Theoretical Study on the Formation of Ni(PR₃)(Aryl)F Complexes Observed in Ni-Catalyzed Decarbonylative C–C Coupling of Acyl Fluorides

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ABSTRACT: Recently a promising, conceptually new base-free, nickel-catalyzed decarbonylative Suzuki–Miyaura coupling method was reported which employs acyl fluorides to produce transmetalation-active catalytic intermediates. In the present study we have performed computations to identify the reaction mechanism of the formation of these intermediates and to address important reactivity issues. We have contrasted the effect of two typical phosphine ligands (P = PCy₃, PPh₂Me), which show different behaviors according to two recent but separate experimental reports. We have also considered different experimental (stoichiometric and catalytic) conditions to elucidate the corresponding experimental observations. The free energy profiles of the most likely mechanisms supported the more facile formation of the transmetalation-active catalytic intermediate with PPh₂Me and also justified why the intermediate of the oxidative addition cannot be observed for this ligand. A crucial ingredient of the mechanisms is the cis–trans rearrangement in the square-planar ligand structure around the Ni(II) center to stabilize the complexes and to facilitate the Ni insertion preceding the decarbonylation. We obtained two distinct pathways for this rearrangement: either a square-planar–tetrahedral conformational transition or a route through five-coordinated, more fluxional configurations, depending on the phosphines. In fact, molecular dynamics simulations revealed that the mobile trigonal-bipyramidal structures can remarkably simplify the decarbonylation mechanism predicted by optimization calculations, implying an even faster decarbonylation.

INTRODUCTION

C–C coupling plays a crucial role in organic synthetic strategies ranging from constructing backbones to performing late-stage functionalization of target molecules. As these processes require catalysis, highly efficient methods have been developed and are being actively studied. Among them, the palladium-catalyzed Suzuki–Miyaura coupling has exceptional robustness and versatility which have been improved remarkably since its inception. The reaction is initiated by the oxidative addition of an aryl halide to the low-valent Pd(0) center to yield an intermediate in which the halide ligand is replaced by another alkyl or aryl ligand via transmetalation by an organoboron species. The final step is reductive elimination, where the C–C bond is formed and the product is released from the complex. Recent trends in catalyst design involve the replacement of palladium by the cheaper and more accessible nickel while the scope of the halide-based electrophiles and the variety of reaction conditions are expanded. Directly relevant to this work is the application of carbonyl compounds, such as acyl halides and esters, in the first oxidative addition step. These reactions are termed decarbonylative cross-couplings, since they formally involve the elimination of a CO moiety, as is typical in nickel chemistry. On one hand this produces NiLₓ(CO)ₘ complexes that may provide a thermodynamic driving force for the otherwise not spontaneous reactions. On the other hand, such carbonyls are considerably inferior catalysts, reducing or even eliminating the available active nickel species in solution as the reaction proceeds. Therefore, these decarbonylative cross-coupling reactions require the use of nickel catalysts in higher concentrations. Another important aspect of employing carbonyl substrates is that one can obtain “transmetalation-active” intermediates directly in the oxidative addition step. This is due to the possibility of introducing fluoride via acyl fluorides instead of employing other halide ligands that require activation (e.g., replacement with a hydroxide group) with additives such as bases. As external bases may introduce undesired side reactions, this base-free approach provides a more robust alternative to common coupling reactions. The

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concept is built on the earlier work of Schoenebeck, where decarbonylative trifluoromethylation of acyl fluorides was disclosed with Pd catalysis. The summary of the concept is given in Scheme 1. Given the novelty of the process, a mechanistic understanding can contribute in several ways to improve the process such as explaining the apparently different behavior of the employed phosphine ligands. For example, the authors of ref 7a proposed that the observed more rapid decarbonylation with PPh2Me in comparison to PCy3 results in higher selectivity toward the desired biaryl product. The monodentate nature of these ligands implies further intricacies in comparison to other common phosphines, as cis–trans isomerization may take place around the metal center, leading to additional transient intermediates.

In this work, we aim to provide insights into these issues using static DFT calculations and QM/MM molecular dynamics simulations. The solid experimental foundation provided in the reports of the Sanford and Nishihara groups hints at several key features for a possible mechanism, which we use as a basis of this discussion. In line with their results, we develop possible decarbonylation mechanisms for the PPh2Me and PCy3 complexes to help understand their findings. In particular, we address the following issues: identifying the initial resting states, formation of the catalytically active species, mechanism of the oxidative addition and decarbonylation, effect of the ligands on the composition of the ligand sphere of Ni(II), and seeing how the stoichiometric and catalytic conditions affect the reaction mechanisms. We note that the results may also be useful in a larger array of decarbonylative reaction patterns of acyl fluorides, where a Ni(PR3)2(Ph)F-type active intermediate is present. In addition, our results can be inserted into a wider context of the analogous computational models of Pd- or Ni-catalyzed decarbonylative couplings of other carbonyl derivatives such as esters, amides, aldehydes, anhydrides, carboxylic acids, etc.

Our present approach does not address the full reactions disclosed in ref 7. Instead we focus on the formation of the crucial aryl–Ni–F intermediates, scrutinize the corresponding reaction mechanisms, and analyze the effect of the ligands and conditions on the reactivities leading to the formation of the product. Therefore, the present study does not wish to address the debate of the sequence of the decarbonylation and transmetalation. In this regard it is important to recall that both mechanistic scenarios have support. For the original Pd-catalyzed decarbonylative trifluoromethylation reaction Schoenebeck et al. found that transmetalation precedes decarbonylation. For the present concept, Wang et al. also proposed that, with 1-naphthyl fluoride as the substrate, the transmetalation→decarbonylation sequence is more favorable than the decarbonylation→transmetalation sequence within a 2 kcal/mol margin. On the other hand, experimental indications and also calculations for other substrates suggest that decarbonylation precedes transmetalation and that this intermediate plays a crucial role in the mechanism. Note that, although a deeper understanding of this topic would be clearly helpful, using the isolated, bench-stable aryl–Ni–F species avoids ketone byproducts which likely come from a transmetalation-first mechanism.

**COMPUTATIONAL DETAILS**

The DFT calculations were carried out using the Gaussian09 software package. The dispersion-corrected B3LYP-D3 functional was used for optimizations and vibrational analysis in the static calculations. The geometries were optimized inside the solvent (tetrahydrofuran, THF) cavity, which was modeled with the implicit SMD solvent model. The LANL2TZ(f) ECP/basis set was employed on nickel, together with the double-ζ SVP basis set for the nonmetal atoms for structure optimization and frequency calculations. The electronic energies were then calculated using the triple-ζ def2-TZVP basis set for nonmetal atoms and the M06L functional, which proved to be fairly accurate for organometallic reactions. Throughout the work, we report relative Gibbs free energies (∆G) for 25 °C for the reactions under stoichiometric conditions and for 100 °C when the reactions under catalytic conditions are modeled. The pressure was set to 1 atm, which corresponds to 0.04 mol/dm3 concentration, compatible with that applied in experiments. To take into account the selected metal to ligand ratio (1:p, where p = 2, 3), the ligand free energy value is corrected by the factor RT ln(p) when it is necessary. In order to locate the most stable conformers of the stationary states, we have performed conformational searches using the xtlib semi-empirical package. The QM/MM molecular dynamics calculations were performed to obtain information about the stability and structural properties of the most important intermediates in explicit solvent. The simulations were performed using the CP2K software, where the QM subsystem, consisting of the complex itself, was described with DFT, using the PBE functional with D3 dispersion. The MM part contained 187 and 188 THF molecules for the PPh2Me and PCy3 complexes, respectively. The processes were simulated inside a periodic 30.00 × 30.00 × 30.00 Å3 cube, yielding a density approximately the same as that of pure THF (0.889 g/cm3). More details about the QM/MM simulations can be found in the Supporting Information.

### Table 1. Reaction Free Energies (∆G°, kcal/mol) of cod → Phosphine (P) Ligand Exchange Processes at 1:2 and 1:3 Ni to P Ratios at 25 °C

| entry no. | reactants | products | ∆G°c(PPh2Me) | ∆G°c(PCy3) |
|-----------|-----------|----------|---------------|------------|
| 1         | Ni(cod)2 + 3 P | NiP3 + 2 cod | −5.3          | +4.9      |
| 2         | Ni(cod)2 + 2 P | 2/3 NiP3 + 1/3 Ni(cod)2 + 4/3 cod | −3.1          | +3.8      |
| 3         | Ni(cod)2 + 2 P | 1/2 NiP(cod) + 1/2 NiP3 + 3/2 cod | +1.9          | +9.1      |
| 4         | Ni(cod)2 + 2 P | NiP3 + 2 cod | +17.1         | +12.3     |
| 5         | Ni(cod)2 + 2 P | NiP3(cod) + cod | −8.4          | +10.2     |
RESULTS

Resting State. The first step in the calculations is to determine the initial resting state. As the experimental methodologies start with mixing Ni(cod)$_2$ with the phosphine ligand dissolved in an organic solvent, the substrate acyl fluoride is most likely introduced into a solution containing NiP$_3$(cod)$_{m}$ type complexes. Evaluating the stabilities of the possible nickel—phosphine species is therefore necessary to determine the composition of the precataltyst. Both the ligand affinities toward Ni and the amount of phosphine excess (1:2$^{37}$ or 1:3$^{16}$ Ni to P ratio) can influence the equilibrium composition. The results are summarized in Table 1. The most stable species is the diphosphine-cod complex for the PPh$_2$Me ligand (entry 7), whereas it is the initial Ni(cod)$_2$ complex followed by the tris(phosphine) complex (entries 1 and 2) in the presence of PCy$_3$. Table 1 therefore indicates that for both 1:2 and 1:3 Ni to P ratios the smaller PPh$_2$Me ligand (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respectively) will form a NiP$_2$(cod) complex accommodating (the cone angles are 136 and 170° for PPh$_2$Me and PCy$_3$, respecti...
the stoichiometric studies, which is a possible indication of a slow oxidation addition followed by faster reaction steps. An additional important difference between the paths with the two ligands is the origin of the barrier: with PCy₃, the crucial step is the C–F bond breaking, while for PPh₂Me it is the substrate coordination. This can be explained by the extra stabilization of the Ni(PPh₂Me)₂(cod) state, which increases the initial barrier (reactant state stabilization), and also by the smaller size of the phosphine ligands, allowing an easier oxidative addition step.

**Formation of the Transmetalation-Active Nickel Fluoride Intermediates.** In the following we focus on the computed decarbonylation pathways. Since the acyl intermediates III are considerably lower in energy than the initial phosphine complexes for both ligands, the decarbonylation is assumed to proceed from this state. This is supported by the experimental isolation of the PCy₃ complex IIIa. First, we scrutinize the routes obtained with PCy₃ ligands. The mechanism presented in Figure 2 starts with an endergonic phosphine dissociation to reach the tricoordinated 4ₐ intermediate, from which the C–C bond cleavage of the carbonyl and phenyl carbons requires only an ~4 kcal/mol additional energy investment to yield 5ₐ. The next crucial step is the CO dissociation. We found that neither intramolecular CO loss (Figure S1 and Scheme S1) nor intermolecular CO/phosphine ligand exchange can occur for 5ₐ. In fact, the calculations revealed that, if a phosphine ligand attacks intermediate 5ₐ, then IIIa is formed again through a high barrier on a reverse path (see Scheme 2 and Scheme S2). Isomerization initiated by ligand dissociation was also found to be energetically highly unfavorable. Instead, the square-planar complex 5ₐ undergoes isomerization to 6ₐ. This step is necessary to reach a ligand arrangement suitable for decarbonylation via exchange with a PCy₃, as Scheme 2 shows. For square-planar complexes this isomerization takes place via a tetrahedral ligand arrangement. As ligand field splitting considerations dictate, this process may involve a transition between the lowest singlet and triplet surfaces. Indeed, the singlet surface features a high activation barrier (37 kcal/mol; see Figure S2), whereas a metastable intermediate could be located on the triplet surface (Int₅ₐ at 26.8 kcal/mol). The crossings between the singlet and triplet surfaces occur at ~3 kcal/mol higher energies in both directions toward the square-planar intermediates 5ₐ and 6ₐ. Such an equilibrium between the diamagnetic (singlet, square-planar) and paramagnetic (triplet, tetrahedral) isomers is well-known for Ni(II) complexes. 6ₐ is then attacked from the axial direction by the returning PCy₃ ligand. On going through an additional 3.6 kcal/mol barrier, the incoming phosphine replaces the CO moiety to yield the experimentally observed complex IVₐ. There are two key aspects of this mechanism which need to be highlighted. The first one is the 5ₐ to 6ₐ isomerization step, which we found to be necessary to avoid the otherwise more facile conversion back to the initial IIIa complex, as shown by Scheme 2. In fact, the calculations showed that the configuration around the Ni(II) center determines the outcome of the phosphine substitution. The other crucial issue is the fate of the released CO molecule. There are two distinct cases, depending on the experimental conditions. Under stoichiometric conditions, when the metal is in sufficient excess to take up the byproduct CO, all of the substrate molecules form acyl complexes (III) and the remaining Ni(0) species can react with the free CO, yielding carbonyl complexes and making the process thermodynamically sufficiently favorable by ~9.4 kcal/mol (see the Supporting Information for details). Indeed, the formation of the Ni(PCy₃)₂(CO)₂ complex was observed experimentally by Sanford et al., when they used 2 equiv of excess nickel. Under catalytic conditions, however, the thermodynamic driving force of Ni(PCy₃)₂(CO)₂ formation is not present because of the small amount of the Ni catalyst. The driving force here is instead the irreversible escape of CO from the solvent to the gas phase. This is indicated by setting the free energy level to zero. Overall, it is also seen that the profile for the catalytic route indicates a faster decarbonylation, chiefly because of the higher temperature. These results point out important

**Scheme 2. Depending on the Configuration Around the Ni(II) Center Phosphine Attacks Can Lead to the Formation of Intermediate IIIa or IVₐ**

![Scheme 2](https://example.com/scheme2)

*Detailed routes are given in the SI.*

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**Figure 2. Energy profiles of the decarbonylation and CO dissociation when the ligand is PCy₃.** For the color code see Figure 1. Dotted lines indicate transitions between singlet and triplet energy surfaces. The crossing blue (singlet) and green (triplet) curves illustrate the singlet–triplet crossings along the planar–tetrahedral–planar conformational change governing the ligand swapping in 5ₐ to yield 6ₐ. The red values are the calculated electronic energies at the crossing points relative to the energy level of the triplet tetrahedral intermediate Int₅ₐ. Note that the free energy level of 8ₐ is shifted slightly above the level of TS₅ₐ₆ₐ by the large-basis-set calculations. While it is a real TS by the optimization and by vibrational analysis, the larger-basis-set calculations slightly shifted these levels.
limitations of the strategy on conducting stoichiometric studies for assessing the analogous catalytic process: variations in the thermodynamic parameters (concentrations, temperature) can alter the relative order of the free energy levels. This implies that the results of the stoichiometric studies cannot always be translated straightforwardly to the catalytic route in question.

Figure 3 displays the calculated free energy profiles for the PPh₂Me ligand. Both indicate somewhat faster processes in comparison to the routes with PCy₃ ligands. It is also seen that the different conditions induce only small differences between the profiles. The mechanism revealed by the calculations for the ligand PPh₂Me shows important variations from that for the PCy₃ ligand. The mechanism shown in Figure 3 is initiated with acyl C–C bond cleavage between the carbonyl and phenyl groups in III₀ to yield a distorted-trigonal-bipyramidal intermediate, 4b. Such a geometry is not stable for the PCy₃ ligands, and the analogous structures always lost a phosphine ligand during the calculations. In fact, III₀ can also lose a phosphine ligand to yield a three-coordinated complex which requires around a 25 kcal/mol free energy investment. However, the intramolecular rearrangement to form the five-coordinated Ni carbonyl complex 4b goes through a barrier of only ca. 18 kcal/mol (TS₃ab–4b); therefore, this is the preferred direction. 4b then stabilizes by releasing the CO to form 5b (vide infra). This step requires 25.0–25.5 kcal/mol activation energy depending on the conditions. The free CO is either bonded to the excess Ni catalyst to form the Ni-(PPh₂Me)₂(CO)₂ complex or escapes to the gas phase, which shifts completely the equilibrium toward the formation of 5b under catalytic conditions (free energy level is set to 0).

Intermediate 5b obtained after CO loss, however, is the less favorable isomer, featuring the fluoride and phenyl ligands in cis positions, instead of the preferred trans configuration. The second half of the mechanism describes the isomerization process. The calculations revealed that the most likely route of this isomerization involves a partial phosphine dissociation. Indeed, if one of the phosphine ligands departs, this facilitates the cis-to-trans rotation of the fluoride relative to the phenyl ligand via a barrier of 18–20 kcal/mol, depending on the temperature. In the subsequent steps the loosely bonded phosphine returns to the empty cis site and intermediate IVₐ is formed in an overall slightly exergonic process. In general, at variance with the mechanism found for the PCy₃ ligand, for the ligand PPh₂Me we obtained a reversed sequence of isomerization and decarbonylation and found that only partial dissociation is required for isomerization along these routes. These observations can be related to the larger size of PCy₃ and the steric conflicts in its five-coordinated compounds.

Overall, an inspection of the profiles reveals that the rate-determining steps are condition-dependent for both ligands: for the ligand PCy₃ under stoichiometric conditions the ratetermining step of the total route from reactant state to IVₐ is the isomerization step linking 5a and 6a whereas it is the CO dissociation under catalytic conditions. For the ligand PPh₂Me the rate-determining step was computed to be the CO formation. Note that the experimental finding that intermediate III₀ cannot be observed cannot be explained by the late rate-determining step. However, the CO evolution is predicted to have a barrier of height comparable to that of the step leading to III₁ therefore, this trend could be attributed to the uncertainties of the computations. We have therefore decided to study this issue further (see below). Another important observation is that the profiles predict slower reactions for the PCy₃ ligand than for the PPh₂Me ligand (as the higher barriers suggest), again in agreement with experiments where formation of III₀ was reported to be much faster than that of III₀ under stoichiometric conditions.

Dynamic Effects. In the previous discussion we have identified key ingredients in the mechanisms: differences in the ligand-sphere composition before the CO dissociation step (four- vs five-coordination) and the cis–trans isomerization to reach the thermodynamically stable and transmetalation active intermediate state. A crucial difference induced by the ligands along the profiles is that Ni insertion requires phosphine dissociation for intermediate III₀ whereas for III₀ it occurs in the presence of both PPh₂Me ligands. Note that phosphine dissociation from III₀ is computed to be unfavorable kinetically. Our experience and the a posteriori analysis of exploratory free energy simulations suggest that the dissociation processes may be affected quite significantly by the presence of the solvent molecules and this effect cannot be captured sufficiently by the instantaneously adapting continuum approach of the implicit solvent model. Therefore, we have decided to probe the mechanisms by QM/MM simulations: (i) we contrasted the possible phosphine ligand dissociations from intermediates III₀ and IV₀ using metadynamics and (ii) inspected the dynamics of the presumably quite fluxional intermediate 4b to determine its role in CO release.

Calculation of the activation free energy of a dissociation often poses problems for static calculations, as the entropic stabilization of the stationary states cannot be obtained directly from the typical total energy calculations; instead, it is calculated using the vibrational spectra of the stationary states and the harmonic oscillator/rigid rotor/ideal gas approxima-
tion as a postprocessing treatment. The advantage that QM/MM free energy methods offer is that the various entropy contributions can be explicitly taken into account in the simulations and, once a reliable reaction coordinate is identified, a sufficiently accurate free energy profile can be obtained. In the present case the free energy information has been collected by employing metadynamics that proved to be very efficient for chemical reactions and in general for rare events. The phosphine ligand dissociations were described by simple coordination numbers (CNs). A CN is a smooth function (see Figure S4) of the distance between the separating atoms with the intuitive behavior to gradually decrease its value by unity upon a dissociation event. In our case the initial coordination number of Ni is 2 (two phosphine ligands), which becomes 1 after one of the phosphines leaves the ligand sphere.

Figure 4 displays the free energy profiles of the phosphine dissociations. Note that we performed the simulations for the first barrier crossings only; thus, the dissociated states and the corresponding free energy wells have not been fully explored. Comparison of the PCy3 and PPh2Me energy profiles in Figure 4 reveals that the larger PCy3 ligand is more likely to dissociate: the dissociation barrier is 21 ± 4 kcal/mol, whereas for PPh2Me it is 35 ± 6 kcal/mol. We have obtained the same trend from static calculations, although the calculated values were somewhat lower. The discrepancies between the values obtained from the two methodologies can be explained by the effect of the explicit solvent molecules and partially the different functionals (B3LYP followed by M06L and PBE+D3). However, as both M06L and PBE+D3 are local functionals, the differences point to the importance of the explicit solvent molecules, which represent a considerable hindrance against the dissociation of the ligands. Still, the larger ligand PCy3 dissociates more easily, despite being a stronger σ donor than the ligand PPh2Me, which we can explain by the larger steric conflict in intermediate IIIb in comparison to IIIa (reactant state destabilization).

The key decarbonylation step for PPh2Me where intermediate 4b releases CO and forms 5b (Figure 3) is an analogous situation: the smaller phosphine ligands allow the formation of a five-coordinated Ni(II) complex. In addition, a very large fluxionality can be postulated for this five-coordinated complex 4b, which is in sharp contrast with the more rigid square-planar structure of a typical four-coordinated d8 complex. To address this situation, we have performed unconstrained QM/MM MD simulations and followed the behavior of intermediate 4b in the presence of 187 explicit THF molecules. An analysis of these trajectories reveals an isomerization between the trigonal-bipyramidal structure (shown also in Figure 3) and an alternate square-pyramidal state. To quantify the results, a τ parameter is introduced which describes the fluctuations between these two extreme configurations. The temporal variation of τ in a typical simulation is plotted in Figure 5. The curve indicates that initially within a short period there is a dynamic fluxional
behavior around the trigonal-bipyramidal structure. However, as the simulation proceeds, the square-pyramidal form starts to dominate. The trajectories revealed that most frequently the CO ligand occupies the unfavorable axial position in the square-pyramidal structures. The inset in Figure 5 reveals that the Ni(PPh₂Me)₂ species in light of the results of the QM/MM simulations. The thermodynamic driving force for decarbonylation under stoichiometric conditions is provided by the presence of excess Ni to bind CO, whereas under catalytic conditions the exergonicity is provided by the irreversible removal of CO from the solution phase. This is an important feature, as the formation of the transmetalation-active species under catalytic conditions would not be thermodynamically favorable otherwise. The above results also imply that the reaction mechanism observed under stoichiometric conditions cannot be straightforwardly assigned to other conditions.

Reaction steps where the effects of thermal fluctuations could be significant have also been scrutinized by QM/MM simulations. These calculations have confirmed that the acyl intermediate III can become three-coordinated by releasing a phosphine ligand considerably more easily in the case of PCy₃ than in the case of PPh₂Me. This could be explained by the destabilizing effect of the steric conflicts due to the presence of the larger PCy₃ ligands. Simulations also revealed that the smaller size of PPh₂Me also enables the formation of highly fluxional five-coordinated species, where the thermal fluctuations can remarkably simplify the mechanism predicted by static calculations, and this implies a very fast decarbonylation. We can conclude that an enhanced level of statistical treatment is needed to properly describe this step.

We believe that these results will contribute to a better understanding of these new nickel-catalyzed decarbonylation reactions and provide the experiments with new insights into the catalyst design strategy, which can help to extend the applicability of this new catalytic concept. 7 In addition, we think that our combined computational approach demonstrated that a reaction mechanism obtained by traditional static calculations with an implicit solvent treatment can be and should be improved by simulations taking into account thermal effects explicitly whenever indications of high configurational freedom warrant.

## CONCLUSION

In this work we have computed reaction pathways for the formation of the transmetalation-active NiP₂(Ar)F complexes that have been experimentally characterized recently. Two phosphines have been considered, and on the basis of the calculated free energy profiles we have identified the most likely reaction mechanisms for both ligands. In the calculations we have considered the circumstances defining the stoichiometric and catalytic reaction routes. The two ligands induce notable differences on the profiles. The PCy₃ ligand prefers the square-planar ligand field around Ni(II), whereas the smaller PPh₂Me ligands allow the formation of the more flexible five-coordinated structures as well. We have shown that under stoichiometric conditions the rate-determining step for PCy₃ is a rearrangement necessary for a reasonably fast CO release, whereas for PPh₂Me it is the formation of the initial oxidative addition complex. These findings explain the experimental observations: the isolable intermediate (product of oxidative addition) for PCy₃ (the rate-determining step is a later event along the reaction path), while for PPh₂Me such an intermediate cannot be isolated (because the rate-determining step precedes this stage); overall the reaction is faster with PPh₂Me than with PCy₃ ligands (higher overall barrier for the latter). Under catalytic conditions the CO dissociation is the rate-determining step in the presence of PCy₃, whereas for PPh₂Me the rate-determining step remains the formation of the Ni(PPh₂Me)₃ species in light of the results of the QM/MM simulations. The thermodynamic driving force for decarbonylation under stoichiometric conditions is provided by the presence of excess Ni to bind CO, whereas under catalytic conditions the exergonicity is provided by the irreversible removal of CO from the solution phase. This is an important feature, as the formation of the transmetalation-active species under catalytic conditions would not be thermodynamically favorable otherwise. The above results also imply that the reaction mechanism observed under stoichiometric conditions cannot be straightforwardly assigned to other conditions.

## ASSOCIATED CONTENT

* Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.0c00387.
Additional details of QM/MM simulations and metadynamics and additional calculations (PDF)
Cartesian coordinates (XYZ)

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**Notes**
The authors declare no competing financial interest.

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(22) The free energy difference between the two metal-to-ligand ratios (1:2 and 1:3) is equal to RT ln(3/2).

(30) Note that in a followup study Sanford et al. also looked into the reactions at lower temperatures and found very limited conversions (11% and 24% at rt and 60 °C, respectively). In fact, these conversions indicate a reaction with Ni(cod)_2 as a reactant binding the byproduct CO_2; see ref 18a.

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computed to be more favorable than the triplet tetragonal conformations. Certainly, the ligand field generated by the ligands has a profound effect on stabilizing the spin states.

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