrile additive hydrated.

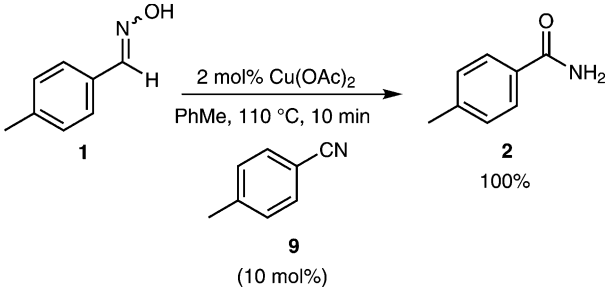
In order to achieve the desired rate acceleration effect without reducing the potential conversion of oxime into amide attainable, the rearrangement of 4-methylbenzaldehyde oxime was performed in the presence of 10 mol% of the corresponding nitrile, 4-methylbenzonitrile **9** (Scheme 8).

After 10 min under these new conditions the reaction was complete, demonstrating a significant rate increase when compared with the reaction run without the nitrile additive, which showed only a 17% conversion into amide after the same length of time.

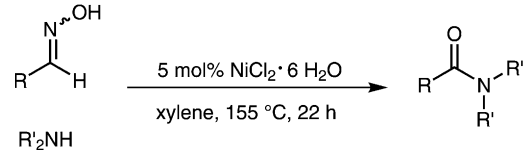
The results of the ^{18}O-labelling studies provide further evidence in support of an aldoxime rearrangement mechanism that proceeds *via* nucleophilic attack of a metal-bound nitrile species by an aldoxime molecule (Scheme 3). It has also been found that such a mechanism is universal to all of the catalysts investigated. Within this mechanism, initial dehydration of a coordinated aldoxime to form a metal-bound nitrile species is thought to be the rate-determining step. This was evidenced by the comparatively slow initial reaction rate observed in the conversion *vs.* time study in conjunction with the rate enhancement observed for rearrangements run in the presence of catalytic quantities of a nitrile.

***(iv) Mechanism studies on the nickel catalyzed acylation of amines with aldoximes*:** We then turned our attention to further probing the mechanism of the nickel-catalyzed acylation of amines using aldoximes (Scheme 9).[12] There are several possible mechanisms where the amine attacks at a different stage of the catalytic cycle (Scheme 10).

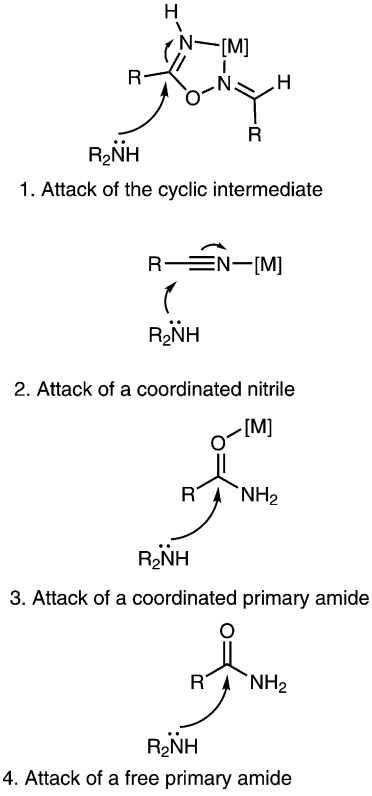
The reaction of benzylamine **10** with butyraldoxime **3** in the presence of 5 mol% $NiCl_2$ was followed over time to see if any significant reaction intermediates could be observed (Table 5). The results clearly show a build up of the primary amide **5** (rearrangement product of butyraldoxime) before the secondary amide **11** is seen in the reaction mixture. Based on this observation it is apparent that the aldoxime is undergoing the rearrangement into the primary amide and it is this species that is then coupling to the amine. Whether it is the free primary amide or the



Scheme 8. Rearrangement of 4-methylbenzaldoxime in the presence of 4-methylbenzonitrile.



Scheme 9. Nickel-catalyzed acylation of amines with aldoximes.



Scheme 10. Proposed mechanisms of secondary amide formation in the nickel-catalyzed acylation of amines with aldoximes.

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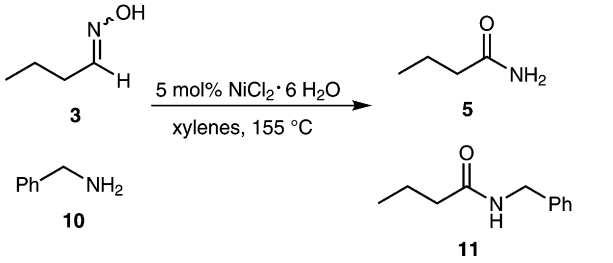
Table 5. Reaction of benzylamine and butyraldoxime over time.

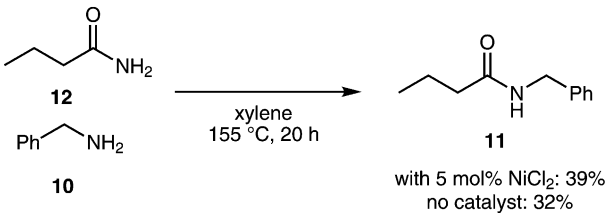


Entry	Reaction time [h]	Conversion into 1° amide **5** [%]	Conversion into 2° amide **11** [%]
1	2	35	18
3	4	48	52
4	6	26	74
5	16	2	98
6	24	4	96

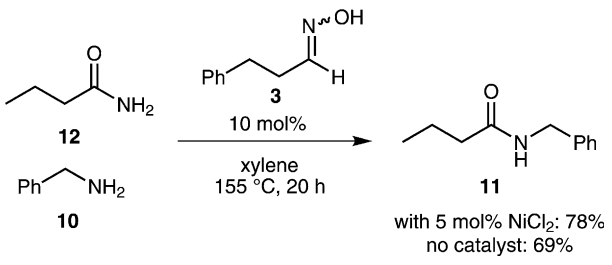
metal-bound primary amide that is attacked was unclear at this stage.

The reaction of butyramide **12** with benzylamine was run with and without the $NiCl_2$ catalyst to see if the metal was involved in the primary amide and amine coupling. In both reactions, a similar conversion into the secondary amide was seen; 39% with the nickel catalyst and 32% without (Scheme 11). This suggests not only that the nickel is not involved in this step of the mechanism but also that direct attack of the amine on the free primary amide is not the major reaction pathway in operation.

When the same reaction was run with a catalytic amount of butyraldoxime, a significant increase in conversion into the secondary amide was observed (Scheme 12).



Scheme 11. Reaction of butyramide and benzylamine.



Scheme 12. Reaction of butyramide and benzylamine in the presence of 10 mol% butyraldoxime.

These results clearly indicate that the oxime is in some way acting catalytically in the reaction between the primary amide and the amine. An increased rate of reaction is seen when the aldoxime species is used in slight excess (compared with the amine), a result which can be justified by the oxime acting catalytically to couple the primary amide and amine. Potentially, this could either be hydrogen bonding activation of the amide by the oxime or by nucleophilic catalysis.

The mechanism of the nickel-catalyzed acylation of amines with aldoximes has been shown to proceed *via* the primary amide (formed by the rearrangement of the aldoxime). The subsequent coupling of the primary amide and amine has been shown to be catalyzed by the aldoxime itself. Further investigation into this interesting property of oximes is currently underway in our laboratory.

Experimental Section

Experimental Procedure I: $^{18}OH_2$ Additive Study

4-Methylbenzaldoxime (0.405 g, 3 mmol) was added to an oven-dried carousel tube along with the appropriate catalyst. ^{18}O-labelled water ($^{18}OH_2$) (0.07 mL, 4 mmol, 97 atom% ^{18}O) and anhydrous toluene (1.5 mL) were added, then the carousel tube was sealed and if necessary purged with nitrogen. The reaction mixture was heated at 110 °C for 24 h, then allowed to cool to room temperature before the solvent was removed under vacuum and the crude reaction mixtures were analyzed by ^{1}H and ^{13}C NMR and mass spectroscopy.

Experimental Procedure II: ^{18}O-Labelled Aldoxime Study

^{18}O-labelled 3-phenylpropanal oxime (0.038 g, 0.25 mmol) and unlabelled butyraldehyde oxime (0.024 mL, 0.25 mmol) were added to an oven-dried carousel tube followed by the appropriate catalyst. The tube was then sealed and if necessary purged with nitrogen for 10 min. Anhydrous toluene (0.5 mL) was then syringed into the tube and the reaction mixture was heated at reflux (110 °C) for 24 h. After allowing the reaction mixture to cool to room temperature, it was filtered through a short plug of Celite, eluting with dichloromethane and was then concentrated under vacuum. The isolated material was analyzed by ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

Experimental Procedure III: Aldoxime-Catalyzed Transamidation

Butyramide (0.087 g, 1 mmol), benzylamine (0.11 mL, 1 mmol) and 3-phenylpropionaldoxime (0.015 g, 0.1 mmol) were added to an oven-dried carousel tube. *p*-Xylene (1 mL) was added to the tube which was then sealed and heated at reflux (155 °C) for 20 h. The reaction mixture was then allowed to cool to room temperature before the solvent

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was removed under vacuum and the crude reaction mixture was analyzed by ^{1}H NMR and ^{13}C NMR spectroscopy.

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