FINAL VERSION ACCEPTED

CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.200((will be filled in by the editorial staff))

Stable N-Heterocyclic Carbene-Palladium(0) Complexes as Active Catalysts For Olefin Cyclopropanation Reactions with Ethyl Diazoacetate

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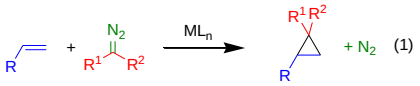
Dedication ((optional))

Abstract. The Pd(0) complexes $NHCPdL_n$ (NHC = N-heterocyclic carbene ligand; L = styrene for n = 2 or PR_3 for n = 1) efficiently catalyze the olefin cyclopropanation using ethyl diazoacetate (EDA) as the carbene source with activities that improve any other previous described catalytic system based on this metal. Mechanistic studies have shown that all those catalyst precursors deliver in solution the same catalytic species (IPr)Pd(sty), a 14e, unsaturated intermediate that further reacts with EDA to afford (IPr)Pd(=$CHCO_2Et$)(sty), from which cyclopropane is formed.

Keywords: diazoester • cyclopropanation • homogeneous catalysis • palladium

Introduction

Cyclopropanes are widespread in nature and constitute the building blocks of biologically active compounds.[1] Among the various methods used for their preparation, the transition metal catalyzed cyclopropanation of olefins with diazo reagents has attracted great interest (Eq 1).[2] Many transition metal complexes, especially those containing rhodium,[3] copper,[2e, 4] cobalt,[5] iron,[5f,5k, 6] or ruthenium[7] have been employed to induce such transformation. Interestingly, one of the most commonly employed metals in homogenous catalysis, palladium, has been scarcely described as catalyst for this process, in spite of its discovery for this purpose in the mid sixties.[8] During the last decade, a number of contributions related to the use of diazomethane as carbene reagent and palladium-based catalysts have appeared,[9] a topic recently reviewed by Wang and co-worker.[10] However, such catalysts seem to fail with alkyl diazoacetates as the reactant,[9a,9b,11] in spite of the fact that the latter are stable, commercial or easy-to-prepare reagents, in contrast with the well-known instability of diazomethane.



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The already described Pd(0)-based catalysts for these transformations contain phosphanes or olefins as ancillary ligands.[9d,11c] On the other hand, Pérez and coworkers have reported that group 11 metal complexes containing NHC ligands (NHC = N-heterocyclic carbene) are active catalysts toward the carbene transfer from ethyl diazoacetate (N_2CHCO_2Et, EDA) to several saturated or unsaturated substrates.[4q,12] Although Pd(0)-NHC compounds have been successfully employed as catalysts in several reactions such as C-C and C-N coupling reactions, oxidations, telomerizations and hydrogenation,[13] to our knowledge there is no report about the use of such compounds in olefin cyclopropanation.[14] In addition, there is still a debate[15] about the oxidation state of the palladium catalytic species.

On the basis of the above, we decided to prepare a series of novel (NHC)Pd(0) complexes and to investigate their potential as catalysts for the olefin cyclopropanation reaction with alkyl diazoacetate reagents. We have found that they are quite active catalysts for the olefin cyclopropanation reaction. A detailed mechanistic study, including kinetic and thermodynamic data, has led to the proposal of the mechanism for this transformation.

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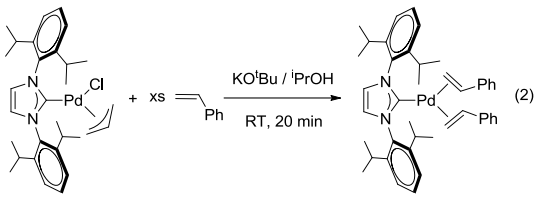
Results and Discussion

Synthesis and Characterization of Complex (IPr)Pd^0(sty)$_2$, 1. Although several methods have been employed for the synthesis of mono-NHC-Pd^0-alkene complexes,[16,17] we have prepared complex **1** in good yields following a method reported by Nolan and co-workers for the preparation of mono-NHC-Pd^0-PR$_3$ complexes from (NHC)Pd(allyl)Cl.[18] Thus, the reaction of (IPr)Pd(allyl)Cl (IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene) with one equiv of KO^{t}Bu in ^{i}PrOH in the presence of an excess of styrene (Eq 2) led to the formation of **1** in high yields (80 %). This complex is stable in the solid state and can be kept for an unlimited period of time under an inert atmosphere.



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Complex **1** was characterized by NMR spectroscopy and by X-ray crystallography. It shows a fluxional behaviour as inferred from the line broadening observed NMR spectra at variable temperature (see Supporting Information). At room temperature the resonances corresponding to C*H* protons of ^{i}Pr and vinyl protons of the olefin appear as three broad peaks at δ 3.07, 3.19 and 3.89 ppm in the ^{1}H NMR spectrum, which may result from (i) fast (on the NMR time-scale, Figure 1) exchange processes with free olefin, and/or (ii) fast rotation of the olefin around the palladium-olefin bond axis. At low temperature (-40 ºC), the resonances of the methine C*H* group of the ^{i}Pr groups split in two signals at δ 2.83 (heptet, J = 6.5 Hz, 2H) and 3.43 (heptet, J = 6.5 Hz, 2H) whereas the olefinic protons appear as three signals at 2.94 (d, J = 9.0 Hz, 2H), 3.07 (d, J = 12.4 Hz, 2H), and 3.75 (dd, J = 9.3 Hz, J = 12.4 Hz, 2H), at much higher field than in free styrene (5.00, 5.59 and 6.55 in C_6D_6), indicating strong back donation of electron density from the palladium metal into the π* orbitals of the alkene. Accordingly, in the ^{13}C{^{1}H} NMR spectrum of **1** at -40 ºC, the olefin carbons resonate at δ 74.7 (s, *C*H olefin) and 53.0 (s, *C*H$_2$ olefin) (135.5 and 112.0 for the free olefin).[19] Since we could not extract fair conclusions from the VT NMR studies of the sole complex, we studied the effect of the presence of olefin excess on the ^{1}H NMR spectrum at room temperature (Figure 1). Thus, the addition of 6 equiv of free olefin afforded even broader peaks for the protons of the coordinated olefin. Although this behaviour is expected for an associative olefin-exchange process at the metal center,[20] we could not discard the dissociative mechanism since at 60 ºC just a set of signal was observed for the methines and the methyls of the ^{i}Pr groups of the NHC ligand. Additionally, the Eyring plot obtained by this VT ^{1}H NMR study (monitoring the change of the signals corresponding to the methyl groups of the IPr ligand) in presence of olefin (Figure 2) enabled the determination of activation parameters: $\Delta H^{\neq}$ = 22,4±1.6 Kcal/mol and $\Delta S^{\neq}$ = 31±5 ue. It is the positive value of the activation entropy that supports the proposal of a dissociative mechanism. Such pathway would involve the formation of the unsaturated 14e$^-$ species (IPr)Pd(sty) similar to that proposed by Elsevier and co-workers in the (NHC)Pd-catalyzed transfer hydrogenation of alkynes.[21]

The proposed structure of complex **1** has being confirmed by single-crystal X-ray analysis (recrystallized using toluene as solvent). An ORTEP diagram of **1** is shown in Figure 3. The asymmetric unit of the structure in the crystal is formed by two half-molecules of carbene complexes symmetrically independents, but

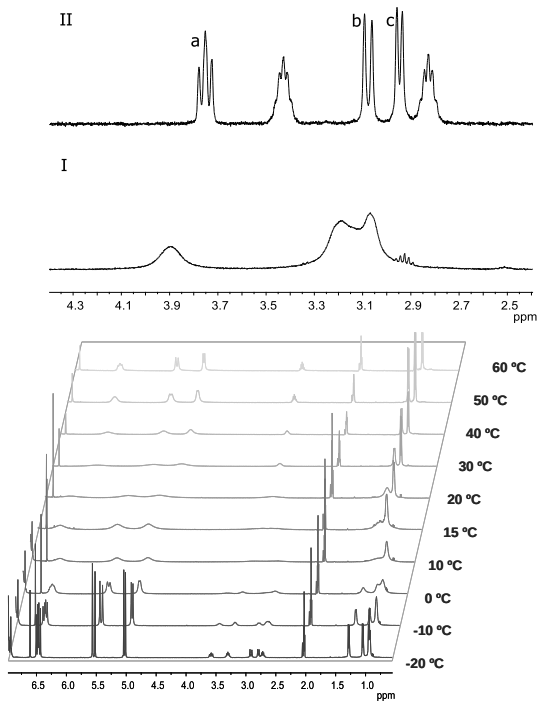


Figure 1. Top: Olefinic resonances (labeled as a, b and c) in the ^{1}H NMR spectrum of **1** at low and room temperature. Bottom: VT ^{1}H NMR spectra of **1** in presence of 6 equiv of styrene. Sample conditions: [Pd] 14 mM, [sty] 84 mM, toluene-d_8.

both structurally equivalent, with the others half generated by a crystallographic twofold axis of symmetry (see supporting information). The distance Pd-C(1), 2.101(7) Å, is somewhat longer than those found for other NHC-palladium olefin complexes,[16a-c] but similar to the reported for (IMes)Pd(DMF)$_2$.[16d] The C=C double bonds of the coordinated styrenes, C(15)-C(16) 1.397(8) Å, are longer in free styrene (1.346(20) Å).[22] That distance is similar to the reported for the Rh(I) complex [Rh(PNP)(styrene)]X (PNP = 2,6-bis((diphenylphosphino)methyl)pyridine; X = BF_4^-) and longer than for Pt(II) and Pd(II) complexes.[23] Again, this is consistent with a significant metal to olefin π-back-donation. The NHC plane is oriented at an angle of 59.87(26)° to the coordination plane of the styrenes (C(15)-Pd-C'(15)), similarly to the complex (IMesPd)(DMF)$_2$. The Pd–C(15) distance, 2.147(6) Å, is shorter

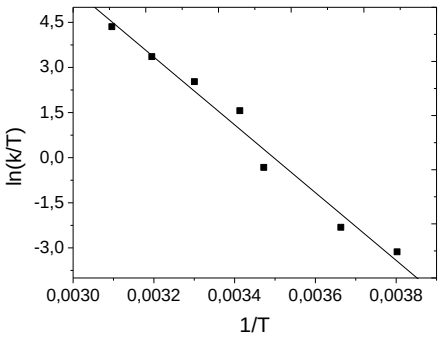


Figure 2. Eyring plot of the temperature dependent behavior of the olefin exchange. Sample conditions: [Pd] 14 mM, [sty] 84 mM, toluene-d_8.

than Pd–C(16) 2.189(6) Å, as already reported for other styrene complexes.[24] The dihedral angle between the coordination planes of the two styrenes (Pd-C(15)-C(16) and Pd-C(24)-C(25)) of 11.23(35)º (only slightly higher than in case of (IMes)Pd(DMF)$_2$),[16d] therefore the two styrene molecules are coordinated to the metal almost in a planar fashion.

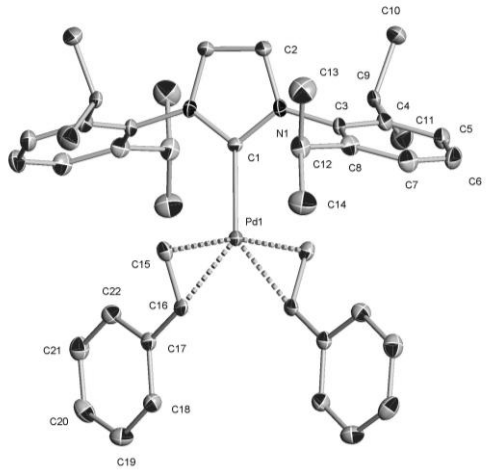
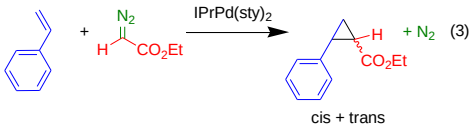
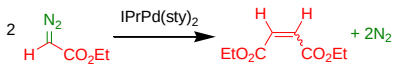


Figure 3. ORTEP diagram of (IPr)Pd(sty)$_2$ (**1**). Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at the 30% probability level. Selected Bond Lengths (Å) and Angles (deg) for **1**: Pd─C(1) 2.101(7), C(15)-C(16) 1.397(8), Pd─C(15) 2.147(6), Pd─C(16) 2.189(6), C(1)-Pd-C(15) 97.89(17), C(1)-Pd-C(16) 135.23(15), N(1)-C(1)-N'(1) 104.6(6).

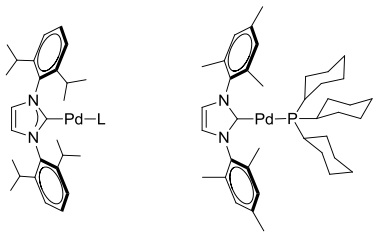
Catalytic Cyclopropanation Reaction of Styrene Using NHC-Pd(0) Complexes as Catalysts. Once complex **1** was characterized, it was tested as catalyst precursor in the styrene cyclopropanation reaction using ethyl diazoacetate (EDA) as the carbene source. A solution of the Pd(0) complex (0.01 mmol) in dichloromethane was charged with 5 mmol of styrene and 1 mmol of EDA, accounting for a [Pd]:[EDA]:[styrene] ratio of 1:100:500. The reaction was monitored by GC, showing the gradual disappearance of EDA and the appearance of cyclopropanes. After 4h, no diazocompound was detected in the reaction mixture, the analysis of the reaction crude (after volatles removal) showing the formation of a mixture of the corresponding *cis*- and *trans*-ciclopropanes (Eq 3) in 98% yield (EDA-based). The remaining initial diazoacetate was converted in a mixture of diethyl fumarate and maleate, a process also catalyzed by complex **1** (Eq 4).





After the finding of the catalytic capability of IPrPd(sty)$_2$ toward styrene cyclopropanation with EDA, we decided to screen a series of related complexes of composition (NHC)PdL for this probe reaction (see Experimental for their preparation or in situ generation). Complexes **2-4** contain IPr as well as a PR$_3$ ligand; complex **5** corresponds to a biscarbene Pd(0) complex whereas complex **6** bears an IMes ligand along with PCy$_3$. Data in Table 1 show that complexes **1-4** and **6** display nearly identical catalytic behaviour in terms of activity or diastereoselectivity, only the biscarbene complex IPr$_2$Pd being ineffective. Entries 1, 3 and 6 correspond to experiments carried out with a [Pd]:[EDA]:[styrene] ratio of 1:100:500, i. e., 1 mol% of the Pd catalyst, and provided nearly quantitative conversions into the desired cyclopropanes. Interestingly, the *cis:trans* ratio was also identical, in what could be considered as an indication of the existence of a common catalytic species, at least for **1-4** as catalysts. A second series of experiments carried out with 0.5 mol% of the catalyst ([Pd]:[EDA]:[styrene] = 1:200:1000), with similar conversions, yields and diastereoselection, although larger reaction times where required.

Table 1. Styrene Cyclopropanation Using the NHC-Pd(0) complexes **1-6** as Catalysts.



L = PCy$_3$, **2**; PPh$_3$, **3**; P(o-tolyl)$_3$, **4** **6**

L = IPr, **5**

Entry	Catalytic Precursor	Time (h)	conversion %[c]	Yield %[c]	*cis:trans*
1	(IPr)Pd(sty)$_2$, **1**[a]	4	99	98	38:62
2	(IPr)Pd(sty)$_2$, **1**[b]	24	98	98	37:63
3	(IPr)PdL, **2-4**[a]	4	99	98	37:63
4	(IPr)PdL, **2-4**[b]	24	99	93	37:63
5	(IPr)$_2$Pd, **5**[a]	48	2%	n. d.	n. d.
6	IMesPd(PCy$_3$), **6**[b]	24	99	90	37:63

[a] [Pd]/[EDA]/[olefin] 1:100:500. [b] [Pd]/[EDA]/[olefin] 1:200:1000. The conversions were determined by ^{1}H NMR spectroscopy. [c] Percentage of cyclopropanes at the end of the reaction using 1,4-dimethoxybenzene as internal standard (diethyl fumarate and maleate accounted for 100% of EDA).

As mentioned above, very few examples of the use of palladium-based catalysts for olefin cyclopropanation with diazoacetates have been described. Most of them employ a Pd(II) precursor. Seminal work was described by Noels and co-workers with Pd(OAc)$_2$ as the catalyst precursor.[11c] Styrene and EDA were employed using a 15:1 ratio to give 98% conversion into cyclopropanes. They also reported the use of Pd(PPh$_3$)$_4$ as the catalyst for the same reaction, although only 57% yield of cyclopropanes was achieved. In our case, the Pd(0) complexes **1-4** and **6** improved such activity, with the added value of employing only a 5:1 [styrene]:[EDA] ratio. Importantly, high yields of cyclopropane (80% in 4h) were obtained even when the reaction carried out using only a 1:1 [styrene]:[EDA] ratio. This is remarkable result since in previous palladium-based catalytic systems an excess of the olefin was used. Clearly, the replacement of phosphine ligands with IPr seems to be the key for this success. However, these systems are less active than those reported for other

transition metals. For instance, Pérez´s group has reported that the TOF value for $Tp^{Ms}Cu$ (Tp = hydrotris(3-mesitylpyrazolyl)borate) complex is 250 mmol h^{-1}, whereas in case of **1** the TOF value is 24 mmol h^{-1}.[4s]

Table 2. Cyclopropanation of 1-hexene and cyclooctene olefins using EDA and (IPr)Pd(PPh_3), **3**, as catalyst precursor.[a]

Entry	Olefin	Time (h)	Conversión %[b]	Yield %[c]	*cis:trans*
1	1-hexene	24	98	95	40:60
2	cyclooctene	24	63	58	13:87

[a] [Pd]/[EDA]/[olefin] 1:100:500. [b] The conversions were determined by ^{1}H NMR spectroscopy. [c] Percentage of cyclopropanes at the end of the reaction using 1,4-dimethoxybenzene as internal standard (diethyl fumarate and maleate accounted for 100% of EDA).

The singularity of our system extends to other usually less reactive olefins such as 1-hexene or cyclooctene. As shown in Table 2, both olefins can be converted into cyclopropanes in high (95%) or moderate (58%) yields, respectively. These yields are much higher that those reported with $Pd(OAc)_2$ for the same olefins: 30 % for 1-hexene and 20 % for cyclooctene, assessing that the Pd(0)-based catalysts reported herein are quite active.[11c] Competition experiments carried out with styrene, 1-hexene and cyclooctene have established the relative reactivity of these three olefins as 3.80 : 1.20 : 1.00, respectively. The trend is similar to that found by Noels and coworkers with $Pd(OAc)_2$ as the catalyst (2.36: 1.31: 1.00), with the aforementioned differences in activities favouring the NHCPd(0)-based system.

Mechanistic studies: (a) Kinetics.

Once demonstrated the unprecedented catalytic activity of the above Pd(0) complexes toward the olefin cyclopropanation reaction with diazoacetates as the carbene source, we focussed on the elucidation of the reaction mechanism. To gain information about it, we first monitored the evolution of nitrogen in the decomposition of ethyl diazoacetate in the abscense and in the presence of styrene, with $IPrPd(sty)_2$ (**1**) as the catalyst precursor. Figure 4 shows that in the absence of styrene, the reaction does not reach completion (1 mmol of EDA should provide 1 mmol of N_2), in contrast with the experiment carried out with styrene, where all the initial EDA is consumed. The use of a phosphine-containing precatalyst such as $IPrPd(PPh_3)$ (**3**) provided additional information. In this case, an induction period of ca 50 min was observed prior to nitrogen evolution (Figure 5a). A series of experiments in which different amounts of PPh_3 were added led to the observance of an increase of the induction period (Figure 5, b-c) until inhibition of the reaction (Figure 5d). From data in Figures 4 and 5 we have extracted the following conclusions: with the PPh_3-containing precatalyst, the first step must consist of PPh_3 decoordination to generate the IPrPd species. Their equilibrium is greatly affected by addition of free phosphine. The generation of the IPrPd species, common for **1** or **3** as precatalysts, initiates the catalytic cycle. In the absence of styrene, that species catalyzes the diazo coupling reaction, that originates diethyl fumarate (DEF) and diethyl maleate (DEM). These olefins would bind the IPrPd unit to give $IPrPd(DEF)_2$ or $IPrPd(DEM)_2$, blocking the active catalytic site. It is worth mentioning that Cavell and co-workers have reported the complex $(IMes)Pd(DMF)_2$ (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; DMF = dimethyl fumarate).[16d] The formation of $IPrPd(DEF)_2$ or $IPrPd(DEM)_2$ in the presence of a large excess of styrene would be precluded, explaining the observance of complete EDA consumption and subsequent cyclopropane formation. To be sure that this proposal is correct, we run two identical cyclopropanation experiments and added, after 1 h, a certain amount of diethyl

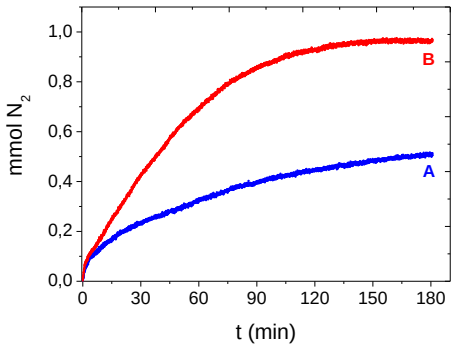


Figure 4. Plot of nitrogen evolution in the reaction of EDA in absence (A) and in presence of styrene (B), catalyzed by **1**. Reaction conditions: A) [catalyst] : [EDA] = 1 : 48; [**1**] = 0.02 mmol; [EDA] = 0.95 mmol, solvent : 10 mL CH_2Cl_2.; B [**1**] : [EDA] : [styrene] = 1 : 48 : 250; [**1**] = 0.02 mmol; [EDA] = 0.95 mmol; [styrene] = 5 mmol, solvent : 10 mL CH_2Cl_2.

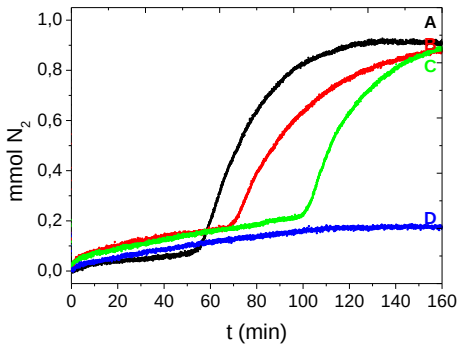


Figure 5. Plots of nitrogen evolution in the reaction of EDA in presence of styrene and different amounts of PPh_3 added catalyzed by **3**. Reaction conditions: [**3**] : [EDA] : [styrene] = 1 : 48: 250; [catalyst] = 0.02 mmol; [EDA] = 0.96 mmol; [styrene] = 5 mmol; solvent : 10 mL CH_2Cl_2. Amount of PPh_3 added: A) None, B) 0.01 mmol, C) 0.02 mmol, D) 0.03 mmol.

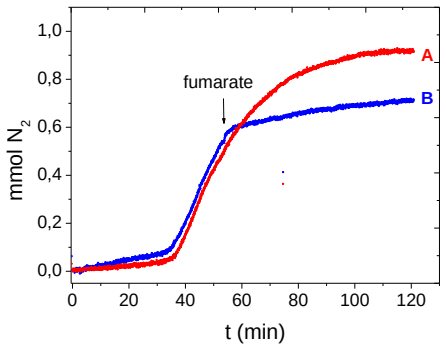


Figure 6. Plot of nitrogen evolution in the reaction of EDA and styrene catalyzed by **3**. Reaction conditions: [**3**] : [EDA] : [styrene] = 1 : 48 : 250; [**3**] = 0.02 mmol; [EDA] = 0.95 mmol; [styrene] = 5 mmol; solvent : 10 mL CH_2Cl_2. Diethyl fumarate 5 mmol) were added after 50 min in experiment B.

fumarate (Figure 6). Both experiments showed nearly identical nitrogen evolution curves until that moment, in which that containing added DEF dramatically decreased the reaction rate, assessing the validity of the proposal of inhibition commented above.

We have also carried out experiments to study the effect that a variation in $[Pd]_{tot}$ would induce in the reaction rate of the cyclopropanation of styrene using **1** as precatalyst. As shown in Figure 7 there exist a linear dependence of k_{obs} with $[Pd]_{tot}$.

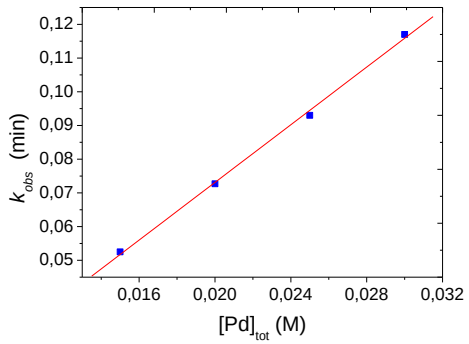
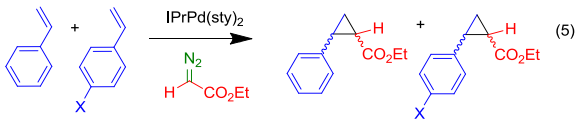


Figure 7. Variation of k_{obsd} vs $[Pd]_{tot}$ for N_2 evolution using **1** as the catalyst precursor at room temperature

(b) The role of the olefin: a Hammett's plot.

Noels and co-workers proposed that in Pd-catalyzed olefin cyclopropanation, coordination of the olefin is crucial for the reaction to occur, in an intramolecular fashion (both the carbene and olefin units are bonded to the metal). This is at variance with other copper- or rhodium-based systems where the reaction between the metallocarbene and the olefin takes place intermolecularly, the non-coordinated olefin attacking the metallocarbene carbon atom. Aimed at collecting data to support one route or the other, we have performed competition experiments with a series p-substituted styrenes and complex **3** as catalyst (Eq 5) and plotted the relative rates against Hammett's constant σ. As shown in Figure 8, data nicely fits into a Hammett's plot, although with a positive slope. This is in contrast with most of the catalytic systems previously described that provided correlations with negative slopes. The fact that the reactivity of an olefin toward cyclopropanation increases when bearing electron-withdrawing groups must be considered as the result of a previous coordination of the olefin to an electron rich metal-center, i. e., to the IPrPd fragment.



We have already mentioned hat the observance of similar activities and diastereoselectivities induced by complexes **1**-**4** in the styrene cyclopropanantion reaction with EDA supports the proposal of a common intermediate. On the basis of the data obtained from the previously discussed competition experiments, such species should be the 14e$^-$, unsaturated IPrPd(olefin) complex that could be formed from **1** by olefin decoordination or from **2**-**4** by simultaneous

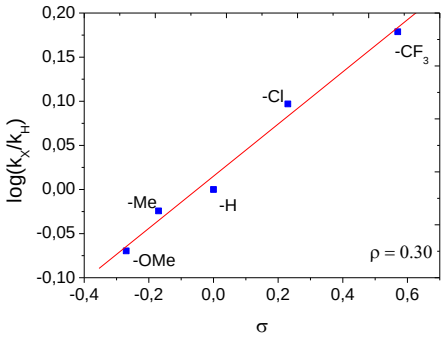
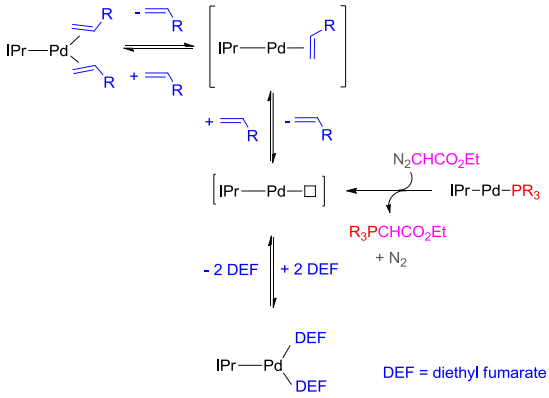


Figure 8. Hammett plot reflecting electronic effects of the olefin in the cyclopropanation reactions using complex **3** as the catalyst.

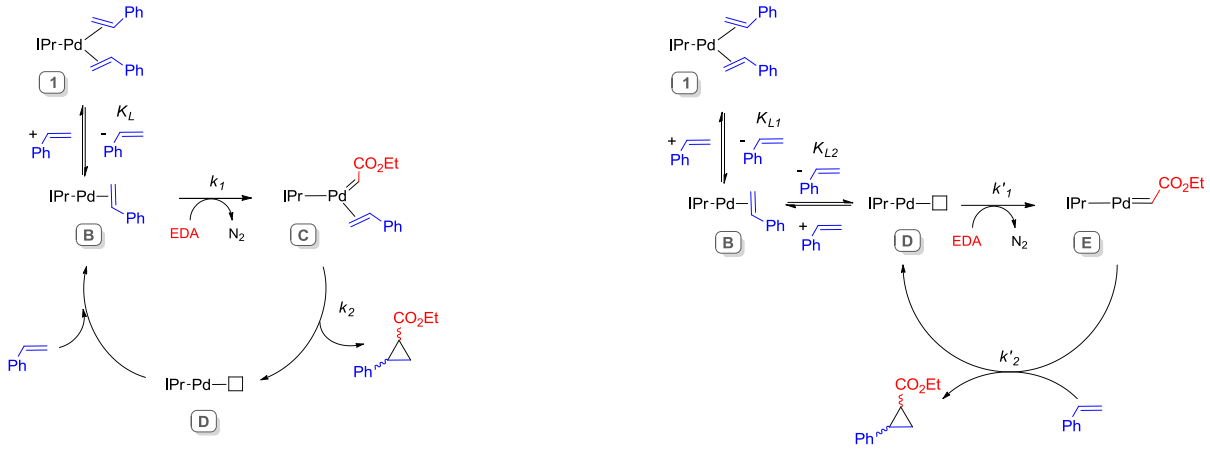
phosphine decoordination and olefin addition (Scheme 1). These equilibria would control the relative amount of IPrPd(olefin) available to react with EDA in the first step of the catalytic cycle. However, dissociation of styrene from **1** would take readily at room temperature whereas loss of the PR_3 from IPrPd(PR_3) seems to be much slower, as inferred from the observance of the induction period (Figure 6). On the basis of the already described formation of



Scheme 1. Equilibria leading to the generation of the catalytic species.

a phosphine ylide from the reaction of $Pd(PPh_3)_4$ with the diazo ketone N_2CHCO^tBu,[25] we searched for such compound in the reaction mixture when using **3** as the catalyst precursor. We have observed that when 3 equiv EDA were added to a solution of **3** in C_6D_6 (0.6 mL), the resonance corresponding to **3** decreased in the ^{31}P NMR spectrum and two new peaks appear at δ 19.3 and 17.5 ppm (ratio 4:1) that correspond to the two geometrical isomers of the ylide (see Supporting information), which ratio depends on the solvent and the temperature.[26] Accordingly, in the ^1H NMR spectrum the resonance of the Ph_3PCH proton for the major isomer (*cis*) could be observed at δ 3.32 ppm (d, J_{HP} = 24 Hz). The induction time observed with IPrPd(PR_3) would then correspond to the time required to consume the PR_3 existing in the reaction mixture, from that point the catalytic reaction being undistinguishable from that carried out with **1** as catalyst.

(c) The rate-law for the styrene cyclopropanation with 1.



$$\frac{d[N_2]}{dt} = -\frac{d[EDA]}{dt} = k_1 \frac{[Pd]_{tot}}{1+\frac{[Sty]}{K_L}}[EDA] \ldots (6)$$

$$k_{obs} = k_1 \frac{[Pd]_{tot}}{1+\frac{[Sty]}{K_L}} \ldots (7)$$

$$\frac{1}{k_{obs}} = \frac{1}{k_1[Pd]_{tot}} + \frac{[Sty]}{k_1 K_L [Pd]_{tot}} \ldots (8)$$

$$\frac{d[N_2]}{dt} = -\frac{d[EDA]}{dt} = k'_1 \frac{[Pd]_{tot}}{1+\frac{[Sty]}{K_{L1}}+\frac{[Sty]^2}{K_{L2}}}[EDA] \ldots (9)$$

$$k_{obs} = k'_1 \frac{[Pd]_{tot}}{1+\frac{[Sty]}{K_{L1}}+\frac{[Sty]^2}{K_{L2}}} \ldots (10)$$

$$\frac{1}{k_{obs}} = \frac{1}{k'_1[Pd]_{tot}}\left[1+\frac{[Sty]}{K_{L1}}+\frac{[Sty]^2}{K_{L2}}\right] \ldots (11)$$

Scheme 2. Catalytic cycles for the styrene cyclopropanation with ethyl diazoacetate and IPrPd(sty)$_2$ as the catalyst: Left: IPrPd(sty) as the species to react with EDA; Right: IPrPd as the species to react with EDA.

Experimental data collected to this point seems to point toward the implication of the IPrPd(olefin) in this catalytic system. However, we have not yet distinguished between the two posible routes that may exist to explain the formation of cyclopropanes. The first pathway would involve the attack of the diazocompound onto IPrPd(olefin) **B** (Scheme 2, left) to give a transient olefin-palladacarbene that would collapse into products. But it could be also possible that the unsaturated, free-olefin IPrPd (**D**) species could react with EDA to give the corresponding palladacarbene IPrPd=C(H)CO_2Et (**E**) that further would interact with olefin (Scheme 2, right). A detailed kinetic analysis for both possible pathways have been carried out, leading to the reaction rate laws , Eqns 6 and 9 (see Supporting Information for the derivation of both equations). The experimentally observed (Figure 7) linear dependence of k_{obs} with $[Pd]_{tot}$ (i. e. the initial amount of **1**) cannot be employed to distinguish between them, since as shown in Eqns 7 and 10, both routes would accomplish with such behaviour. However, there is a significant distinction regarding the dependence of the inverse of k_{obs} and [sty]. In one case, such dependence should be linear; however, for the proposal of the intermediacy of species **E** (with no olefin coordinated at palladium), a second order behavior should be expected. Therefore, a series of kinetic experiments was performed in which only the amount of added styrene was modified. Figure 9 shows the plot of $1/k_{obs}$ vs [sty]. The linear correlation between both magnitudes leaves no doubt about the pathway responsible for this transformation: it is the 14 e- unsaturated IPrPd(sty) species **B** that react with EDA to generate **C** previously to cyclopropane formation. The intercept at y-axis provides the value of $1/k_1[Pd]_{tot}$ and hence a k_1 is determined as 1,77 x 10^2 min^{-1}. The slope corresponds to the value of $1/k_1K_L[Pd]_{tot}$, from which the K_L value of 5x10^{-2} was obtained. This result explains the decrease of the reaction rate with added olefin, since most of the palladium at solution remains as **1**.

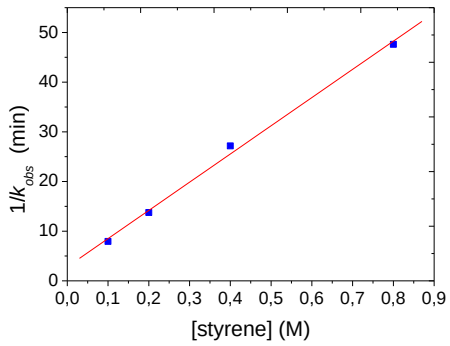


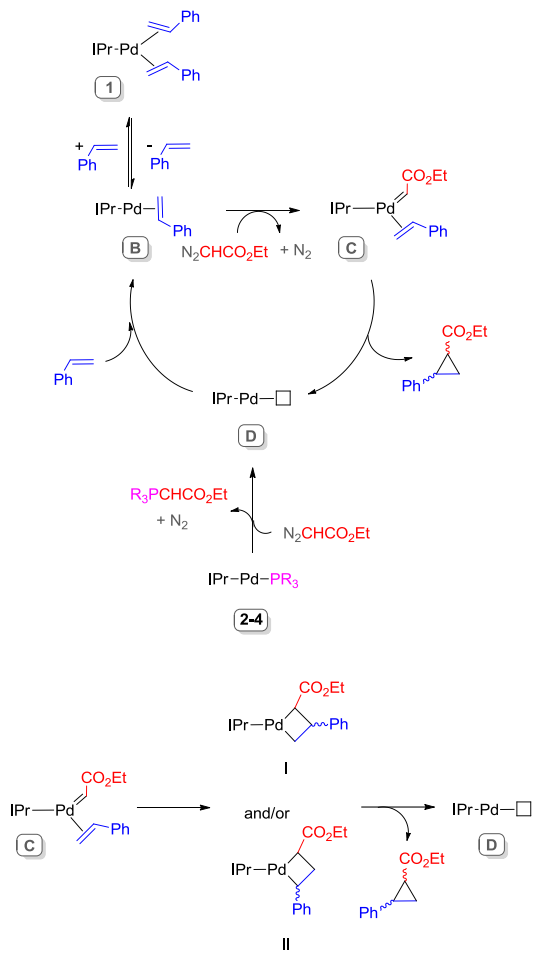
Figure 9. Dependence of 1/kobs on the concentration of Styrene. The value of k_1 is obtained from the intercept and K_L from the slope

Global mechanism.

On the basis of collected experimental data, an overall mechanistic proposal has been built (Scheme 3) for the catalytic styrene cyclopropanation using complexes **1-4** as catalyst precursors. They undergo ligand dissociation (**1**) or ligand transformation into an ylide (**2-4**). In the latter case, the unsaturated species IPrPd (**D**) would be trapped by styrene to give the real catalytic species in this system, the 14 e IPrPd(sty) (**B**). This is responsible to react with EDA to afford the transient metallocarbene IPrPd(=CHCO_2Et)(Sty) species (**C**) that collapses into cyclopropanes (*cis* and *trans*) and produces **D** in the path to **B** to restart the catalytic cycle.

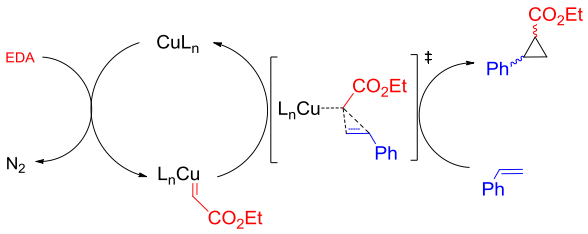
At this stage, only the intimate nature of the coupling of styrene and the carbene unit CHCO_2Et remains somewhat undiscovered. However, this has been proposed to occur by facile and irreversible intramolecular [2+2] cycloaddition to form a palladacyclobutane[27] (Scheme 3). It is worth mentioning that this would be the sole species in the overall catalytic cycle where the metal center would

be in a formal oxidation state +2. The subsequent reductive elimination would afford the cyclopropane and **C**.



Scheme 3. Top: Overall mechanism for the styrene cyclopropanation using complexes **1**-**4** as the catalyst precursors and ethyl diazoacetate as the carbene source. Bottom: Plausible explanation for the intramolecular formation of cyclopropane.

Finally, although the mechanism here proposed is clearly different from those reported for other transition metals as i.e. copper (Scheme 4),[2f, 28] the diastereroselectivity are similar to those observed for other complexes containing NHC ligands. For instance, the N-heterocyclic carbene complex IPrCuCl afforded a diastereoselectivity cis/trans 32:68 in the cyclopropanation of styrene with EDA,[4q] which is almost indentical to those found for the NHC-Pd(0) complexes. Theoretical calculations for copper C_2-symmetric complexes[28b] have revealed that the alkene substituent does not interact significantly with the ligand in any *exo* pathway (structure I in Scheme 3), being the *cis*/*trans* selectivity only a consequence of the relatively weak steric repulsion between carboxylate and alkene substituent in the transition state or intermediate, independently on the mechanism (*via* metallacyclobutane or direct carbene transfer to the olefin). However, other transition metal systems are highly diastereroselective. For example, the $Tp^{Ms}Cu$ complex affords a 98:2 *cis*/*trans* mixture of cyclopropanes from the styrene.[4s] In this case, the combination of the C_{3V} symmetry and steric bulk of the ligand makes the $Tp^{Ms}Cu$ a highly diastereoselective catalyst.



Scheme 4. Proposed mechanism for the styrene cyclopropanation catalyzed by copper systems.

Conclusions

We have shown that several (NHC)Pd(0) complexes can act as very active catalyst in the olefin cyclopropanation reaction with ethyl diazoacetate as the carbene source, improving the previously described catalytic systems based in this metal. On the basis of the kinetic data and other experimental data, we have proposed a mechanism for this transformation in which independently of the catalyst precursor employed [IPrPd(sty)$_2$ or IPrPd(PR$_3$)], the same catalytic species is responsible of the decomposition of EDA and subsequent carbene addition: that is the intermediate IPrPd(sty), that leads to (IPr)Pd(=CHCO$_2$Et)(sty) after interaction with EDA and nitrogen extrusion. The cyclopropane should be formed by a [2+2] cycloaddition reaction involving a palladacyclobutane intermediate. The development of this catalytic system for diazo compound decomposition and carbene transfer along with the knowledge of the intramolecular nature of the reaction (regarding the carbene-olefin coupling) seems promising in terms of the future design of new catalyst to induce high levels of diastereo- or enantioselection upon conveniently modifying the NHC ligand. Work aimed at such catalyst improvements is currently underway in our laboratory.

Experimental Section

General Methods. All reactions and manipulations were carried out under an oxygen-free nitrogen atmosphere by using Schlenk techniques or under nitrogen atmosphere in an Mbraun glovebox. All substrates were purchased from Aldrich. Solvents were dried and degassed before use. The Pd complexes 2-5[18] and the NHC carbene ligands[29] were prepared according to literature methods. NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer. GC data were recorded in a Varian CP-3800. X-ray Crystal Structure Anayse was performed in the Unidad de Analyses Elemental of the Instituto de Investigaciones de Química, CSIC-Universidad de Sevilla and Elemental Analyses in Centro de Investigación en Química Sostenible, CIQSO-Universidad de Huelva.

(IPr)Pd(sty)$_2$ (1). 0.8 mL (6.98 mmol) of styrene were added to a solution of 1.05 g (1.50 mmol) of (IPr)Pd(allyl)Cl[18] and 0.185 g (1.65 mmol) of KO^{t}Bu in ^{i}PrOH (20 mL). Almost immediately, a white precipitate was formed. After 15 min of stirring at room temperature, the solid was filtered and washed with water and ^{i}PrOH . Complex IPrPd(sty)$_2$, **1**, was isolated as a white solid in 90% yield (0.94 g). By recrystallization in toluene at -30 ºC a crystalline solid was isolated (0.84 g, 80% yield). IR (KBr): ν(C=C) = 1505 cm^{-1}. ^{1}H NMR (400 MHz, -40ºC, toluene-d$_8$) δ 6.67 (s, 2H), 3.75 (dd, *J* = 9.3 Hz, *J* = 12.0 Hz, 2H), 3.43 (m, 2H), 3.07 (d, *J* = 12.4 Hz, 2H), 2.94, (d, *J* = 8.9 Hz, 2H), 2.83 (m, 2H), 1.40 (d, *J* =

6.6 Hz, 6H), 1.16 (d, J = 6.5 Hz, 6H), 1.07 (d, J = 7.1 Hz, 6H), 1.05 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz,40ºC,CD_2Cl_2) δ 146.8 (s; *C* arom), 145.8 (s; *C* arom), 144.9 (s; *C* arom), 137.5 (s; *C* arom), 129.5 (s; *C* arom), 127.5 (s; *C* arom), 124.2 (s; *C* arom), 124.1, (s; *C* arom), 123.28 (s; *C*H arom), 124.0 (br s; *C*H imid), 74.66 (s; *C*H olefin), 53.01 (s; CH_2 olefin), 28.93 (s; $CH(CH_3)_2$), 28.32 (s; $CH(CH_3)_2$), 27.21 (s; $CH(CH_3)_2$), 25.28 (s; $CH(CH_3)_2$), 22.84 (s; $CH(CH_3)_2$), 22.31 (s; $CH(CH_3)_2$). Anal. Calcd for $C_{43}H_{53}N_2Pd$: 73.37% C, 7.53% H, 3.98% N. Found: 72.75% C, 7.52 % H, 3.97% N.

In situ preparation of IMesPdPCy$_3$ (6). 6 was generated *in situ* by the following procedure: 30 mg of IMes[28] (0.01 mmol) was added to a solution of 66 mg of $Pd(PCy_3)_2$[30] (0.01 mmol) in 10 mL of CH_2Cl_2. After 10 minutes of stirring the solution was used directly in the cyclopropanation experiments. To characterize **6** by a NMR spectrocopy this complex was also prepared *in situ* by dissolving a stoichiometric amount of IMes and $Pd(PCy_3)_2$ in 0.7 mL of C_6D_6. ^{1}H NMR (400 MHz, C_6D_6) δ 6.79 (s, 4H), 6.21 (s, 2H), 2.30 (s, 12H), 2.16 (s, 6H), 2.0-1.0 (m, 30H). ^{13}C NMR (100 MHz, C_6D_6) δ 198.2 (d, $^2J_{CP}$ = 90.79 Hz, *C* carbene) 138.4 (s, *C* arom), 137.1 (s, *C* arom), 135.3 (s, *C*H arom) 128.7 (s, *C*H arom), 121.2 (d, $^4J_{CP}$ = 4.3 Hz, *C* imid), 34.5 (d, $^2J_{CP}$ = 12.1 Hz, *C*H Cy), 31.9 (d, $^4J_{CP}$ = 7.3 Hz, *C*H_2 Cy), 27.8 (s, *C*H_3), 26.8 (s, *C*H_3), 21.1(d, $^2J_{CP}$ = 16.1 Hz, *C*H_2 Cy), 18.7 (d, $^3J_{CP}$ = 9.0 Hz, *C*H_2 Cy). ^{31}P (100 MHz, C_6D_6) δ 46.6 ppm.

Genaral Catalytic Cyclopropanation Reactions. 1 mmol of EDA (0.12 mL) was added to a solution of 0.01 mmol of the palladium complex (**6** generated in situ) in 10mL of CH_2Cl_2 and 5 mmol of the corresponding olefin. The consumption of the EDA was monitored by GC. When the reaction was finished, volatiles were removed under vacuum and the reaction crude was analyzed by ^{1}H NMR spectroscopy. All the products have been previously described and their identification came straighforward by comparison with reported data.[31] Conversions were determined by ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene as an internal standard.

Reaction of 3 with EDA: ylide formation, Ph$_3$P=CHCO$_2$Et. 3 equiv of EDA (7 μL) were added to a solution of 0.02 mmol of IPrPdPPh$_3$, **3**, in 0.6 mL of C_6D_6. After 24 h the reaction was analyzed by NMR spectroscopy at room temperature and the ylide formation is observed. ^{31}P NMR spectrum of the reaction mixture shows two peaks corresponding to the geometrical isomers of the ylide (δ 19.3 ppm and 17.4 ppm) and, accordingly, a doublet corresponding to the *CH* of the $Ph_3P{=}CHCO_2Et$ can be observed at δ 3.61 ppm ($^2J_{HP}$= 24.0 Hz) in the ^{1}H NMR spectrum.

Reaction of 1 with DEF. Detection of IPrPd(Fumarate)$_2$. 3 equiv of diethyl fumarate (10 μL) were added to a solution of **1** (0.02 mmol) in 0.6 mL of CD_2Cl_2. The reaction was monitored by ^{1}H NMR spectroscopy. At room temperature fluxional behavior was observed. At low temperature (-40 ºC) selected resonances of the adduct $(IPr)Pd(DEF)_2$ can be assigned: two doublets at δ 4.51 and 3.73 ppm (d, 2H, $^3J_{HH}$ = 10.4 Hz) were observed corresponding to the *CH* of the coordinated DEF, assigned by comparison with the related $(IMes)Pd(DMF)_2$.[16d]

Competition Reactions Experiments. 0.5 mmol of EDA (60 μL) were added in one portion to a solution of the complex **(**IPr)Pd(PPh$_3$), **3**, (7.5 mg, 0.01 mmol), styrene (0.28 mL, 2.5 mmol) and 1-hexene or ciclooctene (2.5 mmol) in 10 mL of dichloromethane,. The reaction mixture was monitored by CG until all the EDA was consumed. The volatiles were removed under vacuum and the crude of reaction was analyzed by ^{1}H NMR spectroscopy. The resonances of the corresponding cyclopropanes were assigned in the ^{1}H NMR spectra by comparison with the reported values in the literature.[30] The ratio of the cyclopropanes were obtained by integration (average of at least two runs).

Cyclopropanation Competition Experiments of *para*-Sustituted Styrenes (Hammett's Plot). 0.5 mmol of ethyl diazoacetate were added to solution of **1** (0.01 mmol) and an equimolar mixture of styrene (2.5 mmol) and the corresponding *para*-substituted styrene (2.5 mmol) in 10 mL of dichloromethane. The reaction was monitored by CG. The volatiles were removed under vacuum and the crude of reaction was analyzed by ^{1}H NMR spectroscopy. The resonances of the corresponding cyclopropanes were assigned in the ^{1}H NMR spectra by comparison with the reported values in the literature.[32] The ratios of the cyclopropanes obtained by integration (average of at least two runs): *p*-OMe/H = 0.85; *p*-Me/H = 0.94; *p*-Cl/H = 1.25; *p*-CF_3/H = 1.50.

Olefin Exchange Reaction between (IPr)Pd(sty)$_2$ (1) and styrene (Eyring's Plot). A solution of 6 equiv of olefin (84 mM) and $(IPr)Pd(sty)_2$ (14 mM) (**1**) in 0.6 mL of toluene-d_8 and was transferred to an NMR tube. The solution was monitored by NMR spectroscopy at different temperatures.

Kinetic Experiments. Nitrogen evolution measurements were performed in a device consisting of a stainless-steel gas reservoir doubly connected to a pressure transmitter, and an electronic pressure meter/controller (EL-Press, Bronkhorst HI-TEC). The outlet of the pressure controller was connected to a 100 mL reaction flask, also connected to a Schlenk manifold to allow for manipulation of the reaction and degassing. The N_2 pressure increase was measured after addition of EDA (0.95 mmol) to a stirred solution of styrene and the palladium in dichloromethane at room temperature. The apparatus was tested by carrying out the cyclopropanation reaction of styrene with EDA using $Tp^{Br3}Cu$ as catalyst. 5 mmol of styrene and 0.0025 mmol of $Tp^{Br3}Cu$ were disolved in 10 mL of dichlomethane and 0,95 mmol of EDA were added. The $Tp^{Br3}Cu$ complex catalyzed the decomposition of 0.95 mmol of EDA (100μL) and N_2 pressure increased 0.25 bar.

General Kinetic Experiments. Nitrogen evolution measurements were performed in an apparatus consisting of a stainless-steel gas reservoir doubly connected to a pressure transmitter, and an electronic pressure meter/controller. The outlet of the pressure controller was connected to a 100 mL reaction flask and to a Schlenk manifold to allow for manipulation of the reaction and degassing. The N_2 pressure increase was measured after addition of EDA (0.95 mmol) to a stirred solution of styrene and the palladium catalyst in dichloromethane at room temperature. The apparatus was tested by carrying out the cyclopropanation reaction of styrene with EDA using $Tp^{Br3}Cu$ as catalyst. 5 mmol of styrene and 0.0025 mmol of $Tp^{Br3}Cu$ were disolved in 10 mL of dichlomethane and 0,95 mmol of EDA were added. The $Tp^{Br3}Cu$ complex catalyzed the decomposition of 0.95 mmol of EDA (100μL) and N_2 pressure increased 0.25 bar.

Crystal data for 1. $C_{57}H_{68}N_2Pd$ [$C_{43}H_{52}N_2Pd$, 2(C_7H_8)] , M_w = 887.53, a single crystal of suitable size, yellow prism (0.43 x 0.42 x 0.40 mm^3) crystallised from toluene, coated with dry perfluoropolyether was mounted on a glass fiber and fixed in a cold nitrogen stream [173(2) K] to the goniometer head. Orthorhombic, space group *Pccn* (no.56), a = 19.8389(14) Å, b = 22.3293(14) Å, c = 22.5270(16) Å, V = 9979.2(12) Å^3, Z = 8, ρ_{calcd} = 1.181 gcm^{-3}, λ(Mo $K_{\alpha1}$) = 0.71073 Å, F(000) = 3760, μ = 0.409 mm^{-1}. 163375 Reflections were collected from a Bruker-Nonius X8Apex-II CCD diffractometer in the range 2.74 < 2θ < 56.62° and 12363 independent reflections [R(int) = 0.0695] were used in the structural analysis. The data were reduced (SAINT) and corrected for Lorentz polarisation effects and absorption by multiscan method applied by SADABS[33,34] . The asymmetric unit of **1** is formed by two independent half-complexes having twofold rotation symmetry and also two solvation toluene molecules; one of toluene molecules was observed disordered in two positions with occupancy factor fixed to 0.6 and 0.4

respectively. The structure was solved by direct methods (SIR-2002)[35] and refined against all F^2 data by full-matrix least-squares techniques (SHELXL97)[36] converged to final R_1 = 0.0594 [$I > 2\sigma(I)$], and wR_2 = 0.2017 for all data, with a Goodness-of-fit on F^2, S = 1.072 and 583 parameters.

Acknowledgment. We thank Prof. P. J. Pérez (Univ Huelva) for the helpful and constructive comments on these studies. We thank the Ministerio de Ciencia e Innovación (grants CTQ2008-00042BQU and CTQ2011-24502), the Junta de Andalucía (Proyecto P07-FQM-02794) for financial support. CM thanks the MEC for a research fellowship.

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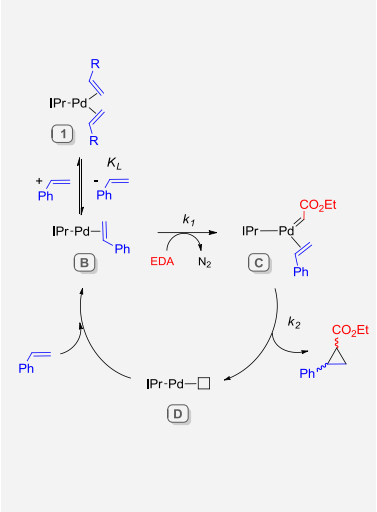
Entry for the Table of Contents

Layout 1:

NHC-Pd(0) complexes as cyclopropanation catalysts

*Carmen Martín, Francisco Molina, Eleuterio Alvarez, Tomás R. Belderrain** Page – Page

Stable N-Heterocyclic Carbene-Palladium(0) Complexes as Active Catalysts For Olefin Cyclopropanation Reactions with Ethyl Diazoacetate



The Pd(0) complexes $NHCPdL_n$ (L = styrene or phosphine) catalyze the olefin cyclopropanation using ethyl diazoacetate (EDA) as the carbene source with activities that improve any other previous described catalytic system based in this metal. Mechanistic studies have shown that all those catalyst precursors deliver in solution the same catalytic species (IPr)Pd(sty), a 14e, unsaturated intermediate that further reacts with EDA to afford (IPr)Pd(=$CHCO_2Et$)(sty), from which cyclopropane is formed.