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Significant Self-Acceleration Effects of Nitrile Additives in the Rhodium-Catalyzed Conversion of Aldoximes to Amides: A New Mechanistic Aspect

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Abstract: It was found that the catalytic activity of rhodium complexes was highly sensitive to the type of N-heterocyclic carbene (NHC) ligands in the conversion of aldoximes to amides. Among those species examined, the (cyclooctadiene)rhodium chloride-carbene complex Rh(cod)(IMes)Cl exhibited the highest reactivity when it was employed in combination with a Brønsted acid, thus allowing mild reaction conditions. A significant rate acceleration effect resulting from the addition of nitrile additives was also observed. With the new protocol, the substrate scope of aldoximes has been widely expanded to include sterically congested and electronically varied derivatives. On the basis of detailed mechanistic studies, it is proposed that the reaction proceeds mainly *via* intramolecular electrophilic addition of aldoxime to rhodium-bound nitrile, which is different from the generally postulated two-step route: dehydration of aldoxime to nitrile followed by hydration of the latter intermediate.

Keywords: aldoximes; amides; N-heterocyclic carbenes; rhodium; self-acceleration effect

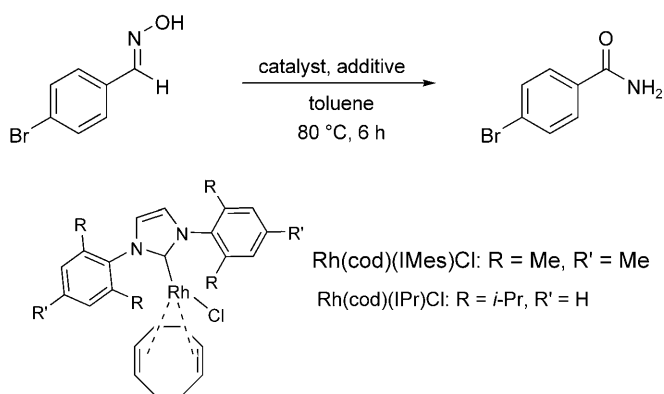
The interconversion between carbonyl compounds is one of the most important transformations that have attracted great interest of organic chemists.^[1] In this context, the conversion of readily available oximes to the corresponding amides has been utilized as a highly versatile and practical synthetic tool.^[2] In fact, ϵ -caprolactam is produced in industry from cyclohexanone oxime for the chemical manufacture of Nylon-6.^[3] However, conventional conditions for the rearrangement usually employ high temperatures and/or strong acidic reagents thus generating by-products.^[4]

To avoid these drawbacks, a range of improved procedures has been disclosed such as methods using supercritical water,^[5] a vapor-phase process,^[6] ionic liquids,^[7] or transition metal catalysis.^[8] Most recently, Mizuno et al. revealed a facile catalyst system of supported rhodium hydroxide for the synthesis of primary amides from aldoximes in water.^[9]

We previously reported that aldoximes can be readily dehydrated under mild conditions to afford nitriles with excellent selectivity when [RuCl₂(*p*-cymene)]₂ was used as a catalyst.^[10a] In line with this research, we tried to develop the direct conversion of aldoximes to amides, and found that the Wilkinson catalyst, RhCl(PPh₃)₃, can carry out this important process.^[10b] However, satisfactory product yields in the latter transformation could be secured only at high temperatures (150 °C) with large amounts of the catalyst. The Rh-catalyzed conversion of aldoxime to amide was assumed to proceed *via* a two-step route: dehydration of aldoxime to nitrile followed by hydration of the latter intermediate.

Described herein is our recent development of a significant improvement of the reaction conditions using an Rh(NHC) catalyst (NHC = N-heterocyclic carbene). More importantly, a significant self-acceleration effect of nitrile additives was observed leading to a new mechanistic proposal that the conversion proceeds mainly *via* intramolecular attack of aldoxime onto metal-bound nitrile, which is different from the generally recognized two-step route.

At the outset of our studies, we tried to improve the reaction conditions in the transformation of 4-bromobenzaldoxime to 4-bromobenzamide (Table 1).^[11] While no conversion was observed in the absence of metal catalysts at 80 °C, the combined use of certain Rh metal species and Brønsted acids resulted in detectable reactivity. For example, when 1.0 mol% of [Rh(cod)Cl]₂ (cod = 1,5-cyclooctadiene) was used along with *p*-toluenesulfonic acid (TsOH/H₂O,

Table 1. Screen of reaction conditions.^[a]

Entry	Catalyst	Additive	Yield ^[b] [%]
1	–	–	<1
2	$\text{RhCl}(\text{PPh}_3)_3$	–	<1
3	$[\text{Rh}(\text{cod})\text{Cl}]_2$	–	5
4	$[\text{Rh}(\text{cod})\text{Cl}]_2$	TsOH/H ₂ O	28
5	–	TsOH/H ₂ O	<1
6	$\text{Rh}(\text{cod})(\text{IMes})\text{Cl}$	TsOH/H ₂ O	90 ^[c]
7 ^[d]	$\text{Rh}(\text{cod})(\text{IMes})\text{Cl}$	TsOH/H ₂ O	<1
8	$\text{Rh}(\text{cod})(\text{IMes})\text{Cl}$	–	17
9	IMes	–	<1
10	IMes	TsOH/H ₂ O	<1
11	$\text{Rh}(\text{cod})(\text{IPr})\text{Cl}$	TsOH/H ₂ O	75 ^[c]

^[a] Reaction conditions: A mixture of 4-bromobenzaldoxime (1.0 mmol), Rh catalyst (1.0 mol%), and additive (10 mol%) in solvent (0.25 mL) was stirred for 6 h at 80 °C.

^[b] NMR yield (internal standard: 1,3-benzodioxole).

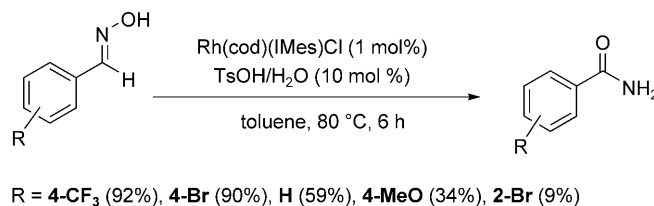
^[c] Isolated yield.

^[d] DMF was used as a solvent instead of toluene.

10 mol%), 4-bromobenzamide was obtained in 28% yield (entry 4).^[12] On the other hand, the acid alone did not carry out the reaction (entry 5). A significant improvement was observed especially when NHC-derived rhodium catalysts were employed in combination with a Brønsted acid.^[13]

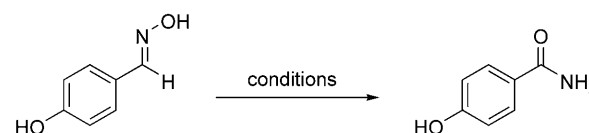
The most effective species among those Rh-NHCs examined was $\text{Rh}(\text{cod})(\text{IMes})\text{Cl}$ in toluene (entry 6).^[14] On the other hand, the same reaction in polar solvents was almost ineffective (entry 7) and the use of $\text{Rh}(\text{cod})(\text{IPr})\text{Cl}$ resulted in reduced yield under the otherwise identical conditions (entry 11).^[15] It should be noted that the Rh-NHC species utilized in this study are easily prepared and highly stable to air, and the amide forming-reaction can be carried out under ambient conditions without requiring an inert atmosphere.

When the optimized conditions were next applied to a range of aldoximes, it was immediately found that certain types of substrates were rather slowly reacting to afford only poor yields (Scheme 1). It turned out that both electronic and steric property of aldox-

**Scheme 1.** (Rh-NHC)-catalyzed reaction of aldoximes.

ime substrates display a significant influence on the reaction efficiency. In fact, whereas the reaction was best performed with electron-withdrawing benzaldoximes, those with electron-rich substrates displayed lower efficiency (e.g., 34% yield from 4-methoxybenzaldoxime). In addition, steric congestion around the reacting site gave significantly lower yields (e.g., 9% from 2-bromobenzaldoxime).

During the course of our subsequent studies, we unexpectedly found that the addition of catalytic amounts of nitrile compounds resulted in a significant increase of the reaction efficiency (Scheme 2). For in-

**Conditions A (50% yield):**

$\text{Rh}(\text{cod})(\text{IMes})\text{Cl}$ (1 mol %), TsOH/H₂O (10 mol %)
toluene, 80 °C, 6 h

Conditions B (99% yield):

Conditions A + 4-hydroxybenzonitrile (0.05 equiv.)

Scheme 2. Nitrile effect on the conversion.

stance, when 4-hydroxybenzaldoxime was treated with the above optimized conditions (conditions A), the desired amide was obtained in 50% yield after 6 h at 80 °C. In contrast, a dramatically increased yield (99%) was achieved by adding 0.05 equivalents of 4-hydroxybenzonitrile to the reaction mixture (conditions B). Interestingly, the same amount of the added nitrile (0.05 equivalents to the amide product) was recovered after the reaction.

The additive effect of nitrile was quantitatively analyzed by obtaining reaction profiles in the conversion of benzaldoxime to benzamide under different conditions (Figure 1). It is noteworthy that the initial rate is significantly increased by the presence of nitrile additive. For instance, while a complete conversion was observed within 6 h in the presence of benzonitrile (5 mol%), the initial reaction rate was much lower without the nitrile complement giving only 19% con-

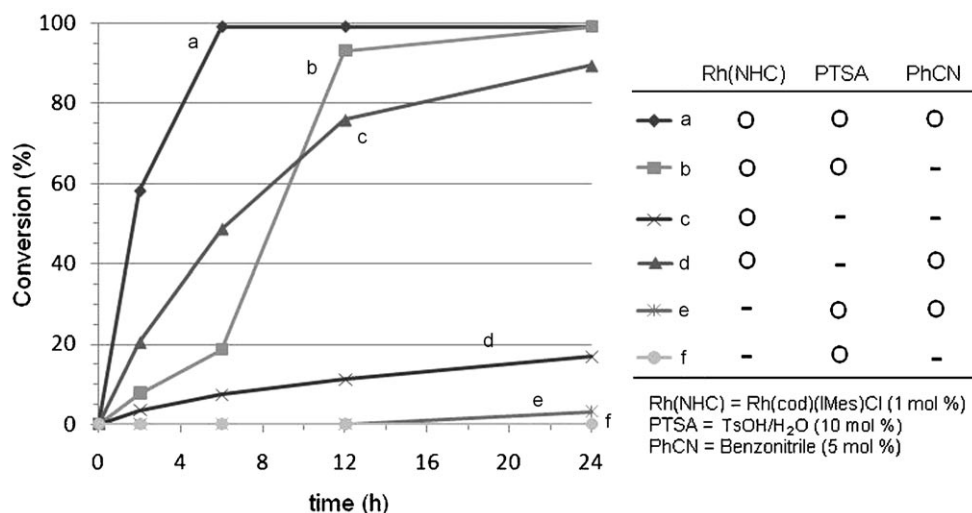


Figure 1. Reaction profiles in the conversion of benzaldoxime to benzamide under various conditions.

version within the same reaction period (6 h) although it reaches a full conversion after 24 h.

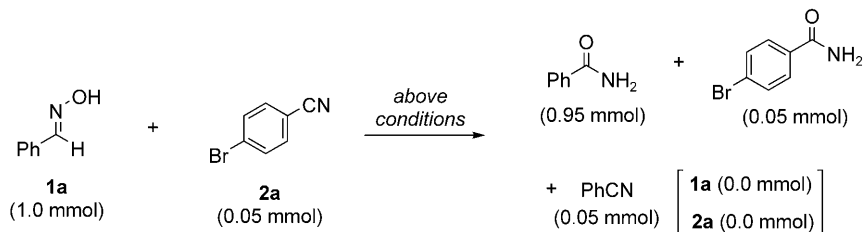
On the other hand, no conversion was observed with ketoximes or *O*-alkylaldoximes. Although hydration of nitriles to amides is known to be catalyzed by rhodium^[9b,12a,16] or other metal species,^[17] nitrile was inert to the hydration when it was allowed to react with water in the presence of [Rh(cod)(NHC)Cl].

When benzaldoxime (**1a**) was subjected to the reaction conditions in the presence of 0.05 equivalents of 4-bromobenzonitrile (**2a**), a mixture of two amides of benzamide and 4-bromobenzamide was obtained in addition to benzonitrile in a quantitative manner (Scheme 3).^[18]

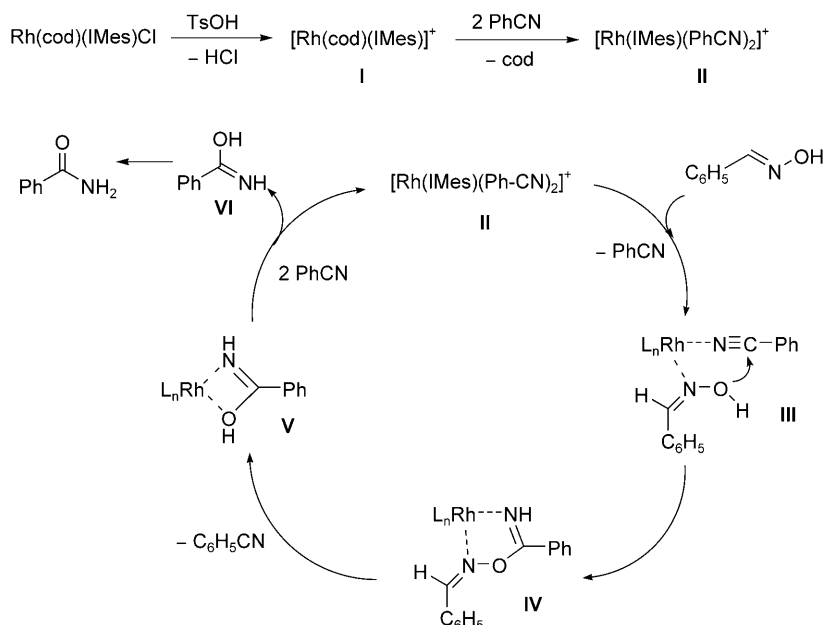
The above results in combination with the reaction profiles suggest that *the main operating mechanistic path of the present process may be different from the generally accepted two-step pathway*, in which dehydration of aldoximes to nitriles was assumed to occur first followed by hydration of the nitrile intermediates.^[9b] In order to accommodate the nitrile effects in our present case, the following mechanistic proposal is presented using benzaldoxime and benzonitrile as a model substrate and additive, respectively (Scheme 4).

It is first assumed that the neutral rhodium precursor is converted to its cationic species **I** by the action of a Brønsted acid,^[19] and then the nitrile additive is associated with the cationic Rh complex giving **II** to release a cod ligand.^[20] We propose that the nitrogen atom of the aldoxime coordinates to the Rh metal center to afford **III**^[21] followed by an intramolecular attack of the aldoxime oxygen onto the metal-bound nitrile leading to an *O*-(iminophenylmethyl)oximate rhodium chelate **IV**.^[22] Alternatively, although aldoximes can bind to the metal complex prior to nitrile as reported by Leusink,^[21] the observed rate acceleration effects of nitrile additives should favor the formation of **II** followed by oxime coordination to form **III**.

In fact, it is known that metal-bound nitrile is activated to a significant extent making it more electrophilic,^[23] thus facilitating subsequent oxime addition *albeit with a stoichiometric manner*.^[24] Next, it is proposed that a nitrile molecule is released from the iminoacyl species **IV** to provide a putative benzimidic rhodium chelate **V**.^[9] It can be postulated that two nitrile ligands then exchange a bidentate benzimidic acid from **V** releasing benzimidic acid **VI** that is readily tautomerized to benzamide. The present mechanistic proposal might also be supported by the observa-



Scheme 3. Cross-over reaction.



Scheme 4. Nitrile-mediated mechanistic proposal of the Rh-catalyzed aldoxime conversion.

tion that nitriles were inert to the direct hydration with water in the absence of aldoximes.^[18]

To further verify the new mechanistic pathway, the total amount of nitriles in the conversion of an aldoxime to an amide in the presence of a different type of nitrile additive was monitored over the reaction progress (Figure 2). While the amount of the added nitrile decreased as it was converted to the corresponding amide, the amount of the nitrile that corresponds to the starting aldoxime increased. As a result, the total amount of the two nitriles remained almost constant along the reaction progress. It can be postulated that this result strongly supports our proposal of the ni-

trile-assisted amide formation since the total concentration of nitriles stays constant only under the current path among other possible mechanistic alternatives.

Although we argue that the nitrile effect may originate from the mechanistic consideration in Scheme 4, other possibilities cannot be completely excluded at least for some types of aldoxime substrates, in which the conventionally accepted two-step pathway would also be accompanied to operate under either metal-mediated or metal-free conditions.

The new protocol of the nitrile-facilitated synthesis of amides could be successfully applied to a range of

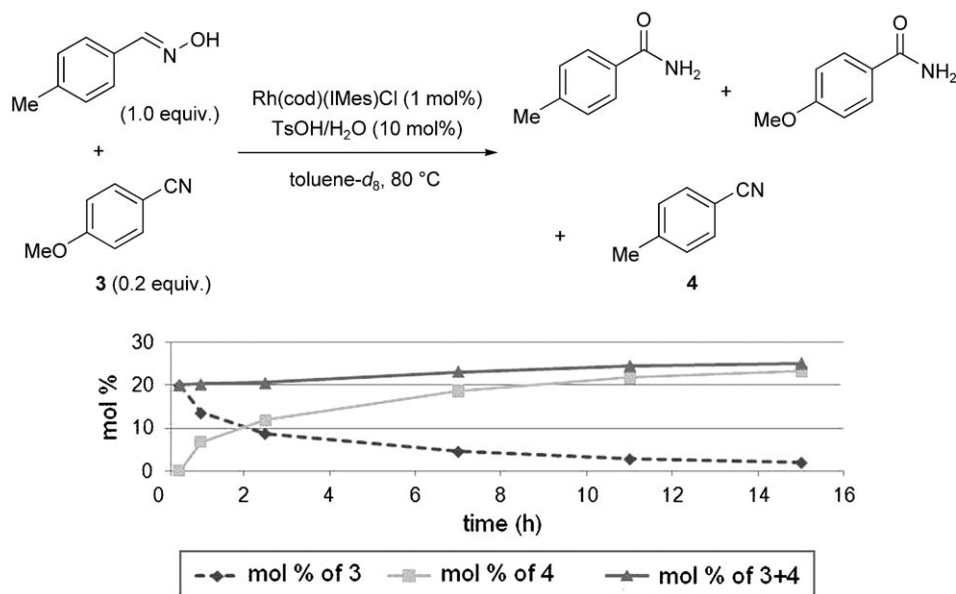


Figure 2. Concentration profile of the added and *in situ* generated nitriles.

Table 2. Rh(NHC)-Catalyzed conversion of aldoximes to amides in the absence and presence of nitriles.^[a]

$\text{R}-\text{C}(\text{OH})=\text{N}-\text{H} \xrightarrow[\text{Toluene, 80 } ^\circ\text{C, 6 h}]{\text{Rh(cod)(IMes)Cl (1 mol\%)} \atop \text{TsOH/H}_2\text{O (10 mol\%)}} \text{R}-\text{C}(=\text{O})-\text{NH}_2$			
Entry	R	Yield ^[b] [%]	
		No Nitrile	Nitrile Additive ^[c]
1	(4-NO ₂)C ₆ H ₄	62	96
2	(4-Cl)C ₆ H ₄	70	99
3	(4-CF ₃)C ₆ H ₄	92	99
4	(4-Br)C ₆ H ₄	90	99
5	C ₆ H ₅	59	95
6	(4-MeO)C ₆ H ₄	34	88
7	(3-MeO)C ₆ H ₄	48	95
8	(2-Br)C ₆ H ₄	9	90
9	2-Thienyl	63	99
10	(4-HO)C ₆ H ₄	50	99
11 ^[d]	CH ₃ (CH ₂) ₅	50(92)	51 (94)

^[a] Reaction conditions: aldoxime (1.0 mmol), Rh catalyst (1.0 mol%), and TsOH/H₂O (10 mol%) in toluene (0.25 mL) for 6 h at 80 °C.

^[b] Isolated yield.

^[c] Complementary nitrile (0.05 equiv. to each aldoxime) was added.

^[d] Yields in parenthesis were obtained from reactions running for 12 h at 80 °C under otherwise identical conditions.

substrates (Table 2). In each case, the complementary nitrile was added in a catalytic amount (0.05 equivalents to the corresponding aldoximes). The nitrile additive effect was displayed with most arylaldoximes examined although the extent of the effect was dependent on the substituents. For instance, the yield of 2-bromobenzamide was dramatically increased by adding catalytic amounts of 2-bromobenzonitrile (entry 8). In general, substrates bearing electron-donating substituents showed more pronounced nitrile effects. Heteroaromatic amides could also be obtained in excellent yield using the developed protocol (entry 9).

Quite interestingly, in contrast to arylaldoximes, aliphatic reactants were not much influenced by the presence of nitrile additives (entry 11). However, it should be mentioned that *satisfactory yields of aliphatic amides can be secured by allowing the transformation to run for a longer reaction time irrespective of the presence of nitrile additives.*

Further studies would be necessary to reason about the less pronounced nitrile effects in the case of aliphatic aldoximes. However, at the moment, it can be speculated that coordination of an aliphatic nitrile to the putative aliphatic iminoacyl rhodium species (**V** in Scheme 4) would be less facile compared to the aryl analogues. Alternatively, coordination of aliphatic oximes to the Rh metal center can be more favored

over aliphatic nitriles to result in diminished effects of nitrile additives.^[21]

In summary, a new efficient procedure for the formation of amides from aldoximes has been developed using the combined use of Rh(cod)(IMes)Cl, a Brønsted acid, and a complementary nitrile. It is proposed that the conversion proceeds mainly *via* intramolecular electrophilic addition of aldoxime to rhodium-bound nitrile, which is different from the generally postulated two-step route of dehydration of aldoxime to nitrile followed by hydration of the latter intermediate.

Experimental Section

General Procedure for the Rh-Catalyzed Conversion of Aldoximes to Amides

To an oven-dried screw-top vial were added benzaldoxime (121 mg, 1.0 mmol), Rh(cod)(IMes)Cl (5.5 mg, 0.01 mmol), benzonitrile (5.2 mg, 0.05 mmol), *p*-toluenesulfonic acid monohydrate (19.0 mg, 0.1 mmol) and toluene (0.25 mL). The reaction mixture was stirred for 6 h at 80 °C and then diluted with ethyl acetate. Organic solvents were removed under vacuum and then benzamide was isolated by a silica gel column chromatography (ethyl acetate/*n*-hexane, 1:1); yield: 115 mg (95%).

Supporting Information

Experimental details and spectroscopic characterization of selected compounds are given in the Supporting Information.

Acknowledgements

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