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Mechanism of C–P bond formation *via* Pd-catalyzed decarbonylative phosphorylation of amides: insight into the chemistry of the second coordination sphere[†]

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We report on the basis of DFT computations a plausible and detailed reaction mechanism for the first Pd-catalyzed decarbonylative phosphorylation of amides forming C-P bonds, which reveals, among other things, crucial events in the second coordination sphere, including ion pair and hydrogen bonding interactions as well as proton transfer.

Organophosphorus compounds, which contain a direct C–P bond, have found a wide range of applications in medicinal chemistry, agrochemicals, and materials sciences.¹ This has motivated research on the methodology for generating C–P bonds. Classical approaches to C–P bonds include the Michaelis–Arbuzov reaction and those using organolithium or Grignard reagents, but these reactions suffer from air sensitivity, toxicity, or poor chemoselectivity.² The Hirao reaction³ ushered in transition metalcatalyzed cross-coupling methods for C–P bond formation, and the C-coupling partners include aryl halides,⁴ sulfonates,⁵ diazonium salts,⁶ boronic acids,⁷ silanes,⁸ pivalates,⁹ and sulfides.¹⁰

Organic amides are stable and readily available compounds. The amide (O)C–N bond is strong due to the $n_{\rm N}$ to $\pi_{\rm C=O}^*$ resonance, and as such, its oxidative addition to a transition metal center is generally extremely difficult. Szostak and co-workers first discovered that *N*-glutarimide amides exhibit unusually high reactivity in Pd-catalyzed acyl and decarbonylative cross-coupling reactions proceeding *via* metal insertion into the amide (O)C–N bond.¹¹ The high reactivity is attributed to a decrease of the π conjugation resulting from the geometric twisting of the *N*-glutarimide amides (Fig. S1, ESI†). Following from the



Scheme 1 Pd- and Ni-catalyzed decarbonylative phosphorylation reactions. Note: dppb = 1,4-bis(diphenylphosphino)butane and dppp = 1,3-bis(diphenylphosphino)propane.

discovery of this unique mode of amide bond activation, Szostak and co-workers have recently accomplished the first transition metal-catalyzed decarbonylative phosphorylation of amides using Pd or Ni catalysts, as shown by the representative reactions in Scheme 1.¹² These reactions form C–P bonds in the products (aryl phosphonates) and show high yields, chemoselectivity, and functional group tolerance, thereby having potential synthetic application. The experimentalists proposed a mechanistic outline involving (O)C–N bond oxidative addition to M(0), decarbonylation, and reductive elimination.

We have chosen to study the Pd-catalyzed reaction (Scheme 1) by DFT computation because it is molecularly better-defined with all the species in homogeneous solution.[‡] We aim at establishing a plausible and detailed mechanism that can elucidate intriguing questions, such as how the dialkylphosphite substrate undergoes formal proton transfer to the glutarimide moiety and why the reaction favors phosphoryl-aryl over phosphoryl-acyl coupling. When we were in the process of carrying out this work, the Yu and Fu group reported a DFT study on the mechanism of the Ni-catalyzed reaction (Scheme 1), which consists of four main steps: oxidative addition (the rate-determining step), phosphorylation, decarbonylation, and reductive elimination.¹³ There are significant differences between their proposed Ni-catalyzed reaction mechanism and the Pd-catalyzed reaction mechanism that we have computed and presented below. The two reactions operate with different metal catalysts under different conditions, so they can have quite different mechanistic details.

In the presence of 1,4-bis(diphenylphosphino)butane (dppb) and Et_3N (Scheme 1), the pre-catalyst Pd(OAc)₂ would be initially

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reduced to active Pd(0) complexes, and this chemistry is known from previous studies.¹⁴ Since one equiv. of dppb is consumed as a reductant, the palladium-containing products would be 1 : 1 Pd : dppb complexes, for which we have optimized three structures: [Pd(dppb)] (1cat), [Pd(dppb)(OAc)]⁻, and [Pd(dppb)(sol)] (Fig. 1).¹⁵ 1cat is the most stable of the three species and therefore considered as the catalyst resting state (Fig. S2, ESI[†]).

Referring to previous computational studies on transition metal-catalyzed (O)C-N bond activation of N-glutarimide amides,16 we envisioned that 1cat would take up the substrate N-benzoylglutarimide via palladium coordination to the benzoyl C=O group. Thus, we located four isomeric complexes (2a-2d, Fig. S3, ESI[†]) by considering the unsymmetrical structures of 1cat and N-benzoylglutarimide, and explored the reaction pathways through each of them. The favorable pathway, which proceeds through 2a, is presented and discussed in the main text, and the analogous, less favorable pathways through 2b-2d are given in Fig. S4-S6 (ESI[†]). As shown in Fig. 2, 2a undertakes oxidative addition via TS1a to insert the metal atom into the amide (O)C-N bond. The Pd-O(glutarimide) ligation at 2.18 Å in TS1a helps stabilize this transition state, which is 17.7 kcal mol⁻¹ with respect to 1cat. TS1a proceeds to the square planar Pd(II) complex 3a, which rearranges to give the more stable 4a with a Pd(II)-N(glutarimide) dative bond. The rearrangement has a sizable driving force $(\Delta G = -12.6 \text{ kcal mol}^{-1})$ because the N atom with a negative charge is a better donor for Pd(n). Decarbonylation from 4a can be ruled out because it would meet the exceedingly high barrier TS2a that is 35.9 kcal mol^{-1} relative to 4a. Thus, we consider 4a to take up the substrate diethylphosphite.

We have traced the interchange transition state **TS3a** where **4a** substitutes diethylphosphite for glutarimide to form **5a**. A salient feature of **5a** is that the glutarimide anion remains in the second coordination sphere through ion pair and hydrogen bonding interactions with the first sphere, forming an $O \cdots H(\text{phosphite})$ hydrogen bond at 2.16 Å. This is crucial for the subsequent steps because separation of the glutarimide anion from the first sphere—the **5a** \rightarrow **6a** process—would incur a huge energy cost and hence shut down the reaction. The phosphite-to-glutarimide proton transfer from **5a** would meet the higher barrier **TS4a**. Thus, **5a** proceeds to **7a** with a $N \cdots H(\text{phosphite})$ hydrogen bond, opening up a lower-energy pathway for proton transfer *via* **TS5a**, which gives **8a** with the detachment of charge-neutral glutarimide



Fig. 1 Three possible Pd(0) dppb complexes from pre-catalyst initiation.

from the second sphere. Complex 8a isomerizes to the more stable 9a with Pd–P ligation because the P atom with a negative charge is a better donor for Pd(II). The reaction pathway thus far is through 1cat $\rightarrow 2a \rightarrow TS1a \rightarrow 3a \rightarrow 4a \rightarrow TS3a \rightarrow 5a \rightarrow 7a \rightarrow TS5a \rightarrow$ 8a \rightarrow 9a, and the two reacting partners converge on the same metal center of 9a. We next consider the ensuing decarbonylation and reductive elimination/coupling processes.

As shown in Fig. 3, no direct decarbonylation pathway from 9a could be found probably due to the increased steric hindrance around the Pd(II) center arising from the Pd-P coordination. Hypothetically, 9a can revert to 8a to launch decarbonylation via the five-coordinate **TS6a**, but this barrier would be 41.7 kcal mol^{-1} with respect to 9a and hence can be ruled out. Phosphorylacyl reductive elimination/coupling from 9a via TS7a would be kinetically viable, giving diethyl benzoylphosphonate and regenerating 1cat, but this step would be highly unfavorable thermodynamically ($\Delta G = 12.1 \text{ kcal mol}^{-1}$). Thus, we continue searching for a pathway leading to the experimentally observed phosphoryl-aryl coupling product. In 9a the diphosphine ligand dppb has four CH₂ units, thereby forming a seven-membered flexible chelate ring, the opening of which through the loss of one of the P coordinations would have a smaller energy cost compared with disrupting five-membered chelate rings. Thus, we have located the open-ring intermediate 10a via the C-C bond rotation, and 10a introduces the four-coordinate decarbonylation transition state **TS8a** that is 31.4 kcal mol^{-1} with respect to **9a**. This barrier, although somewhat high, can be overcome at the experimental temperature (160 °C). It is worth noting that TS8a is lower than TS6a by 10.3 kcal mol⁻¹. TS8a proceeds to 11a, which further isomerizes to the rotamer 12a to undertake intramolecular substitution via TS9a. This interchange step is facile and leads to 13a with the extrusion of the by-product CO(g). Complex 13a then undertakes phosphoryl-aryl reductive elimination/coupling via TS10a to deliver diethyl phenylphosphonate and regenerate 1cat. For the complete reaction pathway (Fig. 2 and 3), the largest energy span is from 9a to TS8a, 31.4 kcal mol⁻¹, which is attainable at the experimental temperature (160 °C). Thus, decarbonylation via TS8a is the rate-determining step. On another important note, the continuous evolution of the gaseous CO by-product in the decarbonylation phase keeps shifting the equilibrium position forward, thereby driving the reaction from 9a to the final products. The formation of diethyl phenylphosphonate (the phosphoryl-aryl coupling product) has a larger overall driving force ($\Delta G = -9.8$ kcal mol⁻¹) than the formation of diethyl benzoylphosphonate (the phosphoryl-acyl coupling product) $(\Delta G = -3.4 \text{ kcal mol}^{-1})$, although the latter is kinetically easier (Fig. 3). Given that the reaction occurs under the conditions of thermodynamic control (160 °C and 16 h), the computed energetics can explain the chemoselectivity that favors phosphoryl-aryl over phosphoryl-acyl coupling.

In summary, we have utilized DFT calculations to elucidate the detailed mechanism of the first Pd-catalyzed decarbonylative phosphorylation of amides. The work has provided valuable insights into this new C–P bond forming reaction. The dialkylphosphite substrate undertakes proton transfer to the glutarimide anion in the second coordination sphere. The flexible diphosphine



Fig. 2 Free energy profile of the pathway from oxidative addition to ligand exchange and proton transfer. Selected bond distances are given in Å (the same below).



Fig. 3 Free energy profile of the decarbonylation and reductive elimination.

ligand can shift between bidentate and monodentate coordination as necessary to enable decarbonylation from Pd(II). The chemoselectivity of C–P cross-coupling originates from a thermodynamic control of product formation. Taken together, the findings of this study will have implications for better understanding transition metal-catalyzed amide bond crosscoupling and C–P bond forming reactions. Finally, we wish to emphasize the important differences between our Pd-catalyzed reaction mechanism and the Ni-catalyzed reaction mechanism described in ref. 13: (1) In the Pd system, the additive Et_3N does not enter the main reaction, and its role is to help initiate the pre-catalyst $Pd(OAc)_2$ as established by earlier studies.¹⁴ The dialkylphosphite substrate undertakes coordination to $Pd(\pi)$, followed by proton transfer to the glutarimide anion in the second coordination sphere, and this process (the **4a–9a** course in Fig. 2) is molecularly well-defined, kinetically feasible, and thermodynamically favorable. In the Ni system, the additive Na_2CO_3 has been entered as a discrete $NaCO_3^-$ ion in the reaction pathway to calculate the deprotonation of the Ni(π)-coordinated dialkylphosphite (see Fig. 1 in ref. 13).

(2) Decarbonylation *via* **TS8a** has been found to be the ratedetermining step in the Pd-catalyzed reaction, whereas oxidative addition has been described as the rate-determining step in the Ni-catalyzed reaction.

(3) The computed energetics can explain the chemoselectivity of the Pd-catalyzed reaction that favors phosphoryl-aryl over phosphoryl-acyl coupling. There is no discussion on chemoselectivity in the work on the Ni-catalyzed reaction.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ Geometries were optimized and characterized by frequency calculations to be minima or transition states at the B3LYP¹⁷/BS1 level in the gas phase, where BS1 represents the mixed basis set with SDD¹⁸ for palladium and 6-31G(d) for other elements. Single-point energies were obtained by M06¹⁹/BS2//B3LYP/BS1 calculations with solvation effects modeled by SMD²⁰ in 1,4-dioxane (the experimentally used solvent); BS2 denoting the mixed basis set with SDD for palladium and 6-311++G(d,p) for other elements. The energies were converted to zero-point energy-corrected Gibbs free energies at 298.15 K and 1 atm, using the B3LYP/BS1 frequencies. All calculations were performed with Gaussian 09.²¹

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