Palladium-catalyzed intramolecular carbene insertion into C(sp^3)-H bonds

Daniel Solé, Francesco Mariani, M.-Lluïsa Bennasar, and Israel Fernández

Abstract: A palladium-catalyzed carbene insertion into C(sp^3)-H bonds leading to pyrrolidines was developed. The coupling reaction can be catalyzed by both Pd(0) and Pd(II), is regioselective and shows a broad functional group tolerance. This reaction represents the first example of palladium-catalyzed C(sp^3)-C(sp^3) bond assembly starting from diazocarbonyl compounds. DFT calculations revealed that this direct C(sp^3)-H bond functionalization reaction involves an unprecedented concerted metalation-deprotonation step.

The development of practical and green methods for C–C bond formation by the selective functionalization of unactivated C–H bonds is an area of great interest that has been extensively studied over the last years. Among the vast array of such transformations, the C–H insertion of metal carbenoids derived from diazocarbonyl substrates constitutes a particularly attractive method (Scheme 1). In this approach, the electron-rich C–H bonds generally exhibit higher reactivity toward the carbene center and show an activation order of tertiary > secondary >> primary C(sp^3)-H. Thus, while the insertion into tertiary and secondary C(sp^3)-H bonds has been thoroughly studied, the analogous process involving primary C(sp^3)-H and C(sp^3)(Ar)-H bonds remains comparatively underdeveloped.

The C–H insertion reactions of diazocarbonyl substrates have been traditionally carried out in the presence of Rh(II) or Cu catalysts. Although other metals have emerged as potentially useful catalysts for this type of transformation, the use of palladium has been restricted to a couple of examples of α-diazo β-ketoester insertion into C(sp^3)-H bonds. This fact is highly surprising if we take into account the great success of Pd catalysis in cross-coupling reactions of diazo compounds with either organic halides or aryloboronic acids.

As part of our research program on the synthesis of azaheterocycles, we have been exploring different ways to increase the versatility of Pd catalysis in C–C bond-forming reactions. In this regard, we decided to investigate the feasibility of Pd as a catalyst for the carbenoid C–H insertion from diazocarbonyl substrates.

Herein we report an operationally simple procedure for the Pd-catalyzed intramolecular assembly of C(sp^3)-C(sp^3) bonds starting from α-diazoesters, in which both Pd(0) and Pd(II) catalysts are effective. Mechanistically, this direct C(sp^3)-H bond functionalization process is different from those reported in the literature based on Rh(II) or Cu catalysts.

Our investigation began by testing the Pd-catalyzed cyclization of α-diazoester 1 in order to assess the regioselectivity of the C–H bond activation process (Scheme 2).

A variety of Pd sources, ligands, additives, and solvents were investigated (see Supporting Information for details). Based on these studies, we established three experimental procedures for the cyclization reaction. Thus, treatment of 1 with Pd(OAc)_2 (10 mol%) and Cs_2CO_3 (2 equiv.) in CHCl_3 at reflux afforded a 2:1 mixture of pyrrolidine 2 and tetrahydroquinoline 3, which resulted from the activation of the C(sp^3)-H and C(sp^3)(Ar)-H bonds, respectively. The use of Pd_2(dbp)_2 (2.5 mol%) as the catalyst in the presence of Cs_2CO_3 (2 equiv.) in 1,2-dichloroethane (DCE) at 80 ºC led to a 2:2:1 mixture of 2 and 3. Finally, among the different ligands explored to modify the selectivity of the C–H insertion from 1, when using Pd_2(dbp)_2 (2.5 mol%) as the precatalyst, we found that the bidentate phosphines dipp, dpf and xantphos (5 mol%) gave slightly better C(sp^3)-H-to-C(sp^3)(Ar)-H activation ratios (2.6-2.8:1).

These results showed that (i) the C–H carbenoid cyclization can be catalyzed by both Pd(0) and Pd(II), and (ii) the C(sp^3)-H insertion is in all cases favored over the C(sp^3)(Ar)-H insertion. With this information in hand, we decided to explore the influence of the introduction of substituents at the aromatic ring on the selectivity of the C–H activation process (see Supporting Information and Table 1).

To our delight, the C(sp^3)-H insertion was the only reaction observed when 2-idoaniline 4a was submitted to the optimized reaction conditions (entries 1-2). It should be noted that no product resulting from the competitive Pd-catalyzed reaction of...
the aryl iodide with the α-diazoester moiety\textsuperscript{[13,16]} was observed in these reaction mixtures. The best result was obtained with Pd(2-dba)\textsubscript{2} in the absence of phosphine ligands, which afforded pyrrolidine 5a in 89% yield (entry 1).

Table 1. Selected Pd-catalyzed C–H insertion reactions of α-diazoesters 4a-i\textsuperscript{[H]}

<table>
<thead>
<tr>
<th>entry</th>
<th>4</th>
<th>[Pd(mol%)]/ligand(mol%)</th>
<th>Solv.</th>
<th>Temp.</th>
<th>Product [%]\textsuperscript{[I]}</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>(2-I) Pd(OAc)\textsubscript{2} (10)</td>
<td>CHCl\textsubscript{3} reflux</td>
<td>reflux</td>
<td>5a (55)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4a</td>
<td>(2-I) Pd(2-dba)\textsubscript{2} (2.5)</td>
<td>CHCl\textsubscript{3} reflux</td>
<td>reflux</td>
<td>5a (69)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4b</td>
<td>(2-Br) Pd(OAc)\textsubscript{2} (10)</td>
<td>CHCl\textsubscript{3} reflux</td>
<td>reflux</td>
<td>5b (51)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4b</td>
<td>(2-Br) Pd(2-dba)\textsubscript{2} (2.5)</td>
<td>CHCl\textsubscript{3} reflux</td>
<td>reflux</td>
<td>5b (66)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4c</td>
<td>(2-Cl) Pd(OAc)\textsubscript{2} (10)</td>
<td>CHCl\textsubscript{3} reflux</td>
<td>reflux</td>
<td>5c (56)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4c</td>
<td>(2-Cl) Pd(2-dba)\textsubscript{2} (2.5)</td>
<td>DCE</td>
<td>reflux</td>
<td>5c (56)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4d</td>
<td>(2-F) Pd(2-dba)\textsubscript{2} (2.5)</td>
<td>DCE</td>
<td>reflux</td>
<td>5d (62)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4e</td>
<td>(2-Me) Pd(OAc)\textsubscript{2} (10)</td>
<td>CHCl\textsubscript{3} reflux</td>
<td>reflux</td>
<td>5e (49)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4e</td>
<td>(2-Me) Pd(2-dba)\textsubscript{2} (2.5)</td>
<td>DCE</td>
<td>reflux</td>
<td>5e (57)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>4f</td>
<td>(3-Cl) Pd(OAc)\textsubscript{2} (10)</td>
<td>DCE</td>
<td>reflux</td>
<td>5f (69)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>4f</td>
<td>(3-Cl) Pd(2-dba)\textsubscript{2} (2.5)</td>
<td>DCE</td>
<td>reflux</td>
<td>5f (69)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>4g</td>
<td>(3-MeO) Pd(OAc)\textsubscript{2} (10)</td>
<td>DCE</td>
<td>reflux</td>
<td>5g (35)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>4g</td>
<td>(3-MeO) Pd(2-dba)\textsubscript{2} (2.5)</td>
<td>DCE</td>
<td>reflux</td>
<td>5g (35)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>4h</td>
<td>(4-Cl) Pd(2-dba)\textsubscript{2} (2.5)</td>
<td>DCE</td>
<td>reflux</td>
<td>5h (51)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>4i</td>
<td>(4-MeO) Pd(OAc)\textsubscript{2} (10)</td>
<td>DCE</td>
<td>reflux</td>
<td>5i (25)</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>4i</td>
<td>(4-MeO) Pd(2-dba)\textsubscript{2} (2.5)</td>
<td>DCE</td>
<td>reflux</td>
<td>5i (25)</td>
<td></td>
</tr>
</tbody>
</table>

[a] Reaction conditions: [Pd]/ligand (see table) and Cs\textsubscript{2}CO\textsubscript{3} (2 equiv.) in CHCl\textsubscript{3} or DCE at the indicated temperature for 24 h. [b] Yields refer to products isolated by chromatography. [c] 16 h. [d] 48 h. [e] \textsuperscript{1}H NMR analysis of the reaction mixture showed a \textasciitilde 4:1 Csp\textsuperscript{2}-H:Csp\textsuperscript{2}-H activation ratio. [f] \textsuperscript{1}H NMR analysis of the reaction mixture showed a \textasciitilde 5:1 Csp\textsuperscript{2}-H:Csp\textsuperscript{2}-H activation ratio.

2-Haloanilines 4b, 4c, and 4d, and 2-methylaniline 4e also selectively underwent Csp\textsuperscript{2}-H insertion (entries 3-9). In contrast, competition between the Csp\textsuperscript{2}-H and Csp\textsuperscript{sp}-(Ar)–H insertions was observed in the reactions involving meta- and para-substituted anilines. While 3-chloroaniline 4f gave a C–H activation selectivity (entries 10-11) similar to the unsubstituted aniline 1, the cyclization reactions of 3-methoxyaniline 4g proceeded with lower regioselectivity (entries 12-13). Interestingly, higher selectivity was obtained with both electron-poor 4-chloroaniline 4h (entry 14) and electron-rich 4-methoxyaniline 4i (entries 15-16).

The C–H insertion reaction was not limited to N-aryl/alkylation but also proved suitable for substituted Csp\textsuperscript{2}-H bonds (Table 2).

Table 2. Pd-catalyzed C–H insertion of α-diazoesters 7a-c\textsuperscript{[H]}

<table>
<thead>
<tr>
<th>Entry</th>
<th>7</th>
<th>[Pd(mol%)]/ligand(mol%)</th>
<th>Solv.</th>
<th>Temp.</th>
<th>Product Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7a</td>
<td>(R,C\textsubscript{6}H\textsubscript{5}) Pd(2-dba)\textsubscript{2} (2.5)</td>
<td>CHCl\textsubscript{3} reflux</td>
<td>reflux</td>
<td>7a (66, cis/trans 5:5:1)</td>
</tr>
<tr>
<td>2</td>
<td>7a</td>
<td>(R,C\textsubscript{6}H\textsubscript{5}) Pd(OAc)\textsubscript{2} (10)</td>
<td>CHCl\textsubscript{3} reflux</td>
<td>reflux</td>
<td>7a (46, cis/trans 4:1)</td>
</tr>
<tr>
<td>3</td>
<td>7a</td>
<td>(R,C\textsubscript{6}H\textsubscript{5}) Pd(2-dba)\textsubscript{2} (2.5)</td>
<td>DCE</td>
<td>reflux</td>
<td>7a (54, cis/trans 4:1)</td>
</tr>
<tr>
<td>4</td>
<td>7b</td>
<td>(R,C\textsubscript{6}H\textsubscript{5}) Pd(2-dba)\textsubscript{2} (2.5)</td>
<td>CHCl\textsubscript{3} reflux</td>
<td>reflux</td>
<td>7b (58, cis/trans 1:7:1)</td>
</tr>
<tr>
<td>5</td>
<td>7b</td>
<td>(R,C\textsubscript{6}H\textsubscript{5}) Pd(OAc)\textsubscript{2} (10)</td>
<td>CHCl\textsubscript{3} reflux</td>
<td>reflux</td>
<td>7b (43, cis/trans 1:7:1)</td>
</tr>
<tr>
<td>6</td>
<td>7c</td>
<td>(R,C\textsubscript{6}H\textsubscript{5}) Pd(2-dba)\textsubscript{2} (2.5)</td>
<td>DCE</td>
<td>reflux</td>
<td>7c (60, cis/trans 1:5:1)</td>
</tr>
<tr>
<td>7</td>
<td>7c</td>
<td>(R,C\textsubscript{6}H\textsubscript{5}) Pd(OAc)\textsubscript{2} (10)</td>
<td>DCE</td>
<td>reflux</td>
<td>7c (45, cis/trans 1:1:1)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: See Table 1. [b] Yields refer to products isolated by chromatography. [c] 39 h.

N-Benzylaniline 7a regioselectively afforded pyrrolidine 8a (5.5:1 cis/trans mixture) in 66% yield when the reaction was performed in the presence of Pd(2-dba)\textsubscript{2} (entry 1).\textsuperscript{[19]} The use of either Pd(OAc)\textsubscript{2} (entry 2) or Pd(2-dba)\textsubscript{2}/dppf (entry 3) as the catalyst afforded slightly lower yields. More importantly, no competition between allylic insertion and cyclopropanation\textsuperscript{[19,20]} was observed in the Pd-catalyzed reactions of N-allylaniline 7b. Thus, treatment of 7b with either Pd(2-dba)\textsubscript{2} (entry 4) or Pd(OAc)\textsubscript{2} (entry 5) in CHCl\textsubscript{3} at reflux afforded pyrrolidine 8b (1:7:1 cis/trans mixture). Finally, N-propylaniline 7c also underwent a similar regioselective insertion at the Csp\textsuperscript{2}-H bond to give pyrrolidine 8c (entries 6-7). Similar to the reactions involving 2-iodoaniline 4a, no product resulting from the Pd-catalyzed reaction of the aryl iodide with the α-diazoester moiety was observed in any of the Pd-catalyzed reactions of 2-iodoanilines 7a-c.

According to previous mechanistic studies, it can be suggested that the Pd-catalyzed transformations described above likely
involve the insertion of the in situ-generated Pd-carbenoid intermediate into the C–H bond. For related Rh(II)- and Cu-catalyzed transformations, this process has been proposed to occur in a concerted but asynchronous manner that directly releases the reaction product and the metal catalyst in one single step.\textsuperscript{[20]}

Density functional theory (DFT) calculations\textsuperscript{[21]} were carried out to gain more insight into the mechanism of the above Pd-catalyzed C\textsuperscript{sp}\textsubscript{3}–H insertions. Thus, Figure 1 shows the corresponding computed reaction profiles of the processes involving INT\textsubscript{0}-A and INT\textsubscript{0}-B, the initial Pd(0) and Pd(II)-carbene complexes formed upon reaction of the active catalytic species Pd(dppp) or Pd(CO\textsubscript{3}) with 1, respectively.

![Figure 1. Computed reaction profiles for the formation of pyrrolidine 2. Relative free energies (\(\Delta G\)\textsubscript{298}, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM(CHCl\textsubscript{3})-M06L/def2-TZVP//RI-BP86-D3/def2-SVP level.](image)

In the Pd(II)-pathway, the initial complex INT\textsubscript{0}-B evolves to carbene complex INT\textsubscript{1}-B via TS\textsubscript{1}-B with an activation barrier of 29.1 kcal/mol in a highly exergonic transformation (\(\Delta G\textsubscript{R} = -15.9\) kcal/mol). This saddle point is associated with the concerted hydrogen migration from the N–CH\textsubscript{3} moiety to the carbonate ligand and Pd–C bond formation (Figure 1). Therefore, this transformation is analogous to related concerted metalation-deprotonation (CMD) C–H activations which are assisted by acetate\textsuperscript{[22]} or carbonate.\textsuperscript{[14b,15e]} Subsequent exergonic (\(\Delta G\textsubscript{R} = -18.3\) kcal/mol) insertion of the carbene carbon atom into the Pd–C bond via TS\textsubscript{2}-B (\(\Delta G\textsubscript{≠} = 11.6\) kcal/mol) leads to the formation of the Pd(II)-complex INT\textsubscript{2}-B. Final protonolysis of the Pd–C bond would afford pyrrolidine 2 and release the Pd(II) catalyst.\textsuperscript{[23]} This reaction is more exergonic (\(\Delta G\textsubscript{R} = -24.3\) kcal/mol) and occurs with a lower activation barrier (\(\Delta G\textsubscript{≠} = 22.4\) kcal/mol) than the CMD process involving TS\textsubscript{1}-B. The readily formed Pd(II)-complex INT\textsubscript{1}-A is finally converted into pyrrolidine 2 in a highly exergonic (\(\Delta G\textsubscript{R} = -12.9\) kcal/mol) reductive elimination through transition state TS\textsubscript{2}-A (\(\Delta G\textsubscript{≠} = 26.8\) kcal/mol) which releases the catalytic species Pd(dppp).

Additional experiments were performed to support the transition metal-mediated 1,5-H migration. Thus, when trideuterated
aniline 1-D$_3$ was submitted to the conditions optimized for the Pd-catalyzed reaction of aniline 1, using Pd$_2$(dba)$_3$/dpff as the catalyst, a 1:2.1 mixture of pyrrolidine 2-D$_3$ and tetrahydroquinoline 3-D$_3$ was obtained (Scheme 3). This result confirms that the deuterium atom was totally transferred to the carbonyl atom, which nicely agrees with the DFT-proposed mechanism. The use of Pd(OAc)$_2$ as the catalyst afforded a similar Csp$^3$–H/Csp$^3$(Ar)–H ratio with complete preservation of the deuterium label at the specific position as well. The reaction also proceeded at room temperature, but required longer times and higher catalyst loading. Interestingly, the regioselectivity of these reactions was very different from that involving aniline 1 under the same conditions, which suggests a primary isotope effect.

In summary, we have developed a regioselective Pd-catalyzed Csp$^3$–H insertion reaction from α-diazoesters to provide pyrrolidines. Both Pd(0) and Pd(II) are effective in this reaction, which represents the first example of Pd-catalyzed carbenoid insertion into Csp$^3$–H bonds. A salient aspect of this transformation is its broad tolerance to reactive functional groups in the starting material. DFT calculations suggest that this transformation does not involve a concerted asynchronous process, but a metatation-deprotonation reaction.

Acknowledgements

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Keywords: palladium-catalysis • carbenoid insertion • diazo compounds • pyrrolidines • DFT calculations


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Palladium also catalyzes the carbenoid C–H insertion of α-diazoesters. We report the first examples of Pd-catalyzed intramolecular assembly of Cap²-Cap³ bonds leading to pyrrolidines. The reaction seems to involve a novel metalation-deprotonation step instead of the usual concerted but asynchronous process.