Derailing the Wacker Oxidation: Development of a Palladium-Catalyzed Amidation Reaction

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ABSTRACT

A conceptually new palladium-catalyzed amidation reaction is described for the synthesis of \( \beta \)-amido ketones based on derailing the Wacker oxidation of enones. This reaction generates a new carbon–nitrogen bond via a palladium-catalyzed conjugate addition of a carbamate nucleophile to an enone. The regiocontrol, mild and neutral conditions, lack of preactivation of the nucleophile, and lack of reoxidation system for the catalyst are attractive features of this transformation.

Molecules bearing 1,3-amino-oxygenated functional motifs are ubiquitous to a variety of biologically important natural products.\(^1\) The development of new methods for their assembly is therefore of considerable synthetic importance.\(^2\) Of particular interest would be a facile method for the construction of \( \beta \)-amino-ketones, as these molecules are versatile precursors for 1,2 and 1,3 amino alcohols and \( \beta \)-amino acids (Figure 1).

The use of transition metal catalysts has influenced the development of new synthetic technology in recent years.\(^3\)

In particular, palladium catalysts have enjoyed widespread use in a large number of chemical transformations due to the versatility displayed by this metal over two stable oxidation states.\(^4\) It is notable, though, that there are fewer developments for palladium(II) catalysts than for the corresponding palladium(0) sources.\(^5\)

We have been interested in how the interaction of electrophilic palladium(II) catalysts with alkenes can activate the carbon–carbon double bond to attack by heteroatom nucleophiles. Our interest in the mechanism of such reactions led us to consider how it may be possible to exploit the electronic structure of the alkene in order to control the regioselectivity of such reactions.

Previous studies on the Wacker oxidation had led us to consider whether the use of nitrogen nucleophiles in a similar type of reaction is possible. Palladium(II)-mediated addition

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(4) Tsuji, J. In Palladium Reagents and Catalysts; John Wiley & Sons Ltd.: Chichester, 1996.


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Figure 1. Examples of 1,3-amino-oxygenated molecules.
of nitrogen nucleophiles to alkenes is a common reaction and is thought to be closely related to the Wacker oxidation. Thus, following the addition of the nucleophile to the palladium-complexed alkene, β-hydride elimination takes place, resulting in a net vinyl substitution to form enamine, enamido, or allylic amide-type products. Most of these examples though, involve an intramolecular nitrogen nucleophile. Few examples of the corresponding intermolecular reaction have been reported. If the conventional Wacker oxidation could be derailed, by preventing β-hydride elimination, it may be possible to form an sp³ hybridized carbon—nitrogen bond.

In this Letter we wish to report our first results on the development of a new palladium-catalyzed amidation. This reaction generates a new carbon—nitrogen bond via a palladium-catalyzed conjugate addition of a carbamate nucleophile to an enone. The regiocontrol, mild and neutral conditions, lack of preactivation of the nucleophile, and lack of reoxidation of the catalyst are attractive features of this transformation.

The Wacker oxidation of α,β-unsaturated esters leads to the exclusive formation a β-ketoester. Such absolute regioselectivity is rare in the oxidation of internal alkenes and is probably controlled by the electronic nature of the carbon—carbon double bond. The intermediate in this reaction must involve the formation of a species such as A (Scheme 1).

![Scheme 1](image)

We were intrigued by the possibility that if we could suppress β-hydride elimination, then A could tautomerize to the palladium enolate A—I, forming a 1,4-addition product instead of the following the conventional Wacker mechanism. A strategy of this nature would be ideal for the assembly of β-aminocarbonyl derivatives.

Our attention was initially focused on the polarized enone system. The preliminary investigations on this reaction appeared promising, with amines such as propylamine adding to simple enones. However, problems were encountered with the isolation of these β-amino ketones, presumably due to facile β-elimination. Furthermore, aliphatic amines are known to readily displace complexed alkenes from palladium and it is possible that the formation of the product was the result of uncatalyzed Michael addition. Changing the nitrogen source to a carbamate overcame these problems. The carboxy group reduces the binding ability of the nitrogen atom to the palladium center, thus preventing an undesirable interaction with the alkene—palladium complex while maintaining sufficient nucleophilic character to attack the activated enone.

Therefore, in the presence of 10 mol % of bis(acetonitrile) palladium(II) chloride and benzyl carbamate (1.5 equiv) in anhydrous dichloromethane (0.5 M wrt enone), enone 1a (1 equiv) was converted to the β-amido ketone 2a in 83% isolated yield. The reaction was complete after stirring for 24 h at room temperature under an inert atmosphere. Dichloromethane was determined to be the superior solvent for the reaction, and raising the temperature made little difference to the outcome of the reaction. There was no reaction in the absence of the catalyst, indicating that this was indeed a palladium-mediated reaction.

To explore the scope of the reaction, a number of simple enones were tested under the optimized reaction conditions (Table 1). Acyclic enones 1a–e were smoothly converted to the corresponding β-amido ketones 2a–c in good yields after purification by flash silica gel chromatography. Enone 1d did not react, possibly because reaction would require the breaking of the conjugated system between carbonyl and aryl groups. Cyclic enone 1e was also a good substrate for the reaction and generated 2e in 65%. Interestingly, changing the ratio of ketone to carbamate influences the reaction. When the enone was in excess, the reaction times were found to be longer. When the carbamate was in excess, the reaction times were found to be shorter. However, in our hands their results could not be reproduced and substantial modifications of the reaction conditions were required in order to produce a reliable quantity of the desired product. We also note that 1b was the only enone with which good results could be obtained.

(10) No reaction was observed with α,β-unsaturated esters under the conditions described in ref 13. In comparison to the intermediate palladium enolate A/A-I, Scheme 1, the corresponding intermediate developed from the α,β-unsaturated ester we believe would be less stable and hence less likely to form.

(11) Initial experiments were also conducted using benzyl alcohol. Thus, enone 1b could be converted to the corresponding β-benzxyo ketone in good yield. This reaction has been noted previously: Hosokawa, T.; Sinohara, T.; Ooka, Y.; Murahashi, S.-I. Chem. Lett. 1989, 15, 5741. However, in our hands their results could not be reproduced and substantial modifications of the reaction conditions were required in order to produce a reliable quantity of the desired product. We also note that 1b was the only enone with which good results could be obtained.

(12) Ketones 2a–h were characterized by H and 13C NMR (500 and 62.5 MHz, respectively) spectroscopy and high-resolution mass spectrometry.

(13) Representative procedure: A solution of enone (1 equiv) and benzyl carbamate (1.5 equiv) in anhydrous dichloromethane (1 mL per mmol enone) was added to a stirred solution of bis(acetonitrile)palladium(II) chloride (10 mol %) in anhydrous dichloromethane (1 mL per mmol enone) under an inert atmosphere. The reaction mixture was stirred at room temperature until completion, shown by TLC analysis. The reaction mixture was diluted with diethyl ether and filtered through a pad of silica, and the filtrate was concentrated and purified by flash chromatography.
to be significantly reduced and the yields increased to around 80%. Increasing the concentration of the enone may favor the formation of the alkene–palladium complex in solution and thus decreases the time required for completion of the reaction. This observation also suggests that the reaction may be reversible and that an excess of either reagent can drive the reaction to completion. Nevertheless, this allows the development of a second set of reaction conditions where the ratio of ketone to carbamate is 2–3:1 in a dichloromethane solution (0.5 M with respect to carbamate). Hence, the new reaction offers an unprecedented level of flexibility with respect to the use of excesses of reagents. It is possible to perform the reaction either with excess enone or with excess carbamate.

Trisubstituted alkenes are less reactive than their mono- and disubstituted homologues due to increased steric interaction with the palladium center. We were pleased to discover that trisubstituted enones could be converted to the corresponding β-amido ketones in some cases (Table 2).

For example, mesityl oxide 1f was converted to 2f in good yield. However, its regioisomer 1g does not react at all. Cyclic enone 1h, though, can be converted to 2h, albeit in modest yield after extended reaction time. The reactivity of 1h compared to 1g may be due to release of the inherent ring strain from 1h upon formation of the product. The relative stereochemistry of 2h is anti, based on the 1H NMR coupling constant (J = 11.0 Hz).

Other palladium(II) catalysts were also tested in this reaction. The results are summarized in Table 3. From the optimization studies, we had determined that bis(acetonitrile) palladium(II) chloride was the catalyst of choice from the range of available neutral palladium(II) salts. However, we were intrigued by the possibility that cationic palladium salts may also catalyze the reaction. Indeed, tetrakis(acetonitrile) palladium(II) tetrafluoroborate promotes the reaction. Using this catalyst the amount required can be dramatically reduced to 1 mol % without affecting the yield. This is also important for any future development of an asymmetric version of this reaction, as it would reduce the amount of catalyst and ligand used.

Although the mechanism of this reaction is still unclear, some proposals can be put forward. First, if the reaction were to follow a Wacker-type mechanism, then the initial step

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**Table 1.** Palladium(II)-Catalyzed Amidation on Enones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enone</th>
<th>Time hr</th>
<th>Yield</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>14</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>24</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>24</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>48</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>20</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>9</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>9</td>
<td>81</td>
<td></td>
</tr>
</tbody>
</table>

* All reactions were carried out on 1 mmol scale under an argon atmosphere at room temperature with 10 mol % of (MeCN)2PdCl2, Cbz-NH2 (1.5 equiv) in anhydrous dichloromethane (0.5 M). After purification by flash silica gel chromatography. Cyclohexenone: Cbz-NH2 = 2:1. Cyclohexenone: Cbz-NH2 = 3:1.

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**Table 2.** Palladium(II)-Catalyzed Amidation on Trisubstituted Enones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enone</th>
<th>Time hr</th>
<th>Yield</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1f</td>
<td>8</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1g</td>
<td>48</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1h</td>
<td>36</td>
<td>55</td>
<td></td>
</tr>
</tbody>
</table>

* All reactions were carried out on 1 mmol scale under an argon atmosphere at room temperature with 10 mol % of (MeCN)2PdCl2, Cbz-NH2 (1.5 equiv) in anhydrous dichloromethane (0.5 M). After purification by flash silica gel chromatography.

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**Table 3.** The Effect of Cationic Palladium(II) Catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Amount</th>
<th>Time hr</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(MeCN)2PdCl2</td>
<td>10 mol %</td>
<td>20</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>Pd(MeCN)4BF4</td>
<td>10 mol %</td>
<td>0.5</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>Pd(MeCN)4BF4</td>
<td>5 mol %</td>
<td>0.5</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>Pd(MeCN)4BF4</td>
<td>1 mol %</td>
<td>1</td>
<td>78</td>
</tr>
</tbody>
</table>

(14) There was no reaction using Pd(OAc)2, (PPh3)2PdCl2, or Pd(TFA)2.
would be formation of a $\pi$-alkene–palladium complex, X-I (Scheme 2). This complex would activate the enone by enhancing the partial positive charge on the $\beta$-carbon atom. Heteroatom nucleophilic addition to alkenes tends to occur from the opposite face to that occupied by palladium (distall addition) and would lead to the formation of X-II. The palladium bond in X-II is weakened by the presence of the adjacent ketone group and may tautomerize to enolate X-III. The palladium is then eliminated from the substrate through protonolysis, forming the product and regenerating the catalyst. It is not clear whether protonolysis occurs through X-II or X-III. Evidence for the location of the palladium on the $\alpha$-carbon atom is drawn from the relative reactivities of enones 1f and 1g. When the enone bears a substituent at the $\alpha$-position, the reaction is retarded, suggesting that an unfavorable steric interaction may result from the location of the palladium at this position.

An alternative explanation involves enone activation through palladium complexation to the carbonyl oxygen atom (not shown). This will facilitate a conjugate addition of the nucleophile to the $\beta$-carbon atom. Although this pathway seems unlikely for neutral palladium(II) sources, it may be competitive when cationic catalysts are used.

In summary, a new palladium-catalyzed amidation reaction has been developed that involves the addition of a carbamate nucleophile to an enone. The reaction is performed under extremely mild conditions and has been shown to be amenable to a range of enone substrates. We are currently investigating the mechanism of the reaction and the scope of nitrogen nucleophiles that may be utilized. On the basis of the outcome of these investigations, we will explore an enantioselective reaction using asymmetric catalysts and/or chiral nitrogen sources and whether diastereoccontrol is possible with $\gamma$-substituted enones. We believe that this methodology has a great deal of potential and could find widespread use in organic synthesis.

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Supporting Information Available: Spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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