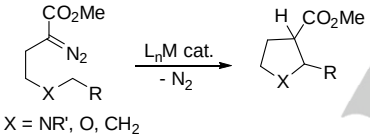
Palladium-catalyzed intramolecular carbene insertion into C(sp^3)-H bonds

Daniel Solé,*[a] Francesco Mariani,[a] M.-Lluïsa Bennasar,[a] and Israel Fernández*[b]

Abstract: A palladium-catalyzed carbene insertion into Csp^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 Csp^3–Csp^3 bond assembly starting from diazocarbonyl compounds. DFT calculations revealed that this direct Csp^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.[1] 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).[2] 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 Csp^3–H. Thus, while the insertion into tertiary and secondary Csp^3–H bonds has been thoroughly studied, the analogous process involving primary Csp^3–H and Csp^2(Ar)–H bonds remains comparatively underdeveloped.



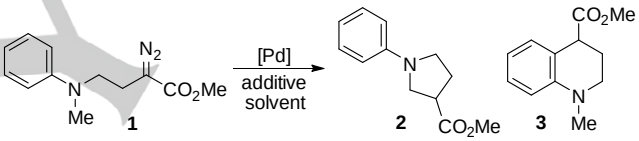
Scheme 1. Metal-catalyzed C–H insertion of diazoesters.

The C–H insertion reactions of diazocarbonyl substrates have been traditionally carried out in the presence of Rh(II)[3] or Cu catalysts.[4] Although other metals have emerged as potentially useful catalysts for this type of transformation,[5-10] the use of palladium has been restricted to a couple of examples of α-diazo β-ketoester insertion into Csp^2–H bonds.[11-12] 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 arylboronic acids.[13]

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.[14-15] 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 Csp^3–Csp^3 bonds starting from α-diazoesters, in which both Pd(0) and Pd(II) catalysts are effective. Mechanistically, this direct Csp^3–H bond functionalization process is different from those reported in the literature based on Rh(II) or Cu catalysts.[3-4]

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).



Scheme 2. Pd-catalyzed cyclization of diazoester **1**.

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 Csp^3–H and Csp^2(Ar)–H bonds, respectively. The use of $Pd_2(dba)_3$ (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 $Pd_2(dba)_3$ (2.5 mol%) as the precatalyst, we found that the bidentate phosphines dppp, dppf and xantphos (5 mol%) gave slightly better Csp^3–H-to-Csp^2(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 Csp^3–H insertion is in all cases favored over the Csp^2(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 Csp^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

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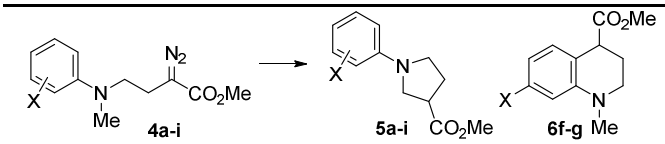
the aryl iodide with the α-diazoester moiety[13,16] was observed in these reaction mixtures. The best result was obtained with $Pd_2(dba)_3$ in the absence of phosphine ligands, which afforded pyrrolidine **5a** in 89% yield (entry 1).

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



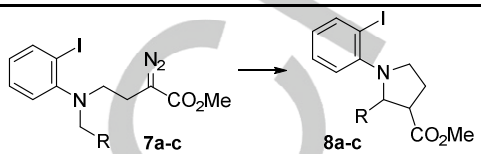
entry	4	[Pd](mol%)/ ligand(mol%)	Solv.	Temp.	Product Yield [%][b]
1	**4a** (2-I)	$Pd(OAc)_2$ (10)	$CHCl_3$	reflux[c]	**5a** (55)
2	**4a** (2-I)	$Pd_2(dba)_3$ (2.5)	$CHCl_3$	reflux	**5a** (89)
3	**4b** (2-Br)	$Pd(OAc)_2$ (10)	$CHCl_3$	reflux	**5b** (51)
4	**4b** (2-Br)	$Pd_2(dba)_3$ (2.5)	$CHCl_3$	reflux	**5b** (66)
5	**4c** (2-Cl)	$Pd(OAc)_2$ (10)	$CHCl_3$	reflux	**5c** (56)
6	**4c** (2-Cl)	$Pd_2(dba)_3$ (2.5) dppf (5)	DCE	80 ºC	**5c** (69)
7	**4d** (2-F)	$Pd_2(dba)_3$ (2.5)	DCE	80 ºC	**5d** (62)
8	**4e** (2-Me)	$Pd(OAc)_2$ (10)	$CHCl_3$	reflux	**5e** (49)
9	**4e** (2-Me)	$Pd_2(dba)_3$ (2.5) dppf (5)	DCE	80 ºC	**5e** (57)
10	**4f** (3-Cl)	$Pd(OAc)_2$ (10)	DCE	80 ºC[d]	**5f/6f** (2:1, 39)
11	**4f** (3-Cl)	$Pd_2(dba)_3$ (2.5)	DCE	80 ºC	**5f/6f** (2.7:1, 45)
12	**4g** (3-MeO)	$Pd(OAc)_2$ (10)	DCE	80 ºC[d]	**5g/6g** (1.3:1, 42)
13	**4g** (3-MeO)	$Pd_2(dba)_3$ (2.5)	DCE	80 ºC	**5g/6g** (1.5:1, 47)
14	**4h** (4-Cl)	$Pd_2(dba)_3$ (2.5) dppf (5)	DCE	80 ºC	**5h** (35)[e]
15	**4i** (4-MeO)	$Pd(OAc)_2$ (10)	DCE	80 ºC[d]	**5i** (25)[f]
16	**4i** (4-MeO)	$Pd_2(dba)_3$ (2.5)	$CHCl_3$	reflux	**5i** (38)[f]

[a] Reaction conditions: [Pd]/ligand (see table) and Cs_2CO_3 (2 equiv.) in $CHCl_3$ or DCE at the indicated temperature for 24 h. [b] Yields refer to products isolated by chromatography. [c] 16 h. [d] 48 h. [e] ^{1}H NMR analysis of the reaction mixture showed a ≈4:1 Csp^3–H:Csp^2–H activation ratio. [f] ^{1}H NMR analysis of the reaction mixture showed a ≈5:1 Csp^3–H:Csp^2–H activation ratio.

2-Haloanilines **4b**, **4c**, and **4d**, and 2-methylaniline **4e** also selectively underwent Csp^3–H insertion (entries 3-9). In contrast, competition between the Csp^3–H and Csp^2(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*-methylanilines but also proved suitable for substituted Csp^3–H bonds (Table 2).

Table 2. Pd-catalyzed C–H insertion of α-diazoesters **7a-c**[a]



Entry	7	[Pd](mol%)/ ligand(mol%)	Solv.	Temp.	Product Yield [%][b]
1	**7a** (R:C_6H_5)	$Pd_2(dba)_3$ (2.5)	$CHCl_3$	reflux	**8a** (66, *cis*/*trans* 5.5:1)
2	**7a** (R:C_6H_5)	$Pd(OAc)_2$ (10)	$CHCl_3$	reflux	**8a** (46, *cis*/*trans* 4:1)
3	**7a** (R:C_6H_5)	$Pd_2(dba)_3$ (2.5) dppf (5)	DCE	80 ºC	**8a** (54, *cis*/*trans* 4:1)
4	**7b** (R:CH=CH_2)	$Pd_2(dba)_3$ (2.5)	$CHCl_3$	reflux	**8b** (58, *cis*/*trans* 1.7:1)
5	**7b** (R:CH=CH_2)	$Pd(OAc)_2$ (10)	$CHCl_3$	reflux	**8b** (43, *cis*/*trans* 1.7:1)
6	**7c** (R:C_2H_5)	$Pd_2(dba)_3$ (2.5)	DCE	80 ºC[c]	**8c** (70, *cis*/*trans* 1.5:1)
7	**7c** (R:C_2H_5)	$Pd(OAc)_2$ (10)	DCE	80 ºC[c]	**8c** (45, *cis*/*trans* 1.1:1)

[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 $Pd_2(dba)_3$ (entry 1).[17] The use of either $Pd(OAc)_2$ (entry 2) or $Pd_2(dba)_3$/dppf (entry 3) as the catalyst afforded slightly lower yields. More importantly, no competition between allylic insertion and cyclopropanation[18-19] was observed in the Pd-catalyzed reactions of *N*-allylaniline **7b**. Thus, treatment of **7b** with either $Pd_2(dba)_3$ (entry 4) or $Pd(OAc)_2$ (entry 5) in $CHCl_3$ at reflux afforded pyrrolidine **8b** (1.7:1 *cis*/*trans* mixture). Finally, *N*-propylaniline **7c** also underwent a similar regioselective insertion at the Csp^3–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.[20]

Density functional theory (DFT) calculations[21] were carried out to gain more insight into the mechanism of the above Pd-catalyzed Csp^3–H insertions. Thus, Figure 1 shows the corresponding computed reaction profiles of the processes involving **INT0-A** and **INT0-B**, the initial Pd(0) and Pd(II)-carbene complexes formed upon reaction of the active catalytic species Pd(dppp) or Pd(CO_3) with **1**, respectively.

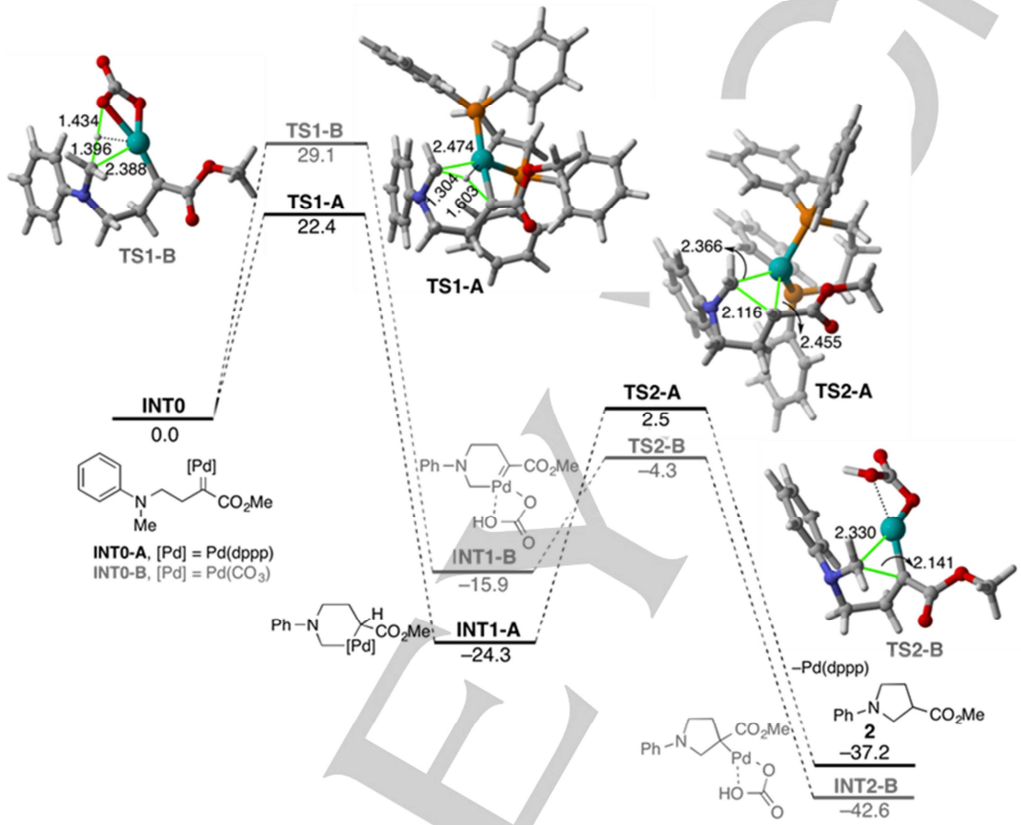


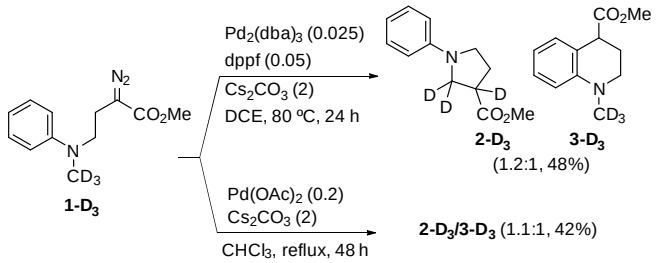
Figure 1. Computed reaction profiles for the formation of pyrrolidine **2**. Relative free energies (ΔG_{298}, at 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data were computed at the PCM($CHCl_3$)-M06L/def2-TZVP//RI-BP86-D3/def2-SVP level.

In the Pd(II)-pathway, the initial complex **INT0-B** evolves to carbene complex **INT1-B** via **TS1-B** with an activation barrier of 29.1 kcal/mol in a highly exergonic transformation (ΔG_R = –15.9 kcal/mol). This saddle point is associated with the concerted hydrogen migration from the N–CH_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[22] or carbonate.[14b,15e] Subsequent exergonic (ΔG_R = –18.3 kcal/mol) insertion of the carbene carbon atom into the Pd–C bond via **TS2-B** ($\Delta G^{\neq}$ = 11.6 kcal/mol) leads to the formation of the Pd(II)-complex **INT2-B**. Final protonolysis of the Pd–C bond would afford pyrrolidine **2** and release the Pd(II) catalyst.[23] This protonolysis may occur either by intramolecular proton transfer from the HCO_3^- ligand or, more likely, by transmetalation into a cesium enolate, followed by intermolecular protonation with the HCO_3^- released in the reaction medium.[24]

The initial Csp^3–H activation in the Pd(0) pathway, which proceeds through the transition state **TS1-A**, resembles the above discussed CMD process in the sense that this transformation also involves a concerted metalation-deprotonation step. However, in this case the process also forms the new C–H bond. Therefore, this single step can be viewed as a Pd-mediated 1,5-H migration from the N–CH_3 moiety to the carbenoid which results in the formal oxidation of the transition metal.[25] This reaction is more exergonic (ΔG_R = –24.3 kcal/mol) and occurs with a lower activation barrier ($\Delta G^{\neq}$ = 22.4 kcal/mol) than the CMD process involving **TS1-B**. The readily formed Pd(II)-complex **INT1-A** is finally converted into pyrrolidine **2** in a highly exergonic (ΔG_R = –12.9 kcal/mol) reductive elimination through transition state **TS2-A** ($\Delta G^{\neq}$ = 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 $Pd_2(dba)_3$/dppf 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 carbenoid 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^2(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.



Scheme 3. Pd-catalyzed reactions of **1-D$_3$**.

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 metalation-deprotonation reaction.

Acknowledgements

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

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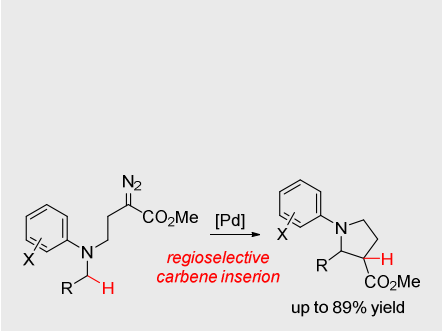
Layout 1:

COMMUNICATION

Palladium also catalyzes the carbenoid C–H insertion of α-diazoesters. We report the first examples of Pd-catalyzed intramolecular assembly of Csp^3–Csp^3 bonds leading to pyrrolidines. The reaction seems to involve a novel metalation-deprotonation step instead of the usual concerted but asynchronous process.



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