Synthesis of Spiro Imines from Oximes by Palladium-Catalyzed Cascade Reaction

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Dedicated to Professor Ryoji Noyori in recognition of his remarkable contribution to the modern synthetic organic chemistry.


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Palladium-catalyzed coupling has been extensively studied in the past decade and has become one of the useful means of carbon–carbon bond formation, while the application to carbon–nitrogen bond formation is less common. Buchwald and Hartwig, recently, have cultivated this area and have developed palladium-catalyzed C–N bond forming reactions directed toward the synthesis of aryl amines and heterocycles.

Recently we found that oxime derivatives reacted with Pd(0) complex to generate alkylideneaminopalladium(II) species, which were used as intermediates of the Mizoroki-Heck-type cyclization of 103,100-unsaturated ketone oxime derivatives to give pyrroles. For example, 4-methyl-1-phenylpyrrole (2) was prepared in 85% yield by the treatment of 1-phenyl-4-pentene-1-one O-pentafluorobenzoyloxime (1) with a catalytic amount of Pd(PPh3)4 and Et3N in DMF at 80 °C. Thus, alkylideneaminopalladium(II) species can be generated from oximes and are useful intermediates for the formation of carbon-nitrogen bond. Therefore, we examined the synthesis of spiro imines by the cascade cyclization starting from dienyl ketone oxime derivatives.

Equation 1

1-Azaspiro[4.4]nonane system is a unique structure and the core skeleton of cephalotaxines, whose analogue shows some pharmacological activity. Various synthetic methods, therefore, have been developed toward the construction of azaspirotononane skeleton, such as acyloin condensation of 1,1-bis(methoxycarbonylmethyl)pyrrolidine, cyclization from 1-formyl-1-(3-iodo-2-propenyl)pyrrolidine using stannyl anion, ald condensation of 1-carbonyl-1-acetylmethylpyrrolidine, intramolecular S_N2' reaction of 1-(3-aminopropyl)-2-(1-hydroxyisopropyl)cyclopenten, and lactam formation from 1-amino-1-(2-methoxycarbonylethyl) cyclo-pentane. In addition, Tietze et al. have recently reported the efficient metal-catalyzed formation of 1-azaspiro[4.4]nonane skeleton based on the Tsuji-Trost allylation.

The outline of our strategy is depicted in Scheme, which is based on the cascade cyclization initiated by the generation of alkylideneaminopalladium(II) specie from O-pentafluorobenzoyloxime having a dienyl moiety.

Scheme

As a model compound, oxime 3a was chosen and the cascade reaction was examined in the presence of palladium catalysts and bases (Table 1). When the reaction was carried out at 80 °C with 10 mol% Pd(PPh3)4 and Et3N in DMF, which are the optimal reaction conditions of the previous pyrrole synthesis, it took 11.5 h to consume 3a, and the desired spiro imine 4a was obtained in 60% yield accompanied with 34% yield of ketone 5a (run 1). Although the use of Pd(dba)2 and PPh3 accelerated the reaction, yield of the cyclized product 4a was not improved but a larger amount of the ketone was obtained (run 2). Palladium(II) complexes such as PdCl2(PPh3)2 and PdCl2(dppf) were not suitable for this coupling.
At a higher temperature (110 °C), the reaction with 10 mol% Pd(PPh3)4 proceeded smoothly and the spiro compound 4a was obtained in 70% yield, though the ketone 5a was still formed considerably (run 3). Although K2CO3 was also efficient as a base like triethylamine, the reproducibility was low (run 4). The reaction worked well in polar solvents, especially DMF was found to be the best choice (run 3, 5, 6).

Addition of molecular sieve 4 Å was efficient to decrease the formation of ketone 5a, and the yield of 4a was improved to 77% (run 7). The role of molecular sieve is considered to trap a trace amount of water and acidic substances to prevent the decomposition of alkylideneamino palladium(II) intermediate to imine, which is then transformed to ketone 5a.

**Table 1** Palladium-Catalyzed Cyclization of O-Pentafluorobenzoate 3a

<table>
<thead>
<tr>
<th>run</th>
<th>Pd cat. (10 mol%)</th>
<th>base (5 eq)</th>
<th>solv.</th>
<th>T / °C</th>
<th>time / h</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh3)4</td>
<td>Et3N</td>
<td>DMF</td>
<td>80</td>
<td>11.5</td>
<td>60 34</td>
</tr>
<tr>
<td>2</td>
<td>Pd(dbta)2 + n PPh3</td>
<td>Et3N</td>
<td>DMF</td>
<td>80</td>
<td>1.8</td>
<td>17.53 78.42</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh3)4</td>
<td>Et3N</td>
<td>DMF</td>
<td>110</td>
<td>2</td>
<td>70 22</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh3)4</td>
<td>K2CO3</td>
<td>DMF</td>
<td>110</td>
<td>1</td>
<td>60.82 20.5</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh3)4</td>
<td>Et3N</td>
<td>DMF, DMF5</td>
<td>110</td>
<td>0.5</td>
<td>58 3</td>
</tr>
<tr>
<td>6</td>
<td>Pd(PPh3)4</td>
<td>Et3N</td>
<td>toluene</td>
<td>110</td>
<td>2</td>
<td>43 44</td>
</tr>
<tr>
<td>7</td>
<td>Pd(PPh3)4</td>
<td>Et3N</td>
<td>DMF</td>
<td>110</td>
<td>0.5</td>
<td>77 trace</td>
</tr>
</tbody>
</table>

*Isolated yield.

*n = 2, 4 or 6.

DMFU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone.

*In the presence of MS 4 Å.

The present method exhibits a wide generality as shown in Table 2. Aromatic ketone oxime derivative 3b cyclized to give 4b in 82% yield (run 1). Tricyclic compound 4c was obtained in a moderate yield as a 1:1 diastereomer mixture (run 2). Compared with 3c, 1-tetralone oxime derivative 3d was converted to tetracyclic imine 4d (diastereomer ratio = 1:1) in a good yield (run 3). Cyclic imine having ethoxy carbonyl group 4e, which is possible to be utilized as an intermediate for the synthesis of cephalotaxines by removal of the ethoxy carbonyl moiety, was also obtained from the oxime derivative of α-keto ester 3e (run 4).

In a similar manner, triple cyclization occurred smoothly in the presence of molecular sieve 4 Å to give the bis-spiro compound 7 as a two diastereomer mixture. All entries are supported by NMR spectra.

**Equation 2**

As described above, spiro imines were synthesized from oxime derivatives having dienyl and trienyl moieties by the palladium-catalyzed cascade reaction.
References and Note


(8) Although the core skeleton of cephalotaxines is expected to be prepared from aldoxime derivative 8, which readily suffer the Beckmann fragmentation to give corresponding nitrile 9.

$$\text{Equation 3}$$


(10) The stereochemistry of 7 is not determined.

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