

Letter

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Rhodium-Catalyzed Oxidative Amidation of Sterically Hindered Aldehydes and Alcohols

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ABSTRACT: A rhodium-catalyzed oxidative amidation reaction has been developed with sterically hindered aldehydes and alcohols for the synthesis of amides containing a quaternary carbon at the alpha position. A variety of amine nucleophiles, both aliphatic and aromatic, are employed and afford the corresponding amides in good to excellent yields. Finally, mechanistic studies are performed to gain insight into both catalytic cycles. *Keywords: rhodium, oxidation, amidation, hindered, amine, aniline*

Amides are one of the most important functional groups in organic chemistry, commonly found in natural products, pharmaceuticals and agrochemicals.¹ Amide synthesis has been traditionally accomplished via the coupling of carboxylic acids and amines, using highly reactive acid chlorides, anhydrides, or coupling reagents.² This method, while effective, generates large amounts of high molecular waste, which led the American Chemical Society Green Chemistry Institute to select 'amide formation avoiding poor atom economy reagents' among the most important tasks facing organic chemists.3 In recent years, metal-catalyzed oxidative amidation of aldehydes and alcohols has emerged as a powerful alternative to traditional methods.⁴ However, sterically hindered substrates have proven to be particularly challenging while less nucleophilic amines, such as anilines, give significantly diminished yields. Reactivity toward more complex compounds like heterocycles has also been identified as an area for improvement.4e



Scheme 1. Unsuccessful amidation of pivaldehyde⁵

Catalytic amidation of aldehydes with amines, a method pioneered by Beller,^{6a} is an attractive, atom-economical method for amide synthesis. Significant progress has been made allowing for broader substrate scope.⁶ Nevertheless, sterically hindered aliphatic aldehydes^{6c-e} and anilines^{6a-b} usually give significantly lower yields. Aldehydes with α -disubstituted carbons have not been reported in this reaction; amides containing α -quaternary carbon have been prepared using less atom-economical methods from Nchloroamines7 or malonitriles.8 We recently reported a rhodiumcatalyzed oxidative amidation of allylic alcohols and aldehydes under biphasic conditions to convert amines and anilines to amides. Substrates with mono-substitution at the alpha position were well tolerated.9 To assess the effectiveness of this method with a more hindered aldehyde, pivaldehyde and aniline were subjected to the reported reaction conditions; however, only the corresponding imine was observed (Scheme 1). By removing water from the setup, the desired product was generated in 56% yield (Table S1, entry 1). Ligand screening revealed diphenylphosphinobutane

(dppb) as the most effective (Table S1, entry 4) and further optimization showed that lower equivalents of amine and oxidant were effective in this transformation (entries 11-16).

These optimized conditions were applied to a reaction of pivaldehyde with morpholine which generated a very small amount of product. A recent report has indicated that different conditions are often required for aliphatic and aromatic amines.^{6k} In our system, optimization showed that a stronger base, Cs₂CO₃, slightly improved yield (Table S2, entries 1-7). Unfortunately, H₂ was not observed to form under the reaction conditions and 2.0 equivalents of methyl methacrylate (MMA) were required to act as a hydrogen acceptor (entries 8-14). Although the addition MMA reduces the atom economy of the transformation, it is an inexpensive commodity chemical used in the synthesis of various polymers and generates the easily removed, low molecular weight methyl isobutyrate as the sole byproduct. Using this new combination, several ligands could be employed (entries 15-23); however, tricyclohexylphosphine, an effective and relatively inexpensive ligand, was chosen for scaling up. These conditions were effective in the amidation reaction of pivaldehyde with aliphatic amines, both secondary and primary.

We next explored the amine scope for the amidation reaction of pivaldehyde (Table 1). Anilines bearing electron donating (**3ab**) or electron withdrawing groups (**3ac**) were effective nucleophiles. Aryl chlorides (**3ad**) and *ortho*-substitution (**3ae**) were also tolerated. Primary aliphatic amines generated products in moderate to good yields, including α -branched substrate (**3aj**). When enantiomerically pure **2j** was used, the product **3aj** was obtained with 98% enantiospecificity. A variety of secondary aliphatic amine, both cyclic and acyclic (**3ak**) were successfully employed, generating the tertiary amide products in good to very good yields, except for the seven-membered ring **3ar**. This low yield could be explained by the increased steric bulk of **2r** compared to the analogous sixmembered ring **2q**. Heterocyclic amines were converted to amides in good yields.

Encouraged by this broad amine scope, we were eager to explore the aldehyde scope (Table 2). Unfortunately, any increase in the size of the aldehyde led to significantly diminished yield (**3ba**) or no reaction (**3ca**). In the case of **3ba**, the remaining mass balance was accounted for by the corresponding imine. Optimization

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^a Isolated yield. Condition A: pivaldehyde (0.64 mmol, 1.0 equiv), aniline (2.5 equiv), [Rh(COD)₂]BF₄ (3.0 mol %), dppb (3 mol %), CsOAc (1.5 equiv), styrene (2.0 equiv), THF (1.4 mL); Condition B: pivaldehyde (0.64 mmol, 1.0 equiv), amine (2.5 equiv), [Rh(COD)₂]BF₄ (3.0 mol %), PCy₃ (6 mol %), Cs₂CO₃ (1.5 equiv), MMA (2.0 equiv), THF (1.4 mL). ^b 1.5 equiv amine, 10 h. ^c 100 °C ^d 48 h.

efforts as well as attempt to alleviate the steric hindrance in 1c by placing the phenyl ring one carbon further did not improve the yield of the desired amide 3da; in all of these reactions the imine was the primary product.

The general mechanism for direct amidation of aldehydes involves the formation of a hemiaminal and subsequent oxidation to the amide.^{4d} In our previous work, the addition of water was observed to significantly improve the yield, as it promoted the equilibrium between the imine/enamine and the key hemiaminal. However, in the present work the addition of water did not increase amide yields, rather it was found to correlate to hgher yields of the





Reaction conditions for 3ca and 3da: aldehyde (0.082 mmol, 1.0 equiv), aniline (2.5 equiv), [Rh(COD)₂]BF₄ (3.0 mol %), ligand (3.0 mol %), CsOAc (1.5 equiv), styrene (2.0 equiv), THF (0.2 mL).^a Isolated yield; see Table 1, condition A. ^b Starting material remained. ^c Imine was the main product.

imine.⁵ The effect of water on the reaction is not well understood, but it is consistent with a recent report by Stahl where the use of molecular sieves, a drying reagent, in an amidation reaction of alcohols leads to significantly higher amide/imine ratio.^{10a} However, molecular sieves and other drying agents were had not effect on the oxidative amidation of 1d.

To investigate the competition between amide and imine formation futher, a time study was carried out with pivaldehyde and 4methoxyaniline. As shown in Figure S2, amide yield increases for 10 hours, while imine yield steadily goes up throughout the course of the reaction. To determine if the imine can be an intermediate in the amidation reaction it was subjected to the reaction conditions, with and without aniline and water. In both cases, imine remained unreacted - only a trace amount of the amide product (3aa or 3ab) was observed.⁵ These results suggest that under these reaction conditions the equilibrium between the hemiaminal and imine lays far to the right and that once the imine is formed it is not converted to the desired amide at an appreciable rate. This is consistent with the Rh-catalyst serving a dual purpose: first it acts as a Lewis acid, binding to the aldehyde and promoting nucleophilic attack by the amine nucleophile and formation of the Rh-bound hemiaminal intermediate that undergoes subsequent β -hydride elimination.





The proposed catalytic cycle for the oxidative amidation of sterically hindered aldehydes is shown in Scheme 2. The aldehyde first reacts with the cationic [Rh(I)] catalyst to form a rhodium-bound aldehyde complex. Nucleophilic attack by the amine and subsequent proton transfer results in a Rh(III) species, which then undergoes β -hydride elimination to generate the desired amide and a rhodium-hydride complex. Insertion of the hydrogen acceptor followed by reductive elimination regenerates the active Rh(I) catalyst. Alternatively, the aldehyde could react with amine in an off-cycle reaction to form the unreactive imine. Control reactions show that catalyst was not required for imine formation.⁵ The relative rate of imine formation increases, when compared to the oxidative amidation reaction, as the steric hindrance of the aldehyde slows its reaction with the cationic Rh catalyst.

In order to address the competitive imine formation, we hypothesized that products 3ba-3da could be prepared from the corresponding alcohols. Previous reports on oxidative amidation of alcohols indicated that free aldehyde might not be an intermediate in the reaction or is only present in very low concentration.^{10b-c} Since the seminal report by Milstein on direct synthesis of amides from alcohols,^{10d} this reaction has attracted considerable attention and significant progress has been made.¹⁰ However, the



General reaction conditions: alcohol (0.64 mmol, 1.0 equiv), amine (2.5 equiv), $[Rh(COD)_2]BF_4$ (3.0 mol %), Xantphos (3.0 mol %), CsOAc (1.5 equiv), F_3CC(O)Ph (2.2 equiv), THF (1.4 mL). ^a Isolated yield ^b Yield in parenthesis was achieved with 1.5 eq amine in 1 h ^c Yield was low due to difficulty in separating product from starting amine. ^d 48 h.

drawback highlighted in Milstein's original study, namely low reactivity of sterically hindered substrates and less nucleophilic amines such as aniline,still remains.^{10b,e-j} The few studies that effectively use aniline nucleophiles all employ benzyl alcohol,^{10o-v} with the exception of a highly specialized Au-Pd resin which catalyzed reaction of aliphatic alcohols with anilines in high yields.^{10w} Highly bulky neopentyl alcohol substrate gives significantly diminished yields (10-20%)^{10,11} and a single example with good yield using this substrate was recently reported by Stahl.^{10a}

To probe the reactivity of sterically hindered alcohols and aromatic amines in our amidation reaction, screenings were carried out using neopentyl alcohol and aniline (Table S3). The conditions optimized for pivaldehyde proved to be ineffective. By changing the ligand to Xantphos and the hydrogen acceptor to 2,2,2-





Reaction conditions: alcohol (0.64 mmol, 1.0 equiv), aniline (2.5 equiv), $[Rh(COD)_2]BF_4$ (3.0 mol %), Xantphos (3.0 mol %), CsOAc (1.5 equiv), $F_3CC(O)Ph$ (2.2 equiv), THF (1.4 mL). ^a Isolated yield ^b aniline 4.0 equiv, $[Rh(COD)_2]BF_4$ 5 mol %, Xantphos 5 mol %, CsOAc 2.0 equiv. ^c $[Rh(COD)_2]BF_4$ 5 mol %, Xantphos 5 mol %, CsOAc 2.0 equiv, 100 °C.



Scheme 3. Synthesis of herbicide Monalide

trifluoroacetophenone, the desired product **3aa** was generated in high yield. With these new conditions in hand, we proceeded to explore the amine scope (Table 3). A variety of substituents on the phenyl ring were tolerated. Remarkably, with more reactive amines such as 4-methoxyaniline, good yield of product **3ab** was achieved after 1 h reaction time. Heterocyclic substrates also formed amides in excellent yields. The apparent lower yield of **3at** was due to difficulty in separating the product from the amine starting material rather than low conversion. When a nucleophile containing both primary and secondary aromatic amines was used, only the primary reacted, affording secondary amide **3ay** in good yield. To demonstrate the scalability of this reaction, **3aa** was prepared on a gram scale (1.3 g, 7.1 mmol) from **3a** and **2a** in 89% isolated yield.

We could now turn our attention to the original challenge of imine formation encountered when α -quaternary aldehydes, other than pivaldehyde, were used. To our delight, products 3ba-3da were all prepared from the corresponding alcohols using the optimized conditions in good to excellent yields (Table 4). Interestingly, alcohol **4e** required more forcing conditions despite the minimal structural change from neopentyl alcohol. We attributed this difference in reactivity to an unfavorable all anti-conformation of 4e. In comparison, cyclic substrate 4b, which is electronically similar to 4e, afforded the amide in higher yield as the additional substituents are conformationally locked gauche. Alcohols containing a ketal group, both cyclic (3fa) and acyclic (3ga), were also excellent substrates for this reaction. To demonstrate the synthetic utility, we applied the methodology to the synthesis of the herbacide Monalide (4ed, Scheme 3). As far as we are aware, the results in Tables 3 and 4 are the highest yields achieved with sterically hindered alcohols and aniline nucleophiles in metal-catalyzed oxidative amidation reactions.

To determine whether the changes in ligand and hydrogen acceptor explain the differences in reactivity of alcohols 4b-d and the corresponding aldehydes 1b-d, these aldehydes were allowed to react with aniline under the alcohol reaction conditions. Unfortunately, this did not lead to any improvement in yields, with 3b and 3d affording primarily imine, while 3c remained unreacted.⁵ The amine scope also differed when alcohols were employed as substrates. Alkylamines were shown to be effective nucleophiles with pivaldehyde (Table 1). However, under the optimized reaction conditions, 4a and benzylamine afford the corresponding amide 3ag in only 20% GC yield (Table S4). Initial screening revealed that changing the ligand to 1,3-bis(diphenylphosphino)propane (dppp) and temperature to 100 °C improved amide formation, as 3ag was isolated in 58% yield.⁵ These differences in the reaction scope suggest that the optimal catalyst for the oxidation of hindered alcohols to aldehydes is a poor catalyst for the oxidative amidation reaction between aldehydes and secondary amines. To further demonstrate the differential reactivity of the two catalysts, a time study of the reaction between neopentyl alcohol and 4methoxyaniline was performed (Figure S3). Unlike with pivaldehyde (Figure S2), yield of amide **3ab** steadily increases with time, and only a very small amount of imine byproduct was observed.¹¹

The proposed catalytic cycle for the oxidative amidation of hindered alcohols is shown in Scheme 4. Oxidative addition of the alcohol, followed by β -hydride elimination and transfer hydrogenation to trifluoroacetophenone generates an aldehyde-bound rhodium complex. Nucleophilic attack by aniline results in a rhodium-



Scheme 4. Proposed catalytic cycle for alcohol amidation

alkoxide species, which can then undergo β -hydride elimination to form the desired product and a rhodium hydride complex. Carbonyl insertion with trifluoroacetophenone followed by reductive elimination regenerates the active Rh(I) catalyst.

In conclusion, we have developed a rhodium-catalyzed oxidative amidation reaction for the synthesis of amides from aldehydes and alcohols containing an α -quaternary carbon. These results represent the best yields of amides from sterically hindered alcohols and aromatic amines. A broader substrate scope was observed with alcohol substrates than the corresponding aldehydes, which either form imine or remain unreacted, indicating that a metal-bound, aldehyde-like species instead of free aldehyde is not an intermediate in the oxidation of alcohols. Efforts to expand the scope of the reaction and better understand the mechanism are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information.

Experimental procedures and characterization data (PDF)

This material is available free of charge via the Internet at http://pubs.acs.org.

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[Rh(COD)₂]BF₄ (3 mol %) Xantphos (3 mol %) CsOAc (1.5 equiv) H₂N R ОН + R CF₃COPh (2.2 equiv) 0 THF, 80 °C, 24 h up to 96% isolated yield



58 59 60