Mechanochemical Regulation of Oxidative Addition to a Palladium(0) Bisphosphine Complex

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ABSTRACT: Here, we report the effect of force applied to the biaryl backbone of a bisphosphine ligand on the rate of oxidative addition of bromobenzene to a ligand-coordinated palladium center. Local compressive and tensile forces on the order of 100 pN were generated using a stiff stilbene force probe. A compressive force increases the rate of oxidative addition, whereas a tensile force decreases the rate, relative to that of the parent complex of strain-free ligand. Rates vary by a factor of ~6 across ~340 pN of force applied to the complexes. The crystal structures and DFT calculations support that force-induced perturbation of the geometry of the reactant is negligible. The force-rate relationship observed is mainly attributed to the coupling of force to nuclear motion comprising the reaction coordinate. These observations inform the development of catalysts whose activity can be tuned by an external force that is adjusted within a catalytic cycle.

INTRODUCTION

It is now well appreciated that coupled mechanical forces can influence the rates and outcomes of covalent chemical reactions in isolated polymers and in bulk polymeric materials (covalent polymer mechanochemistry).[1] Examples of covalent mechanochemistry include biasing and probing reaction pathways,[2] the release of small molecules and protons,[3] stress reporting,[4] stress strengthening,[5] degradable polymers,[6] and fundamental studies of polymer behavior under load.[7] Mechanochemical coupling has been investigated in simple bond dissociation reactions[8] and in a wide variety of reaction classes with respect to regiochemistry,[9] orbital symmetry,[9a, 10] stereochemistry,[11] supramolecular architecture,[12] and dynamic effects.[13] Most reported examples of mechanochemical reactions involve loading geometries in which the applied force directly distorts the bonds or bond angles at the site of bond breaking. It is now appreciated that mechanochemical reactions involve much more than simply breaking of loaded bonds, and that there exists rich opportunities for new reactivity at sites within a molecule that may not be directly coupled to the applied force.[14] For example, mechanochemical loading of a reactant may accelerate a net bond forming transformation by transiently generating a fully bonded but strained reactive intermediate which is then trapped by another reactant in solution. Unambiguous experimental realizations of this scenario are, however, lacking.[15]

Applying mechanical force to transition metal complexes represents a largely untapped strategy to modulate reactivity. Mechanical forces have been used previously to activate latent catalysts by accelerating dissociation of an inhibiting ligand,[16-20] but tuning catalytic activity by force acting on an intact ligand scaffold remains limited to a single demonstration of force-dependent enantioselectivity of asymmetric Heck arylations and Trost allylic alkylations.[21] More recently, mechanical forces coupled to a bidentate ligand were shown to affect the rate of a common elementary reaction, the reductive elimination from a platinum diaryl complex, with a tensile force accelerating and compressive force inhibiting this reaction.[22]

A better understanding of how force applied to ligand spheres alters the reactivity of the metal center offers hitherto unrecognized opportunities in catalysis. Many organometallic reactions occur through multiple microscopic steps between discrete intermediates, and the kinetics of those steps is often affected differentially by ligand geometry. For example, the cross-coupling of aryl halides with organomagnesium reagents catalyzed by palladium bisphosphine complexes (Kumada coupling) is believed to proceed via sequential oxidative addition/transmetallation/reductive elimination.[23-25] However, because the initial oxidative addition of these coupling reactions is likely facilitated by small bite angles,[26-29] whereas product-forming reductive elimination is facilitated by large bite angles,[26, 30-32] the most effective catalyst is believed to represent a compromise among the various microscopic steps,[26, 29, 33] and variations of this fundamental tradeoff apply to many other catalytic transformations. Therefore, catalysts that can be reversibly switched between states that are optimized for distinct elementary steps on the timescale of catalytic turnover[34] or polymer enchainment[35, 36] might circumvent the inherent limitations of geometrically static transition metal catalysts.

Here we report that forces of tension applied to a bisphosphine ligand decelerate the oxidative addition of bromobenzene to a complexed palladium center (Figure 1). Notably, the only bond that is formally broken during the reaction is

the carbon-bromine bond of the freely diffusing (and therefore completely force-decoupled) bromobenzene reagent. The use of macrocyclic force probe ligands allows the force-reactivity relationship to be quantified, and we find that the applied forces exert an opposite effect on oxidative addition relative to that previously reported for reductive elimination, laying the groundwork for mechanically switchable catalysts that can be optimized for individual steps within a closed catalyst cycle.
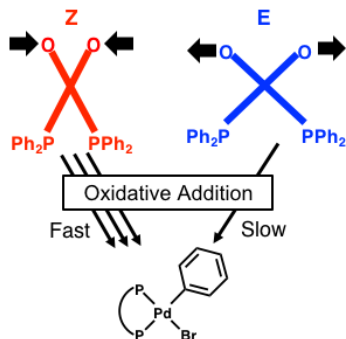

Figure 1. Schematic representation of force probe perturbations on oxidative addition rate.

RESULTS AND DISCUSSION

We chose to study the oxidative addition of bromobenzene to the low-ligated palladium(0) complexes generated via reduction of palladium dichloride complexes containing the macrocyclic bisphosphine ligands E/Z(n,m) (*n,m* = 2,2; 2,3; 3,3; Figure 2). These ligands comprise a stiff stilbene (1,1-biindane) force probe[37] to either stretch or compress the widely-used Biphep [2,2'-bis(diphenylphosphino)-1,1'-biphenyl] ligand.[38] The magnitude of the force imposed by stiff stilbene on the Biphep moiety depends on the isomeric state of stiff stilbene (Z generates compressive force and E tensile force) and the length of the molecular straps connecting it to the Biphep moiety. The nontethered MeOBiphep and unconstrained Indande-Biphep ligands were employed as force-free controls (Figure 2). The oxidative addition of bromobenzene to low ligated Pd(0) complexes (Scheme 1) was targeted for investigation because this transformation mimics the oxidative addition event in the Kumada coupling and related cross coupling reactions,[39-41] proceeds quantitatively on conveniently measured time scales near ambient temperature, and is uncomplicated by the endergonic dissociation of strongly bound ligands such as PPh3 or DBA prior to the oxidative addition event and the more complex reductions associated with Pd(OAc)2.[42]
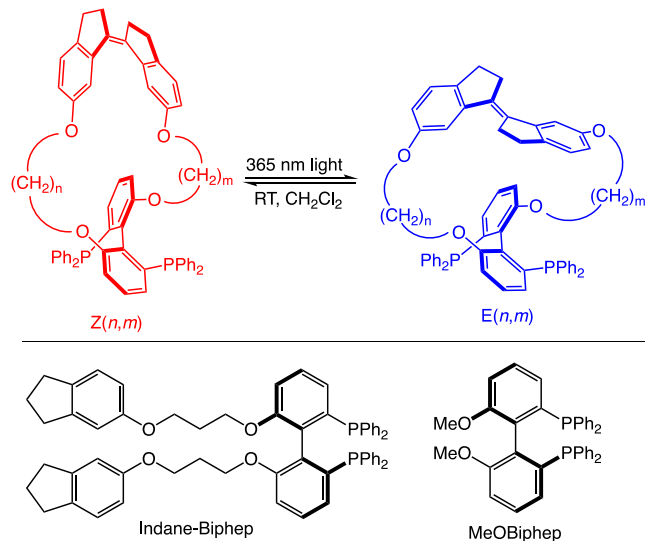

Figure 2. Force probe ligands **Z**(n,m) and **E**(n,m) with various tether lengths are photoswitched at 365 nm in the absence of palladium and isolated (red and blue); strain-free control ligands (black).

We quantified the mechanical effect of the stiff stilbene on the Biphep ligand as the restoring force of its $_{biphen}O^{...}O_{biphen}$ coordinate using a previously described and validated approach.[42-44] Briefly, we first calculated the correlation between the $_{biphen}O^{...}O_{biphen}$ distance in the two-coordinate (MeOBiphep)Pd and three-coordinate (MeOBiphep)PdCl$^-$ complexes and force acting between their respective pairs of MeC atoms by relaxed potential energy scan of the MeC...MeC distances. We then used these correlations to estimate the force imposed by stiff stilbene on the Pd(biphen) moiety in the corresponding complexes from their calculated $_{biphen}O^{...}O_{biphen}$ distances. For palladium complexes with multiple thermally accessible conformers, the force was estimated for each conformer and the forces were ensemble-averaged. For the same ligand conformer, the difference of the forces in the two-coordinate and three-coordinate complex was <20 pN. Thus, the geometry of the ligand backbone is correlated quantitatively with the force applied to the (P-P)Pd(0) complex. We chose the $_{biphen}O^{...}O_{biphen}$ coordinate to quantify the externally imposed load to enable comparisons with previous work on mechanocatalysts and to guide future work incorporating palladium bisphosphine complexes into stretched polymers. Our calculations suggest that across the macrocyclic ligands described here, the force varies over 340 pN, comparable to the range accessed in, for example, constant velocity single molecule force spectroscopy studies of mechanically coupled reactions.[44]

The requisite palladium dichloride precursors (P-P)PdCl2 (P-P = force probe ligand) were isolated as yellow solids from reaction of (COD)PdCl2 with force probe ligands (Scheme 1). Of these complexes, [Z(3,3)]PdCl2 and (MeOBiphep)PdCl2 were characterized in the solid state by single crystal X-ray diffraction (see SI). We were unable to isolate the palladium dichloride complex [*E*(2,2)]PdCl2, indicating that the most extended force probe ligand *E*(2,2) is too open to bind the palladium center in a bidentate fashion.

Scheme 1. Oxidative addition of bromobenzene to (P-P)Pd(0) complexes.
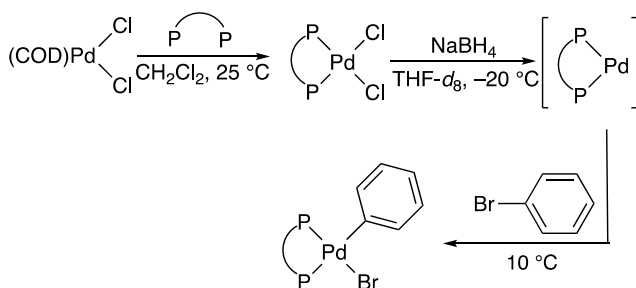
The reactive low ligated (P–P)Pd(0) (P–P = force probe ligand) complexes were generated in situ via reduction of the corresponding (P–P)PdCl$_2$ compounds in THF at –20 °C with triglyme solution of NaBH$_4$. This procedure, which represents a modification of the method reported by Pregosin, led to quantitative reduction with stoichiometric NaBH$_4$.[46] With the exception of the indane-Biphep complex (vide infra), reduction of (P–P)PdCl$_2$ quantitatively generated a single (P-P)Pd(0) complex as judged by the presence of a single sharp resonance in the ^{31}P NMR spectra of the symmetric 2,2, 3,3, and MeOBiphep complexes and two broad resonances in the ^{31}P NMR spectra of the nonsymmetric 2,3 complexes. For all these ligands except Z(3,3), the ^{31}P NMR resonance of the (P–P)Pd(0) complex was shielded by $\Delta\delta$ = 2.2 - 3.0 relative to the corresponding (P–P)PdCl$_2$ complexes, whereas the ^{31}P NMR resonance of the [Z(3,3)]Pd(0) complex was shielded by $\Delta\delta$ = 4.0 relative to [Z(3,3)]PdCl$_2$. The larger shift in resonance suggests that the structure of the Z(3,3)Pd(0) complex differs from that of the other complexes. The modest force exerted by the Z(3,3) ligand suggests this behavior is not related to force, which is expected to be minimal, but perhaps something particular to the Z(3,3) macrocycle.

In contrast to all other (P–P)PdCl$_2$ complexes investigated, reduction of (indane-Biphep)PdCl$_2$ in THF at –20 °C formed two discrete (indane-Biphep)Pd(0) complexes as revealed by presence of a ~2:1 ratio of resonances at δ 19.79 and 18.85 in the ^{31}P NMR spectrum. The chemical shift of the lower frequency resonance is similar to that observed for [Z(3,3)]Pd(0) (δ 18.78) and the higher frequency resonance is similar to that observed for (MeOBiphep)Pd(0) (δ 20.15). As described in detail in the Supporting Information, [Z(3,3)]Pd(0) and the minor (indane-Biphep)Pd(0) species are both spectroscopic and reactive outliers, as the addition of C$_6$H$_5$Br to these complexes is significantly faster than to any other Pd(0) complex studied here. Because equilibration between the two (indane-biphep)Pd(0) species is considerably slower than is oxidative addition of bromobenzene to either species, the minor (indane-biphep)Pd(0) complex did not affect the observed reactivity of the major species. Given their distinct spectroscopy and reactivity, [Z(3,3)]Pd(0) and the minor (indane-Biphep)Pd(0) species are not comparable to any other Pd(0) complex studied here and we therefore excluded them from our analysis of force on reactivity.

The kinetics of oxidative addition were evaluated as follows. Addition of excess bromobenzene (20 equiv, 0.32 M) to solutions of (P–P)Pd(0) complexes (16 mM) in THF-d_8 at 10 °C yielded the corresponding (P–P)Pd(Ph)Br complexes exclusively, with complete consumption of (P–P)Pd(0), followed by ^{31}P NMR (Table 1). Formation of (P–P)Pd(Ph)Br

was established by the appearance of a diagnostic pair of mutually coupled doublets at δ ~23 and ~7 ($^2J_{PP}$ = 40-42 Hz) (Table 1). The kinetics of the addition followed the pseudo-first order law, and the resulting pseudo first-order rate constants were used to assess the impact of force on the relative reactivity. The rate of oxidative addition varied ~6-fold across the series of six complexes studied. Qualitatively, compressive forces accelerate the reaction, whereas tensile forces decelerate it (Figure 3a).

Table 1. Pseudo-first order rate constants, the restoring forces of the (P–P)Pd(0) complexes for the oxidative addition of bromobenzene to (P–P)Pd(0) complexes in THF-d_8 at 10 °C. [PhBr]$_0$ = 0.32 M; [(P–P)Pd(0)]$_0$ = 16 mM. P–P coupling constants for the (P–P)Pd(Ph)Br products.

P–P	$(10^4)k_{obs}$ (s^{-1})[a]	Force (pN)	$^2J_{PP}$ (Hz)
Z(2,2)	7.83 ± 0.27	–73	41.5
Z(2,3)	6.94 ± 0.01	–3	41.4
MeOBiphep[b]	5.77 ± 0.39	0	42.0
Indane-Biphep[c]	3.57 ± 0.12	0	42.2
E(2,3)	1.35 ± 0.03	270	40.2
E(3,3)	1.14 ± 0.01	273	40.2

[a]Average of two independent experiments. [b][(P–P)Pd(0)]$_0$ = 5 mM. [c]Major species.
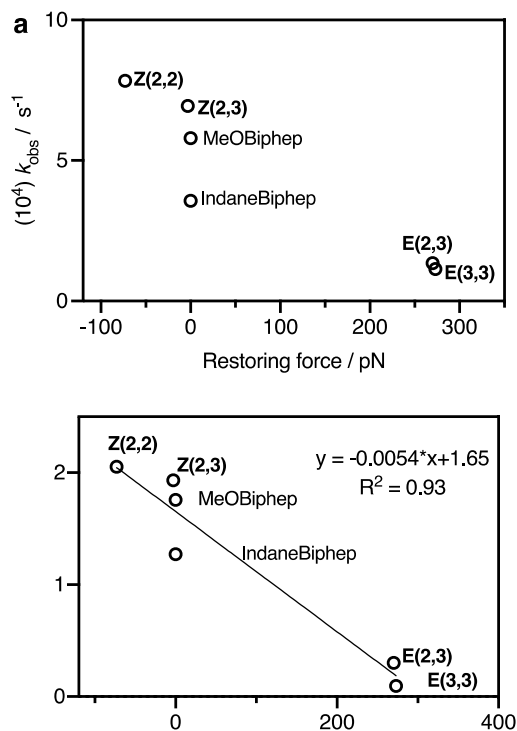
Figure 3. a. Rate constants of oxidative addition at different restoring forces; b. Natural logarithm of rate constants versus restoring forces.

The force-dependent reactivity of the (P-P)Pd(0) complexes with bromobenzene is notable, as the carbon-bromine bond undergoing insertion is completely decoupled from the applied force. Instead, force is loaded into bond angle deformations that are remote from, but associated with,

the specific bond making and bond breaking events that define the oxidative insertion of Pd into the C-Br bond. In addition, with few exceptions[14b] quantitative studies of force-coupled mechanochemical reactions reported to date have focused on reactions that are accelerated by tension (decelerated by compression). For example, tension accelerates the complementary process of reductive elimination from Pt complexes bearing the same family of bisphosphine ligands employed here.[22] The opposite dependence is observed here; oxidative addition is decelerated by tension (accelerated by compression). The inverse dependencies of reductive elimination and oxidative addition are consistent with these two processes traversing a similar transition state in opposite directions and thus experiencing opposite changes in the P–M–P bond angles on the reaction coordinate proceeding to the transition state. The magnitude of the effect observed here, ~6-fold decrease in rate over ~300 pN of force, is comparable to the 3-fold acceleration of reductive elimination across a similar range of forces.

Table 2. Computed forces of the O···O coordinate and P–Pd–P bond angles in optimized geometry of (P-P)Pd(0) and (P-P)Pd(0)Cl$^-$ complexes.

P–P	(P-P)Pd(0)		(P-P)Pd(0)Cl$^-$	
	Force (pN)	P–Pd–P (°)	Force (pN)	P–Pd–P (°)
Z(2,2)	–73	117	–55	106
Z(2,3)	–3	119	–20	105
MeOBiphep	0	118	0	107
E(2,3)	270	120	260	109
E(3,3)	273	120	285	108

The effect of mechanical force on rate can be thought of as arising from two mechanistic extremes:[47-48] (i) "static" mechanical distortions to the geometry of the complex, such as a change in L-M-L bond angle or M-L bond lengths or (ii) "dynamic" mechanochemical coupling of force to the nuclear motions associated with the progress of the reaction from reactant to transition state. The former can alter catalytic activity either by changing the sterics of the active site or adjusting the energy and shape of molecular orbitals that participate in catalytic reactions and are akin to the perturbations generally taken into account when evaluating classic bite angle effects.[26,29] The latter changes the activation free energy, relative to the force-free reaction, by altering the strain of molecular degrees of freedom outside the reactive site. Whereas the "static" effects cannot be predicted quantitatively for a general reaction, a usefully accurate estimate of the "dynamic" contribution is approximated as $-f \cdot \Delta x^{\ddagger}$,[49] where $\Delta x^{\ddagger}$ is the difference in the molecular length along the pulling axis (O···O in our case) and f is the applied force (Figure 4). Stretching force is assumed to be positive, and compressive negative, so that a transition state that is longer along the pulling axis than the reactant is stabilized by tensile force and destabilized by compressive force. In mechanochemical reactions analyzed to date,[46] dynamic coupling dominates. Although dynamic mechanochemical coupling has not been considered explicitly as a parameter to rationalize bite angle effects in bisphosphine transition metal complexes, Casey's concepts of natural bite angle (β_N) and ligand flexibility clearly acknowledge the potential modulation of the reactivity of a transition metal

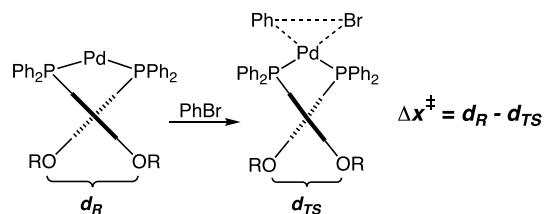complex by a bisphosphine ligand in a manner distinct from perturbations of the P–M–P bite angle.[50]

Figure 4. Correlation between O···O distance and oxidative addition, shown for the reaction of a (P-P)Pd(0) complex. As the coordination number at Pd increases during the addition to accommodate the substrate, a contraction in P-Pd-P angle and the O···O distance is expected. When the O···O distance is coupled to an applied force f, the coupled mechanical potential energy of the reaction changes by –fΔx. If Δx is constant, this leads to an exponential dependence of rate on force.

Across the forces involved here, available evidence suggests that the geometry of the first coordination sphere of Pd varies negligibly with force. For example, the ^2J(P–P) of the (P–P)Pd(Ph)Br products of oxidative addition vary by <2 Hz across the full series (Table 1). Previous literature reports reveal that ^2J(P–P) is sensitive to the geometry of similar complexes (see **SI**), increasing from 27 to 54 Hz[51] with only a 6° increase in the P–Pd–P angle.[26] Unfortunately, the absence of P–P coupling in the reactive (P-P)Pd(0) complexes precluded similar analysis. However, DFT calculations of conformational ensembles of two-coordinate (P–P)Pd(0) complexes and the minimum-energy conformers of three coordinate (P–P)Pd(0)Cl$^-$ complexes-point to minimal structural perturbations of the coordination sphere of low-ligated (P-P)Pd(0) complexes. The structures were optimized at the B3LYP/6-31G(d) level (LANL2DZ for Pd) in THF represented with the CPCM model and the single-point energies calculated at M06-2L/6-311+G(d) (LANL2TZ for Pd). In both 2-coordinate and 3-coordinate Pd complexes, the P-Pd-P angles increased by only <0.8° per 100 pN, corresponding to the variation of ~3° across the series (Table 2).

The minimal structural perturbations of the reactants suggest that the observed rate change is predominantly 'dynamic' in origin. The conclusion is consistent with both the linear scaling of the log of the observed rate constant with the calculated ensemble-average restoring force (Fig. 3b) and the results of the DFT calculations.

As the coordination number at Pd increases during the addition to accommodate the substrate, a contraction in P-Pd-P angle and the O···O distance is expected (Figure 4).[39-41] Such a contraction is expected regardless of whether the resting state is two or three coordinate, but our calculations suggest that under standard conditions in THF, 2-coordinate (P-P)Pd(0) complexes are more thermodynamically stable than their charged 3-coordinate (P-P)Pd(0)Cl$^-$ analogs by 10-13 kcal/mol and that addition of C_6H_5Br traverses a single transition state containing formally a four-coordinate Pd center (Fig. S11). Attempts to optimize the transition state for addition of C_6H_5Br to 3-coordinate (MeOBiphep)PdCl$^-$ complex resulted in the same transition state structure as in Fig. S11 and unbound Cl$^-$. The

formation of the transition state requires contraction of the P-Pd-P angle (by 13° in (MeOBiphep)Pd and 9° in [Z(2,2)]Pd) and of the O···O distance in [Z(2,2)]Pd by 0.04 Å. As such, a compressive force on the Biphep ligand achieves some of the necessary contraction in the reactant, and reduces the energy needed to form the transition state.

Although the effect of force on the rate of oxidative addition reported here is modest, these results are mechanistically and practically significant. In the current system, force transduction from stiff stilbene to the phosphorous atoms is limited owing to excessive crowding in the phosphine PPh$_2$ cleft of the MeOBiphep moiety. Calculations on the free ligand suggest that the change in P···P distance is only ~20% of the change in O···O distance that drives the distortion in the active site (note that this effect is different from the coupled motion between oxygens to geometric changes that occur in response to chemically triggered geometry changes in the phosphine binding cleft). As a result, large stresses in the macrocycle are generated, but they are partially accommodated outside the binding site of the complex. In the future, we posit that less crowded phosphines in the binding cleft should result in a more efficient transfer of strain from the oxygen atoms to which force is applied into the metal binding site.

CONCLUSIONS

In summary, we have shown that forces of tension decelerate the oxidative addition of bromobenzene to low-ligated (P–P)Pd(0) complexes. This behavior contrasts that previously documented for the reductive elimination from platinum biaryl complexes, which was accelerated by forces of tension. The difference in the metal notwithstanding, demonstrating that two key steps in catalytic cross coupling – oxidative addition and reductive elimination – are affected differently by forces that can be achieved reversibly, repeatably, and rapidly in existing soft mechanochemical devices,[52] is central to the future realization of mechanically responsive catalysts possessing activity than cannot be realized by static catalysts. Slightly greater forces, such as those generated in E(2,2), might elicit qualitatively different responses from those observed here, for example by enabling isolation of hitherto unobservable intermediates. We also see significant room to improve the force sensitivity of both oxidative addition and reductive elimination by exploiting the lever effect in ligand design. Finally, tunable structural distortion of ligand spheres that is amenable to quantitation by restoring force, might also provide a quantitative framework through which to interpret and optimize other responsive catalyst designs, including those switched photochemically[53] and those that are regulated by allosteric binding.[54]

ASSOCIATED CONTENT

Supporting Information

An experimental section comprising procedures and characterization data for palladium complexes and procedures and analysis of kinetic data. X-ray crystallographic data for (MeOBiphep)PdCl$_2$ and [Z(3,3)PdCl$_2$ in CIF format. Calculated cartesian coordinates for (P-P)Pd and (P-P) PdCl⁻ complexes.

This material is available free of charge via the Internet at http://pubs.acs.org

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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