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Communication

Rh(III)-catalyzed oxidative amidation of aldehydes: An efficient route to *N*-pyridinamides and imides

Wei Dai ^{a,*}, Yuchen Liu ^a, Tao Tong ^a, Xingwei Li ^b, Fang Luo ^{a,#}^a College of Chemistry and Life Sciences, Zhejiang Normal University, Jinhua 321004, Zhejiang, China^b Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, Liaoning, China

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ABSTRACT

A novel Rh(III)-catalyzed direct amidation of aldehydes featuring Ag₂CO₃ as the oxidant is described. This selective procedure provides a variety of *N*-pyridinamides and imide derivatives in good yields.

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The amide group constitutes the core unit of a large number of natural products and other biologically active organics. The generation of amide bonds in molecular frameworks is of paramount interest in organic synthesis and this functional group is widely used in the production of pharmaceuticals, fine chemicals, and polymers [1–4]. Therefore, extensive efforts have been focused on finding the best reaction conditions for amide preparation [5–7]. The typical method for the preparation of amides is to couple activated carboxylic acid derivatives and amines [8,9]. However, tedious reaction conditions and the reactivity of the activated carboxylic acid derivatives to hydrolysis limit the scope of its usage and lead to unwanted side reactions [10,11]. Several other amide formation methods have been developed to overcome these shortcomings [12–18], including oxidative amidation of alcohols with amines [19–21] and amidation of aldehydes with azides [22–24]. Among

them, the direct amidation of aldehydes with amines [25–28] and the transition-metal-catalyzed direct reactions of aldehydes with amines [16,29–31] have invoked tremendous interest. A limited number of rhodium-catalyzed direct reactions of aldehydes with amines and sulfamides have been reported [32–37]. Beller's group [32] first reported rhodium as an attractive catalyst for the Rh(I)-catalyzed amination of aldehydes. However, high temperature, a large amount of aldehyde reagent and amine by-products limit the utility of this method (Scheme 1(a)).

Recently, Rh(III) catalysts, especially Cp*Rh(III) compounds, have been reported to be powerful catalysts for C–N bond formation with high efficiency and good functional group tolerance [38–40]. Nevertheless, the employment of Cp*Rh(III) in transition metal-catalyzed oxidative amidation is rare. Based on the aforementioned works, we believe that amino alcohols,

* Corresponding author. Tel: +86-579-82296655; Fax: +86-579-82282610; E-mail: daiwei@zjnu.cn# Corresponding author. Tel: +86-579-82296655; Fax: +86-579-82282610; E-mail: luofang19@zjnu.cn

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(a) Beller's work about Rh(I)-catalyzed the reactions of aldehydes with amines

(b) Our proposal in the Rh(III)-catalyzed reactions of amino alcohol to amide

(c) Our work about Rh(III)-catalyzed the reactions of aldehydes with amines

Scheme 1. The Rh-catalyzed direct reactions of aldehydes with amines.

generated from aldehydes and amines, could undergo Rh(III)-catalyzed oxidation for conversion into amide products [41–43] (Scheme 1(b)). Herein, we report the Rh(III)-catalyzed oxidative amidation of aldehydes in the presence of oxidants which is useful for the synthesis of *N*-pyridinamides and imides (Scheme 1(c)).

In this study, we attempted to synthesize *N*-(2-pyridyl) amides, which widely used as pharmaceuticals [44,45], from *N*-(2-pyridyl) amines and aldehydes. Preliminary investigations were carried out by employing benzaldehyde (**1a**) and pyridin-2-amine (**2a**) as the model substrates. The desired product (**3aa**) was detected in trace amounts when **1a** and **2a** were treated with 4.5 mol % of [RhCp*(MeCN)₃](SbF₆)₂ in acetone at 100 °C for 12 h, while the addition of 2 equiv of Cu(OAc)₂ or Ag₂CO₃ as the oxidant led to a better yield (Table 1). The optimal reaction conditions for the Rh(III)-catalyzed oxidative amidation of aldehydes were identified as follows: 4.5 mol % of [RhCp*(MeCN)₃](SbF₆)₂, 2 equiv of Ag₂CO₃ in 2 mL acetone, 100 °C, and 12 h.

The same process was also tried with pyridin-2-amine, and the results are summarized in Table 2. As expected, various *N*-(2-pyridyl) amines worked well under these reaction conditions. In addition, remarkable functional group tolerability was observed with this Rh catalyst. Particularly, cyano- and halogen-substituted pyridin-2-amines reacted well with benzalde-

hyde (Table 2, **3ae–3ag**). The cyano group and halogen atom remained intact and could be valuable for further manipulation. The electronic properties of substituents on the pyridine ring significantly affected the amidation. Electron-withdrawing substituents on the pyridine ring were beneficial for the transformation, whereas electron-donating substituents decreased the yield (Table 2, **3ad** and **3ae**). Moreover, introduction of steric hindrance in pyridin-2-amine had no obvious effect on the outcome (Table 2, **3ab–3ad**). Different positions of substituted methylpyridin-2-amine all led to good yields. For example, reaction products **3ab**, **3ac**, and **3ad** had yields of 86%, 90%, and 79%, respectively. The methodology also worked well with aryl-substituted benzaldehydes and heteroaromatic aldehydes (Table 2, **3bb–3eb**). An *N*-heterocyclic amine such as isoquinolin-1-amine was also found to react with benzaldehyde, producing the corresponding amide with 55% yield (Table 2, **3ah**).

After a broad scope of *N*-(2-pyridyl) amides were synthesized, we further explored the synthesis of various imides. Under the standard conditions, a number of amides were then varied by using **1a** as the coupling partner, and as expected, the substituted primary benzamide derivatives and aliphatic amide such as acetamide reacted to afford the final products with moderate yields (Table 3, **3ai–3an**).

In summary, we have developed an efficient rhodium(III)-catalyzed amidation process using Ag₂CO₃ as the oxidant. This oxidative amidation of the aldehyde afforded the amides or amide derivatives in good yields. Many types of amide derivatives were prepared: *N*-pyridinamides, *N*-isoquinolinamides, and imides. This new catalyst worked remarkably well with a range of functional groups, and should be very useful for organic synthesis.

Table 1

The reaction of 1a and 2a catalyzed by Rh-based catalyst.

Reaction scheme showing the synthesis of **3aa** from **1a** and **2a**.

Entry	Catalyst	Oxidant	Solvent	Yield ^a (%)
1	[RhCp* (MeCN) ₃](SbF ₆) ₂	—	acetone	<10
2	[RhCp* (MeCN) ₃](SbF ₆) ₂	Cu(OAc) ₂	acetone	65
3	[RhCp* (MeCN) ₃](SbF ₆) ₂	Cu(OAc) ₂	CH ₃ CN	45
4	[RhCp* (MeCN) ₃](SbF ₆) ₂	Cu(OAc) ₂	DCM	46
5	[RhCp* (MeCN) ₃](SbF ₆) ₂	Ag ₂ CO ₃	acetone	84 ^b (75)
6	—	Ag ₂ CO ₃	acetone	<5

Reaction conditions: **1a** (1.2 mmol), **2a** (1 mmol), catalyst (4.5 mol %), oxidant (2 eq.), solvent (2 mL), 100 °C, 12 h.

^a Isolated yield.

^b 80 °C.

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Table 2Synthesis of *N*-(2-pyridyl) amides catalyzed by Rh-based catalyst.

Substrate 1	Substrate 2	Product 3	Yield ^a (%)	Substrate 1	Substrate 2	Product 3	Yield ^a (%)
1a			86		2b		74
1a			90		2b		86
1a			79		2b		58
1a			93		2b		80
1a			84	1a			55
1a			95				

Reaction conditions: substrate **1** (1.2 mmol), **2** (1 mmol), [RhCp*([MeCN]₃)](SbF₆)₂ (4.5 mol%), Ag₂CO₃ (2 eq.), acetone (2 mL), 100 °C, 12 h.^a Isolated yield.**Table 3**

Synthesis of imides catalyzed by Rh-based catalyst.

Substrate 2	Product 3	Yield ^a (%)	Substrate 2	Product 3	Yield ^a (%)
		50			54
		55			40
		42			42

Reaction conditions: **1a** (1.2 mmol), **2** (1 mmol), [RhCp*([MeCN]₃)](SbF₆)₂ (4.5 mol %), Ag₂CO₃ (2 eq.), acetone (2 mL), 100 °C, 12 h.^a Isolated yield.turvedi V, Sinha S, Mishra N N, Shukla P K, Tripathi R P J. *Comb Chem*, 2009, 11: 422[5] Sheng G Z, Zhang W. *Chin J Org Chem* (盛国柱, 张伟. 有机化学), 2013, 33: 2271[6] Yang M, Li M, Zheng H J, Li X J. *Chin J Catal* (杨敏, 李敏, 郑宏杰, 李贤均. 催化学报), 2005, 26: 175[7] Hu J J, Zuo X J, Huang H M. *Chin J Catal* (胡金金, 左秀锦, 黄汉民. 催化学报), 2013, 34: 1644

Graphical Abstract

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Wei Dai*, Yuchen Liu, Tao Tong, Xingwei Li, Fang Luo*

Zhejiang Normal University; Dalian Institute of Chemical Physics, Chinese Academy of Sciences

A novel Rh(III)-catalyzed direct amidation of aldehydes is described, featuring Ag_2CO_3 as the oxidant. Many types of amide derivatives were prepared: *N*-pyridinamides, *N*-isoquinolinamides, and imides.

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铑(III)催化的醛的氧化胺化：一种有效的构建*N*-吡啶酰胺及酰亚胺的合成方法代伟^{a,*}, 刘玉臣^a, 童涛^a, 李兴伟^b, 罗芳^{a,#}^a浙江师范大学化学与生命科学学院, 浙江金华321004^b中国科学院大连化学物理研究所, 辽宁大连116023

摘要: 描述了一种采用三价铑催化的醛的氧化胺化反应, 利用 Ag_2CO_3 作为氧化剂. 通过该方法可以以良好的收率合成各种类型的*N*-吡啶酰胺及酰亚胺.

关键词: 三价铑催化; 氧化胺化; 醛; *N*-吡啶酰胺; 酰亚胺

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*通讯联系人. 电话: (0579) 82296655; 传真: (0579) 82282610; 电子信箱: daiwei@zjnu.cn

#通讯联系人. 电话: (0579) 82296655; 传真: (0579) 82282610; 电子信箱: luofang19@zjnu.cn

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酰胺基团是许多天然产物及具有生物活性化合物的核心结构单元. 酰胺键在有机合成领域具有重要意义, 已广泛应用于药物、精细化学品及高分子材料的生产中^[1–4]. 因此, 人们在探索酰胺合成反应的最佳条件下做了大量的努力^[5–7]. 酰胺的典型制备方法是通过羧酸衍生物和胺来合成^[8,9]. 然而, 羧酸衍生物易水解和反应条件的苛刻及副产物的产生使反应的范围受到了限制^[10,11]. 随后许多克服此缺点的合成方法得到了大量发展^[12–18], 其中包括醇与胺的氧化酰胺化^[19–21]以及醛与叠氮化物的酰胺化反应等^[22–24]. 在此之中, 醛与胺的直接酰胺化^[25–28]及过渡金属催化的醛与胺的酰胺化反应^[16,29–31]受到了极大的关注. 据报道, 通过铑催化可以实现酰胺和磺酰胺与醛的反应^[32–37]. 其中, Beller课题组首先报道了一价铑催化的醛与胺的反应. 然而, 较高的温度, 过量醛试剂的使用及胺副产物的产生限制了该方法的应用(图式1(a)).

最近, 三价铑催化, 尤其是 $\text{Cp}^*\text{Rh(III)}$ 化合物, 具有高活性和良好的官能团兼容性成为实现C–N键形成的有效催化剂^[38–40]. 然而, $\text{Cp}^*\text{Rh(III)}$ 在过渡金属催化的氧化酰胺化反应中的研究却很罕见. 基于上述工作, 我们相信由醛和酰胺产生的氨基醇可接受三价铑的催化氧化转换为酰胺化合物^[41–43](图式1(b)). 本文中, 我们设计了这样的合成方法, 在氧化剂的存在下, 三价铑催化醛的氧化酰胺化反应用于合成 N -吡啶酰胺和酰亚胺(图式1(c)).

在本研究中, 我们尝试利用 N -(2-吡啶基)酰胺和醛合成被广泛用于药物领域的 N -(2-吡啶基)酰胺^[44,45]. 最初研究中, 采用苯甲醛(**1a**)和吡啶-2-胺(**2a**)作为反应模型进行反应. 当反应物**1a**和**2a**在4.5%摩尔的 $[\text{RhCp}^*(\text{MeCN})_3](\text{SbF}_6)_2$ 及丙酮溶液中反应12 h, 可以观察到少量的目标产物**3aa**, 而当体系中加入2当量的乙酸铜或碳

酸银作氧化剂时产物收率有了显著提高(表1). 因此, 该三价铑催化的醛的氧化酰胺化反应的最佳条件为: $[\text{RhCp}^*(\text{MeCN})_3](\text{SbF}_6)_2$ 摩尔分数4.5%, 碳酸银2当量, 丙酮2 mL, 100 °C, 反应12 h.

用同样的方法与其他吡啶-2-胺反应, 结果总结在表2中. 正如预期的那样, 各种 N -(2-吡啶基)酰胺在该反应条件下都能顺利进行, 该催化剂表现了优异的官能团兼容性. 值得指出的是, 氰基和卤素取代的吡啶-2-胺与苯甲醛反应良好(表2, **3ac–3ag**). 在此反应中, 具有重要合成价值的氰基和卤原子很好地得到了保留, 有利于进一步的合成研究. 在该酰胺化反应中, 吡啶环上取代基的电子效应对反应有一定的影响. 吡啶环上的吸电子基团有利于该反应, 而给电子基团却使得产物收率降低(表2, **3ad**和**3ae**). 同时, 吡啶-2-胺上的位阻效应表现得并不明显(表2, **3ab–3ad**). 不同位置取代的吡啶-2-胺都能得到良好的收率. 例如, 产物**3ab**、**3ac**和**3ad**在该反应中可以分别得到86%, 90%和79%的收率. 再者, 该方法对不同芳基和杂环取代的醛类底物也都适用(表2, **3bb–3eb**). 此外, 其他 N -杂环胺类如异喹啉-1-胺与苯甲醛反应, 可以顺利地得到相应的酰胺55%(表2, **3ah**).

在完成对大量类型 N -(2-吡啶基)酰胺的合成后, 我们进一步探讨酰亚胺的合成. 在标准条件下, 不同的酰胺底物用于与醛**1a**偶联, 而且跟预期一样, 取代的苯甲酰胺衍生物和脂肪族酰胺例如乙酰胺都能以中等收率得到目标化合物(表3, **3ai–3an**).

本文发展了一种使用三价铑作为催化剂, 碳酸银作为氧化剂, 醛作为底物的酰胺化反应. 该醛的氧化酰胺化反应能以良好的收率得到酰胺和酰胺衍生物. 同时, 许多类型的酰胺衍生物得以合成: N -吡啶酰胺, N -异喹啉酰胺和酰亚胺. 该催化体系与多种官能团化合物兼容, 可被广泛用于有机合成领域.