# ORGANOMETALLICS

# Uncovering the Mechanism of Homogeneous Methyl Methacrylate Formation with P,N Chelating Ligands and Palladium: Favored **Reaction Channels and Selectivities**

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Supporting Information

ABSTRACT: The catalytic alkoxycarbonylation of alkynes via palladium and P,N ligands, studied through a prototypical reaction involving propyne methoxycarbonylation yielding methyl methacrylate, has been explored at the B3PW91-D3/PCM level of density functional theory. Four different reaction routes have been probed in detail, spanning those involving one or two hemilabile P,N ligands and either hydride or carbomethoxy mechanisms. The cycle that is both energetically most plausible and congruent with experimental data involves Pd(0) and two P,N ligands acting



cocatalytically in turn to shuffle protons via both protonation and deprotonation reactions. Other mechanisms proposed in the literature can be discounted because they would lead to insurmountable barriers or incorrect selectivities. For the preferred mechanism, the P,N ligand is found to be crucial in determining the strong regioselectivity and intrinsically controls the overall turnover of the catalytic cycle with moderate barriers ( $\Delta G^{\ddagger}$  of 20.1 to 22.9 kcal/mol) predicted. Furthermore, the necessary acidic conditions are rationalized via a potential dicationic channel.

# INTRODUCTION

Alkyne alkoxycarbonylation is a transformation with 100% atom efficiency that forms acrylate esters.<sup>1–8</sup> Methoxycarbonylation of propyne yields methyl methacrylate (MMA), a small-molecule feedstock crucial in industry due to its polymer poly(methyl methacrylate), more commonly known as Perspex. This material has a wide range of uses, which include important surgical roles, cosmetics and coatings, and as a rigid transparent plastic for windows, especially in transport.<sup>10</sup> There is also a growing demand from use in LCD screens.<sup>11</sup> Functionalization of propyne yielding the branched product of methoxycarbonylation has received considerable attention,  $^{2,3,5-7}$  and such chemistry has been extended to higher alkynes such as ethynyl benzene<sup>1</sup> and alkynols.<sup>13</sup> Transition metals are key to many industrial processes,<sup>14-16</sup> and in the example of MMA formation from propyne, palladium complexes with P.N chelating ligands play a key role in this transformation (Scheme 1).

Drent has reported that the presence of a P,N ligand, 2-pyridyldiphenylphosphine (2-PyPPh<sub>2</sub>), is necessary for both high selectivity for the branched product and a high turnover

# Scheme 1. Conditions<sup>2</sup> for the Formation of MMA Involving P,N Ligands from Propyne



frequency (TOF) for carbonylation.<sup>2,3</sup> Ligands based upon 3-PyPPh<sub>2</sub>, 4-PyPPh<sub>2</sub>, and PPh<sub>3</sub> exhibit a reduced efficiency, suggesting that both the presence and location of the nitrogen atom are important. 2-PyPPh<sub>2</sub> allows the methoxycarbonylation of propyne to proceed under mild conditions of 45 °C, attaining a turnover frequency of 40 000 mol (mol Pd h)<sup>-1</sup> with a selectivity of ~99% toward MMA.

P,N ligands are known to coordinate in a number of binding modes. While monocoordination and multiple unidentate coordination are typically through the softer phosphorus atom,<sup>17</sup> many structures have been isolated that show chelation.<sup>18–24</sup>  $2\text{-}PyPPh_2$  may also coordinate metal (hetero)dimers,  $^{4,25-27}$  and structures involving iridium suggest that two 2-PyPPh<sub>2</sub> ligands should be able to coordinate in both unidentate and chelating fashion around a single metal center.<sup>28</sup>

Contrastingly, diphosphine ligands employed in the alkoxycarbonylation of other polymer precursors tend to remain bidentate in their coordination modes.<sup>29–35</sup> The hemilability of P,N-type ligands coupled with a wide range of coordination modes<sup>36</sup> is one of the reasons for their continued use in catalysis<sup>37–40</sup> and nanomaterials<sup>41</sup> and as analytical molecular sensing agents.<sup>42</sup> This intrinsic property of 2-PyPPh<sub>2</sub> has been modes<sup>36</sup> implicated in a number of proposed catalytic alkoxycarbonylation mechanisms.

The 2-PyPPh<sub>2</sub> scaffold is the most effective for the methoxycarbonylation of propyne.<sup>2</sup> Through 6-methylation of the pyridyl moiety the selectivity toward MMA over the linear

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product, methyl crotonate (MC), was enhanced from 98.9% to 99.95% with a 20% increase in activity under some conditions.<sup>3</sup> More than two equivalents per Pd of a strong acid such as methanesulfonic acid (MeSA) are needed for efficient turnover. Such an observation suggests an additional role of the acid beyond removing acetate and allowing coordination of ligands and substrates. Protonation of zerovalent Pd or the nitrogen of a hemilabile 2-PyPPh<sub>2</sub><sup>8</sup> is therefore a plausible pathway for forming the catalytically active species. Weak acids exhibit dramatically decreased TOFs, and halide containing acids retard the reaction. On the basis of such evidence the active catalyst is probably a cationic Pd complex that is deactivated upon coordination of halides.

The simplest routes for catalytic turnover of MMA involve hydride and carbomethoxy pathways (Scheme 2). In the

Scheme 2. Classical Pd-carbomethoxy (A) and Pd-hydride (B) Mechanisms



carbomethoxy route propyne inserts into the metal-carbonyl bond in a 1,2 mode with the bulky substituents at the  $\beta$  position relative to Pd (cycle A). During the hydride cycle, propyne insertion into the Pd-H bond follows a 2,1 mode (cycle B). An increased steric bulk at the 6 position, as in 2-(6-Me)PyPPh<sub>2</sub>, should have reversed effects upon product selectivity in both cases, with the carbomethoxy cycle encouraging MMA formation and preference for MC being increased if a classical hydride mechanism is operating.

It has been argued that the role of 2-PyPPh<sub>2</sub> must extend beyond selectivity enhancement, as the nature of the ligand is closely tied to the overall productivity of the catalytic cycle<sup>2</sup> and therefore is likely acting as a rate-enhancing messenger for protonolysis in a carbomethoxy cycle or as an in situ base expediting the solvolysis of a "nonclassical" hydride mechanism (Scheme 3).

Scheme 3. Nonclassical Pd-carbomethoxy (C) Proposed by Drent and Scrivanti's Nonclassical Pd(0) Mechanism (D) from Labeling Experiments



A nonclassical hydride route operating in the formation of MMA was suggested due to the presence of a Pd vinyl intermediate, based on ethynylbenzene, being readily observed through <sup>1</sup>H NMR studies.<sup>7</sup> Should this route (**D**) be operating, the cycle would be initiated via proton transfer from 2-PyPPh<sub>2</sub>

and subsequent steps would involve CO insertion and solvolysis with 2-PyPPh<sub>2</sub> acting as an in situ base. This nonclassical hydride mechanism is proposed to occur via a Pd(0) complex. These are known to exist in mixtures of tertiary phosphines and protic solvents,  $^{43-45}$  similar to conditions employed in alkoxycarbonylation reactions.

Dervisi et al. countered with evidence that would appear to support a nonclassical carbomethoxy mechanism (cycle C)<sup>5</sup> involving a dicationic complex and terminating protonolysis supported by  $P,N-H^+$ ;  $Pd(2-PyPPh_2)_2(CO_2CH_3)$  was found to be active toward branched small-molecule production under CO pressure in methanol with propyne.

These experiments were conducted in the absence of acid with benzene as solvent, markedly different from turnover conditions, and do not inherently support a messenger protonolysis as in C nor discount either C or D operating in the presence of MeSA. Dervisi later confirmed<sup>6</sup> the presence of the same vinyl intermediate suggested by Scrivanti but could not detect the  $\sigma$ -vinyl analogue expected with propyne, instead finding a phosphonium salt.

Recently Drent and Cole-Hamilton have provided a summary of the experimental evidence for the proposed reaction channels.<sup>1</sup> They argued that the bulkier groups of propyne being situated at the  $\alpha$  carbon in the "nonclassical" Pd(0) mechanism should evoke steric clashes. To overcome this, a concerted protonation and nucleophilic attack of Pd<sup>0</sup>CO on coordinated propyne (Scheme 4) has been proposed. This would

Scheme 4. Alternative Mechanism for the Initial Carbonylation of Propyne Involving a Concerted Nucleophilic Attack and Protonation<sup>1</sup>



then be followed by a methanolysis step as in mechanism **D**. From this data, the exact nature of the catalytic cycle that accounts for the observed regioselectivities remains unknown. Support for a nonclassical mechanism arises from reaction rates for a related transformation, which are found to increase in line with the 2-PyPPh<sub>2</sub>:Pd ratio (until 30:1) and acid:Pd (until 66:1),<sup>46</sup> suggesting two coordinated P,N units with one of them likely protonated.

With these considerations we have tackled this problem using modern density functional methods. When experiment gives rise to ambiguous interpretation, quantum chemistry can offer insight that allows for a more definitive answer,<sup>47–50</sup> thereby aiding rational catalyst improvement. Our primary aims were in establishing an experimentally congruent route for alkyne alkoxycarbonylation, modeled through production of MMA. To this end, we characterized complete catalytic cycles for all four pathways, **A** –**D**, that had been proposed. Any plausible mechanism must have surmountable barriers compatible with the high turnover and must be able to closely reproduce the selectivities observed with both 2-PyPPh<sub>2</sub> and 2-(6-Me)PyPPh<sub>2</sub> ligands. Only one of the four proposed mechanisms, path **D**, is able to achieve this. We have recently communicated the essential features of this mechanism,<sup>51</sup> and in the present paper we give a full account of the results that have led to its identification.

Scheme 5. Methoxycarbonylation at a Pd(II) Center Involving a 2-PyPPh<sub>2</sub> Monochelate Operating through Cycle A<sup>a</sup>



<sup>a</sup>Profile sketched according to computed  $\Delta G$  values (italics). TS4-5 determines regioselectivity, and TS6-7 controls turnover.

# COMPUTATIONAL METHODOLOGY

We have used the B3PW91<sup>52–54</sup> hybrid functional, which has been successfully validated for a range of reactions that rely upon metals<sup>55–58</sup> and has been used to study related (2-pyridyl)thiourea Pd(II) complexes.<sup>59</sup> This method benchmarks well against explicitly correlated CCSD(T)<sup>60</sup> when coupled with Grimme's DFT-D3,<sup>61–63</sup> including Becke–Johnson damping.<sup>64,65</sup> This postcalculation empirical correction serves to account for dispersive forces that are not well described by DFT yet have been shown to be essential for the reproduction of accurate energies, especially when triphenylphosphine and similarly bulky moieties are present.<sup>66,67</sup>

Geometries were computed at the level of B3PW91/ECP1, where ECP1 corresponds with the 6-31G\*\* basis set on all nonmetal atoms and the relativistic SDD pseudopotential and the corresponding valence electron basis set on Pd. Transition states were located at this level either through coordinate driving and subsequent optimization to the transition state or by using the QST3 algorithm.<sup>68</sup> Stationary points were confirmed by the presence of the correct number of imaginary frequencies using the harmonic approximation. These frequencies allowed for corrections to enthalpies and free energies to be evaluated from standard thermodynamic expressions at 298.15 K. Transition states were confirmed to link to the respective reactants and products using intrinsic reaction coordinate (IRC) calculations.<sup>69,70</sup>

Energies were refined through single-point calculations employing the same functional and an ECP2 level, i.e., the same SDD pseudopotential and valence electron basis set for Pd but the larger triple- $\zeta$  6-311+G\*\* basis set on all nonmetal atoms. Bulk solvent effects were included through a polarizable continuum (PCM)<sup>71–74</sup> with methanol as the solvent. We do not include the presence of the weakly coordinating anions arising from the protonation of Pd-coordinated acetate. To these PCM and ECP2 corrected energies DFT-D3BJ corrections were added to accurately account for the missing dispersion.<sup>75</sup> All calculations were performed using Gaussian 09,<sup>76</sup> and structures were built by hand, guided by a small model study (see SI, Scheme S1). A range of low-energy conformers are known to exist for related rhodium species, and preferential orientation is impacted little by the location of the pyridyl group.<sup>77</sup>

# RESULTS AND DISCUSSION

We begin by exploring a carbomethoxy cycle (mechanism **A** in Scheme 2) as a potential route for the classical methoxycarbonylation of propyne to MMA involving one  $\kappa^2$ -(2-PyPPh<sub>2</sub>) ligand at a Pd(II) center. Next, a classical hydride mechanism (**B**) is computed, followed by inspection of the "nonclassical" routes **C**  and **D** using a hemilabile  $\kappa^{1}$ -(2-PyPPh<sub>2</sub>) as a proton relay (Scheme 3).

**1. Classical Carbomethoxy (A).** A classical methoxycarbonylation pathway begins with a single chelating 2-PyPPh<sub>2</sub> ligand and requires the prior formation of a Pd(II) center with coordinated methoxide, such as  $[(2-PyPPh_2)Pd(OMe)]^+$ (**1**, Scheme 5). Complex **1** would be unlikely to be present in significant amounts with excess acid under catalytic conditions; however we sought to exclude this route on the grounds of selectivity and the energetics of individual steps.

The first step of this cycle is the uptake of CO (2) and subsequent migratory insertion of the nucleophilic methoxy unit onto carbon monoxide, affording 3.<sup>78</sup> This process is facile, with a free-energy barrier of 11.6 kcal/mol via **TS2–3**, and coordination of propyne affording **4** should be rapid. Propyne binds in a perpendicular orientation relative to the Pd–N–P plane (Figure 1) that shows no predisposition for regioselectivity at this



**Figure 1.** Geometries involved in Pd(II)-mediated 1,2 insertion of COOMe and propyne. Distances are in Å. Blue = N, orange = P, turquoise = Pd, gray = C, red = O, and white = H.

stage. Subsequent MMA formation occurs via a 1,2 insertion through TS4–5, as opposed to MC formation, which occurs via a 2,1 insertion (for the differences inherent in these processes see section 1.1). At this point in the reaction, coordinated propyne rotates from the perpendicular orientation in 4 toward an inplane mode, decreasing the distance between bond-forming carbon participants from 3.08 Å to 2.02 Å. Concomitantly, the acyl moiety begins to dissociate from Pd and a stronger Pd–C bond with propyne forms to compensate.

The activation energy associated with forming the branched Pd-alkenyl intermediate, **5**, is low, at 13.4 kcal/mol, relative to **4**. Due to the considerable enthalpic and entropic gain upon insertion and the challenging kinetic barrier for terminating protonolysis, the palladium alkenyl ester **5** rests in a deep thermodynamic sink. From **5**, **TS6**–7 has an imposing barrier of 38.0 kcal for solvolysis, incompatible with turnover conditions. This step involves cleavage of a Pd–C bond and the formation of a C–H bond, which is ultimately less favorable than retention of the Pd–alkenyl complex (7 vs **5**).

However, the classic carbomethoxy mechanism is more complex than Scheme 5 suggests. After dissociation of the product, **1a** has the methoxy group *trans* to phosphorus as opposed to *trans* to the nitrogen of chelating 2-PyPPh<sub>2</sub> as in **1**. This leads to a continuation of the cycle to regenerate **1** through isomers **1a** to **7a**. Strictly, two MMA molecules are produced in every turn of this full catalytic engine, and Scheme S2 in the SI illustrates the energetic stipulations of producing MMA through this isomeric pathway.

The largest free-energy span along this second leg is protonolysis between 5a and TS6a-7a at 31.2 kcal/mol, lower than the equivalent process in Scheme 5. Dynamic studies on Pd(II) 2-PyPPh<sub>2</sub> systems have suggested that fluxional and ligand exchange processes are accessible without considerable barriers.<sup>36</sup> If 1 and 1a could interconvert rapidly, the two pathways presented may interweave to allow the system to traverse over the less imposing kinetic barriers and skirt the highest one. For instance, a path leading from 1a via 7a to 1 followed by isomerization of 1 to 1a would avoid the higher barrier via TS6-7.

The trigonal transition state between 1 and 1a has been located and found to be 17.5 kcal/mol relative to 1, while 1a is 11.0 kcal/mol above 1. Due to the kinetic hindrance of this route as opposed to the rapid CO uptake by 1, it is unlikely that this process will form the major pathway. There are other points of such "pathway switching", however, with 3 and 5 being potential locales for isomerization through a trigonal transition state; although irrespective of this, a difficult barrier of at least 31 kcal/mol must be crossed. On the basis of the energy profiles obtained, a classical carbomethoxy route is unlikely. To rule out this path conclusively, we now explore the MMA vs MC selectivity of  $4 \rightarrow 5$  and  $4a \rightarrow 5a$ .

1.1. Classical Carbomethoxy Selectivity. The selectivitydetermining step is the insertion of the perpendicular coordinated alkyne into the  $Pd-C_{(carbonyl)}$  bond via **TS4–5**. Besides this 1,2-insertion step leading to the branched product, an alternative linear route through a 2,1 insertion (**TS4L–5L**) is possible (Scheme 6). Due to the lack of steric bulk surrounding a single chelating 2-PyPPh<sub>2</sub> ligand, there is little discrimination between 4 and 4L, although a distinct kinetic difference is observed between **TS4–5** and **TS4L–5L**.

MMA-affording **TS4–5** is 2.4 kcal/mol higher than MCproducing **TS4L–5L**, leading to the surprising conclusion that 2,1 insertion is more favorable! The same is found for the mechanistic alternative with lower overall barrier (Scheme S2), where  $\Delta\Delta G^{\ddagger}$  between **TS4a–5a** and **TS4aL–5aL** is 2.2 kcal/mol (Scheme S3, SI). Thus, if such a methoxycarbonylation route were operating under turnover conditions, MC should be produced with a high selectivity ( $\approx 2-3\%$  branched product at 45 °C).

The unexpected 2,1 preference arises due to a clash of the propyne methyl with the ester substituent in the branched-forming route. In TS4L-5L, which has the terminal hydrogen of

Scheme 6. Selectivity Determining Pathways for MC (Left) and MMA (Right) Formation in the First Pd(II) Carbomethoxy Pathway<sup>a</sup>



<sup>*a*</sup>Energies are taken against **4**.

 $HCCCH_3$  toward the bulky carbomethoxy group, there is no such close contact, and thus the linear-forming transition state is easier to access. Mechanism **A** can therefore be safely excluded because it affords the incorrect selectivity.

2. Classical Hydride Mechanism (B). We now turn to the classical hydride mechanism starting with Pd(II) hydride 8 (Scheme 7). Surprisingly, no stable intermediate with side-oncoordinated alkyne, i.e.,  $[(\kappa^{1}-(2-PyPPh_{2}))Pd(H)(HCCCH_{3})]^{+}$ , could be located, irrespective of the binding mode of propyne (parallel or perpendicular to the H–Pd-chelate plane).<sup>79</sup> All attempts to optimize such structures result in spontaneous insertion, affording either the branched vinyl complex 9 or the linear analogue 9L. The effect on selectivity is discussed below. Scans from the vinyl intermediates 9 and 9L probing the reaction coordinate associated with the formative C-H bond have been performed. On such a potential energy surface movement of the hydrogen from carbon back to palladium is observed, but no stable minimum with a  $\pi$ -coordination mode of propyne can be located (see SI, section S3). Thus, it may be assumed that uptake of propyne would lead directly to either 9 or 9L, controlled by approach trajectory and orientation.

Therefore, we have computed two reaction profiles, producing either MMA or MC. As with carbomethoxy mechanism **A**, the production of one MMA unit results in a different stereoisomer of the hydride, and thus a full catalytic cycle producing two MMA units and switching the *trans* orientation of P and N of the  $\kappa^2$ -(2-PyPPh<sub>2</sub>) chelate must be considered.

We have explored a route for interconversion between these two half-cycles via trigonal **TS8–8a**, although this is found to be 47.5 kcal/mol uphill relative to **8**, which, in turn, is more stable than **8a** by 15.3 kcal/mol. Such a simple path switching is thus excluded, although we are aware that interconversion might be possible at different stages of the reaction (e.g., at **11**) or through fluxional associative exchange of the 2-PyPPh<sub>2</sub> ligand with one from the bulk.<sup>36</sup> Accordingly, we will limit our discussion to the lowest free-energy spans across individual half-cycles (Table S1) such as that with the most accessible methanolysis, illustrated in Scheme 7.

The rate-limiting barrier on path **B** is associated with terminating methanolysis, which has been found to be a difficult process in prior studies.<sup>80–82</sup> Over the whole pathway, the largest free-energy barriers are predicted between **11a** and **TS12a–13a**, namely, 53.3 kcal/mol (MC-forming) and 54.2 kcal/mol (MMA-forming, Table S1).

#### Scheme 7. Classical Hydride Mechanism Beginning from an N-trans Pd-H Species<sup>a</sup>



<sup>a</sup>TS12–13 is rate-determining.

Even with path switching that would avoid this kinetic bottleneck, free-energy barriers of at least 40.8 kcal/mol (MC forming) and 42.5 kcal/mol (MMA forming) are predicted (relative to the lowest preceding intermediate 11). On the basis of such evidence, this hydride path can already be discounted on energetic grounds.

Assessment of selectivity is difficult in this case, as there is no barrier on the electronic surface for the irreversible 1,2 or 2,1 insertions between propyne and 8(a) on the potential energy surface. Entropic barriers may be expected due to the associative nature of these reactions, but according to the Bell–Evans– Polyani principle, the relative thermodynamic driving forces should govern these barriers and, thus, the selectivity. On the pathway showing the most accessible terminating methanolysis, that of Scheme 7, there is little distinction between 9 and MC-forming 9L. The former is slightly more favorable in terms of enthalpy, by 0.5 kcal/mol, while the latter is barely more stable by 0.1 kcal/mol in free energy, as shown in Table S1. Little, if any, selectivity for MMA over MC would be expected, further disfavoring pathway **B**.

To conclude, the classical hydride mechanism suffers from an essentially insurmountable intramolecular methanolysis step and cannot reproduce the observed selectivity.

**3.** Nonclassical Messenger Carbomethoxy Mechanisms (C and C-II). Drent's original nonclassical carbomethoxy mechanism (C, Scheme 3) can be excluded because the proposed selectivity-determining transition state is the same as in cycle A. Dervisi and co-workers proposed<sup>5,6</sup> a mechanism for the production of MMA from [(2-PyPPh<sub>2</sub>)<sub>2</sub>Pd(CO<sub>2</sub>R)(OAc)], which incorporates two monocoordinating phosphine ligands. Increasing the quantity of both acid and phosphine leads to an observed zero order in acid, and therefore any protonolysis step appears to involve 2-PyPPh<sub>2</sub> acting as a relay. A possible adapted messenger carbomethoxy mechanism accounting for this experimental nuance, which incorporates two monocoordinating phosphines, C-II, is presented in Scheme 8.

The key difference between Drent's original carbomethoxy mechanism, C, and the modified cycle we have investigated, C-II, is that the latter incorporates two 2-PyPPh<sub>2</sub> ligands throughout the reaction. Coordination of both methanol and carbon monoxide (affording 16) is exothermic, but essentially isoergonic

with presumed resting state 14. The following transition state for concerted migratory insertion and deprotonation, TS16–17, emerges as the rate-limiting state at 24.5 kcal/mol. Intermediate 17 is less favorable against both 14 and 16 (when considering free energy), and the resultant uptake of propyne leaves 18 4.0 kcal/mol above 14. All subsequent steps are exergonic, with barriers of 20.5 kcal/mol (protonolysis via TS19–20) or less.

The irreversible regioselective transition state, **TS18–19**, produces a palladium-alkenyl intermediate leading to MMA. Compared to the analogous transition states in cycles **A** and **B**, **TS18–19** incorporates the greater steric bulk of the second phosphine ligand, the influence of which upon selectivity has been explored (Figure 2).

Energetically, the competing transition states do not show a difference that would be compatible with observed selectivity; **TS18–19** is only 0.2 kcal/mol ( $\Delta G$ ) more favorable than **TS18L–19L**, corresponding to a selectivity for MMA of approximately 73%. The change in selectivity from a 2,1 mode in mechanism **A** to a 1,2 mode in **C-II** arises because in the 2,1 process the methyl unit of propyne is orientated toward the pyridyl ring, invoking an unfavorable steric interaction. Despite this, such a clash is apparently not enough to reach the 99% selectivity observed under turnover conditions.

Additional evidence against mechanism C-II emerges from the effect of 6-methylation of the pyridyl rings. While such a modification leads to an increase in selectivity toward MMA from 99% to 99.95% in practice, our density functional calculations with the added 6-Me groups fail to reproduce this noticeable change. In fact we find that the selectivity of mechanism C-II is reversed by 6-methylation, as TS18-19 6-Me is 0.2 kcal/mol less favorable than TS18L-19L 6-Me! A closer inspection of the transition states given in Figure 2 provides some rationale for the low computed selectivity. The regioselective transition states in C-II have the pyridyl rings orientated such that the bulk (and the methyl modification) points away from the plane spanned by the metal and the C atoms involved in migratory insertion. Meanwhile, the clash between the carbomethoxy moiety and propyne methyl in the 1,2 mode is made more severe by the additional methyl unit on the pyridyl ring.

On the grounds of insufficient and incorrect regioselectivity,<sup>83</sup> both mechanisms **C** and **C-II** can be excluded because

# Scheme 8. Carbomethoxy Mechanism C-II Incorporating a P,N Ligand Acting as a Proton Messenger (TS19-20)<sup>a</sup>



<sup>*a*</sup>The rate-determining step is the migratory insertion of methoxide into carbon monoxide (TS16–17), and the selectivity is determined via TS18–19, which irreversibly leads to 19.



**Figure 2.** MC (**TS18L**-19L)- and MMA (**TS18**-19)-forming transition states with 2-PyPPh<sub>2</sub> (top) and 2-(6-Me)PyPPh<sub>2</sub> (bottom). Distances are in Å, and Ph groups have been omitted for clarity. Steric clashes are highlighted in red.

experimental selectivities are not reproduced and subtle ligand effects are incorrectly accounted for. Full C-II energetics, including 2-(6-Me)PyPPh<sub>2</sub>, are given in the SI, Table S2.

4. In Situ Base Mechanism (D). Scrivanti's Pd(0) mechanism (D, Scheme 3) involves formation of a Pd-vinyl species<sup>7</sup> through protonation of coordinated propyne<sup>8</sup> with selectivity imbued during the proton transfer step involving a monocoordinated 2-PyPPh<sub>2</sub> ligand acting as a proton-shuffling relay.<sup>84-86</sup> The precursor species could be  $[(\kappa^1-(2-PyPPh_2))(\kappa^1-(2-PyHPPh_2))Pd(CO)(HCCMe)]^+(21+CO)$ , with a concerted protonation and migratory insertion yielding a palladium-acyl intermediate (Scheme 4).<sup>1</sup> This complex, 21+CO, with the expected tetrahedral geometry was identified as being slightly exergonic relative to 21, and this led us to start the reaction from the more stable planar complex  $[(\kappa^1-(2-PyPPh_2))-(\kappa^1-(2-PyHPPh_2))Pd(HCCMe)]^+$ . The possibility of a

 $[(\kappa^2-(2-PyPPh_2))(\kappa^1-(2-PyPPh_2))Pd(H)]^+$  species being catalytically relevant was also assessed, and calculations excluding a route involving such an intermediate are included in the SI, Scheme S5.

The first transformation that **21** must undergo is regioselective ligand-assisted protonation, as detailed in Scheme 9. Protonation of the alkyne via **TS21–22** needs only 7.2 kcal/mol of activation energy and establishes a cocatalytic role of P,N as an agent for accessible proton transfer. We attempted to locate a transition state such as that outlined in Scheme 4, although ultimately could not characterize such a concerted process. Instead an alternative pathway of **21+CO** undergoing a stepwise protonation, similar to that discussed for **21**, with CO remaining coordinated throughout became apparent. Following insertion, this route leads directly to **24**, but the activation cost of the proton transfer transition state, **TS21–22**. For further details on this process see the SI, section S5.

Key intermediates and transition states of the initial carbonylation steps are displayed in Figure 3. 21 displays strong backbonding between palladium and propyne with Pd–C distances of 2.07 Å. TS21–22 is followed by a series of energetically downhill steps from  $\beta$ -agostic intermediate 22, yielding 24 (Figure 3) following displacement of a chelating binding mode in 23 via CO uptake. Regioselective insertion is therefore practically irreversible under experimental conditions, and this is essential to the high selectivities (discussed below) observed by preventing dynamic communication of branched and linear intermediates.

The migratory insertion into the metal–carbon bond via TS24–25 is easily surmountable, being only 10.3 kcal/mol uphill from the prior intermediate, and is encouraged by formation of a Pd-acyl complex. The now-deprotonated pyridyl acts as an intermittent chelate, stabilizing intermediates that would otherwise be coordinatively unsaturated. Wiberg bond index (WBI)<sup>87</sup> measurements show a significant sharing of electron density between bond-forming carbon centers (0.12) in 24, accounting for the ease of this transformation.

### Scheme 9. Initial Proton Transfer and Carbonylation at Pd(0) with Two Monocoordinated 2-PyPPh<sub>2</sub> Units<sup>a</sup>



<sup>a</sup>TS21-22 imbues regioselectivity.



Figure 3. Intermediates and TS involved in carbonylation of propyne during mechanism D. Distances are in Å.

Unlike the proton transfer steps, CO insertion is reversible with an activation free energy of 10.3 kcal/mol and a backward cost of 16.4 kcal/mol, notably lower than the barrier we compute for methanolysis (Scheme 10). However, as the prior propyne insertion step remains irreversible, the reversibility of CO insertion will not affect the overall regioselectivity. Following carbonylation a terminating alcoholysis step is necessary to yield MMA. Unlike hydride mechanism **B**, this process does not require the costly step of an alcoholic proton being transferred to a Pd(II) center but can rather involve the 2-PyPPh<sub>2</sub> ligand, reprotonating the pyridyl moiety. As demonstrated in Scheme 10, incorporation of the pyridyl as an in situ base offers a far more accessible route.

We note that one limitation of our computations is in the use of a PCM to account for bulk solvation. Methanol molecules in the second coordination sphere around **26** may play a role in accepting and transferring the proton arising from deprotonation away from the Pd center. This would serve to lower the freeenergy cost of the process with an entropic gain from distribution and an enthalpic gain from additional hydrogen bonding. However, since a 2-PyPPh<sub>2</sub> unit must be reprotonated in order to conduct regioselective propyne insertion at **21**, we have not explored this route further.

Displacing chelating 2-PyPPh<sub>2</sub> and binding methanol is slightly endergonic, though by only 0.7 kcal/mol. Reaction entropies for such associative processes are often overestimated by our standard protocol, and it is worth noting that binding is found to be exothermic by 12 kcal/mol (see  $\Delta H$  values in Scheme 10). This methanol coordination preferentially occurs such that the hydroxyl unit orientates its proton toward the basic nitrogen of 2-PyPPh<sub>2</sub>, resulting in the nucleophilic oxygen and acyl carbon being separated by 2.71 Å (Figure 4). Establishing this intramolecular hydrogen bond with a close distance of 1.65 Å between nitrogen and hydrogen is key in facilitating methanolysis through TS26–27. With a  $\Delta G^{\ddagger}$  of 22.9 kcal/mol relative to 25 this is considerably more accessible than the related solvolysis process in mechanism **B**, which requires a barrier exceeding 40 kcal/mol.

In this transition state coordinated methanol is deprotonated by the cocatalytic 2-PyPPh<sub>2</sub> ligand and the transient methoxide attacks the Pd–C<sub>(acyl)</sub> bond. Since the MMA product immediately dissociates away from the primary coordination sphere (**28/28b**), this step is characterized as reductive elimination. Here, the P,N ligand demonstrates its second cocatalytic property as an in situ base, which is essential for the high performance of methoxycarbonylation. Subsequent uptake of propyne to re-form **21** provides the final driving force for closing the catalytic cycle. **TS26–27** also rationalizes why 2-PyPPh<sub>2</sub> has much greater activity than 3-PyPPh<sub>2</sub>.<sup>2,3</sup> In the latter, the orientation of the nitrogen lone pair would not allow for formation of the intramolecular hydrogen bond in **26**, and the ability of pyridyl to act as a cocatalyzing base is decreased.

# Scheme 10. Terminating Methanolysis to Yield MMA<sup>a</sup>



"Energies presented relative to 21. The rate-limiting step is solvolysis (TS26-27), while the overall cycle is thermodynamically driven.



Figure 4. Geometries associated with MMA-producing methanolysis of Pd-acyl species in mechanism **D**. Distances are given in Å.

The MC-forming methanolysis step is of little importance to the overall regioselectivity of the methoxycarbonylation within this reaction mechanism. Even if it is more favorable as a result of lesser steric constraints for reductive elimination of the linear acyl, it will not affect the ultimate product distribution, as this is determined by the irreversible propyne insertion step, the selectivity of which we now explore.

4.1. Selectivity of the in Situ Base Mechanism. The linearforming route through TS21L-22L was compared to the branched-forming TS21-22 (Scheme 11). Thermodynamically, the intermediate that leads to MMA formation (23) is favorable over that leading to MC (23L), and furthermore the associated saddle point (TS21-22) is more accessible than TS21L-22L. The free-energy difference between the kinetic barriers for these processes is 2.2 kcal/mol, a selectivity toward MMA of 98% at 25 °C and 97% at 45 °C that is in line with experimental observations. A concern that had led to the proposal of the concerted pathway<sup>1</sup> outlined in Scheme 4 was the expectation that an alkenyl intermediate with bulk  $\alpha$  to Pd would be less favorable than the linear alternative. Calculations show that the isomeric products are in fact almost equivalent in free energy and the branched transition state does not stifle proton transfer.

Regioselectivity is controlled by steric effects, as in delivering a proton the pyridyl moiety moves into the plane of the  $\pi$ -coordinated propyne (Scheme 11). In **TS21–22** there are no





severe clashes; however in the MC-forming **TS21L**–22L this movement introduces a more pronounced interaction between the pyridyl ring and the methyl group of propyne, resulting in a higher barrier. Interestingly, the irreversible propyne insertion step can be viewed as equivalent to a Markovnikov addition of a strong acid, [(2-PyPPh<sub>2</sub>)Pd(2-PyPPh<sub>2</sub>H)]<sup>+</sup>, to an alkyne. In this analogy, the regioselectivity follows that of protonation at the least substituted carbon of propyne, yielding the Markovnikov product, while the anti-Markovnikov process is less favorable in both kinetics and thermodynamics.

Table 1 reports the free energies governing turnover and selectivity for ligand systems 2-PyPPh<sub>2</sub> and 2-(6-Me)PyPPh<sub>2</sub> within path **D**. Species **22** and **28/28b** are not presented due to their negligible impact on the reaction profile. We detail the selectivities of the less favorable mechanistic alternative from **21+CO** to **24** in SI Table S3, noting here that this route is favorable for MMA production over MC. A comparison of these energies shows that 6-methylation results in improved selectivity for MMA against MC with  $\Delta\Delta G^{\ddagger}$  increasing from 2.2 kcal/mol to 4.1 kcal/mol, arising from a subtle ligand effect.

4.2. Impact of Acidic Conditions. Finally, we turn to the effect of strongly acidic conditions that are essential for achieving

$\Delta G$	21	TS21-22		23	21L	TS21-22L	23L			
2-PyPPh <sub>2</sub>	0.0	7.2		-17.7	1.8	9.4	-17.4			
2-(6-Me)PyPPh <sub>2</sub>	0.0	9.0		-14.7	1.2	13.1	-15.4			
2-PyPPh <sub>2</sub> dicat.	0.0	10.3		-14.2	1.3	13.4	-12.4			
	24	TS24-25	25	26	TS26-27	27	21 + MMA			
2-PyPPh <sub>2</sub>	-22.1	-11.8	-28.2	-27.5	-5.3	-24.9	-36.3			
2-(6-Me)PyPPh <sub>2</sub>	-20.6	-10.3	-25.1	-26.1	-3.7	-25.3	-36.3			
2-PyPPh <sub>2</sub> dicat.	-14.1	-5.2	-24.9	-24.3	-4.8	-24.8	-36.3			
<sup>a</sup> Enthalpies are given in Table S4 in the SI.										

Table 1. Comparative Reaction Profiles ( $\Delta G$ , kcal/mol) for Methoxycarbonylation of Propyne under Differing Experimental Conditions<sup>*a*</sup>

expedient turnover. Under such conditions (and because the pK<sub>b</sub> values of the two remote pyridine bases within the same complex are expected to be very similar) not only one but both pyridyl groups may be protonated.<sup>8</sup> We have thus repeated all calculations summarized in Schemes 9 and 10 for diprotonated, dicationic complexes, and the resulting free energies are included in Table 1 (see 2-PyPPh<sub>2</sub> dicat. entries). According to these data, not only does a dicationic equivalent improve selectivity with  $\Delta\Delta G^{\ddagger}$  between regioselective transition states increasing to 3.1 kcal/mol but, crucially, the methanolysis barrier is also reduced to 20.1 kcal/mol.

Greater regioselectivity arises from protonation removing the weak interaction between the basic pyridyl nitrogen and acidic propyne hydrogen in **TS21L–22L**, which can be seen at the left-hand side of Scheme 11. In the protonated congener of this transition state, the previously basic nitrogen now presents a partially positive hydrogen and the pyridyl group rotates to avoid an unfavorable electrostatic interaction with coordinated propyne. This protonation and subsequent reorientation removes a polarizing interaction that reduces the effective barrier of **TS21L–22L** in the monocationic 2-PyPPh<sub>2</sub> system, and therefore diprotonation leads to enhanced selectivity for MMA.

Excess acid also positively impacts turnover by decreasing the rate-limiting solvolysis barrier to 20.1 kcal/mol. In a dicationic system, the previously basic nitrogen lone pair of the non-participating pyridyl is now replaced by an acidic  $N-H^+$  functionality, which accelerates methanolysis by forming an intramolecular H-bond to the acyl carbon (right-hand side in Figure 5).



Figure 5. Transition states for the monocationic methanolysis, TS26– 27 (left), and dicationic analogue (right). NPA charges on key atoms are included to highlight the different charge distributions.

This is confirmed by analysis of the natural population analysis (NPA) charges and geometries at the methanolysis transition states. On going from the mono- to the dicationic system, the  $O_{(methanol)}-C_{(acyl)}$  separation increases from 1.71 Å to 1.81 Å, consistent with an earlier transition state, and the acyl group

becomes more negative (see the NPA charges in Figure 5), facilitating methanolysis.

**5.** Analysis of Mechanisms A to D: Interpretation through Energetic Span. The energetic span model of Kozuch and Shaik<sup>88–90</sup> allows for the calculation of turnover frequencies from computed free-energy values of reactants, intermediates, transition states, and products. This prescription further affords detail of the most abundant reaction intermediates (MARIs) and the highest energy transition state (HETS) that maximize the energetic span along one complete cycle and exert kinetic control on the propensity of the reaction.

While absolute TOF values are associated with the usual uncertainties of simple transition-state theory, relative TOF values can afford insight into the preferred reaction channels of competing mechanisms. Table 2 reports the relative TOFs of all

Table 2. Mechanisms Relevant to the Methoxycarbonylation of Propyne by  $Pd(P,N)_n$  Systems under the Scrutiny of the Energetic Span Model<sup>*a*</sup>

mechanism	TOF (relative)	MARI	HETS	energy span
$A \; (\text{full} \; 1 \rightarrow 1a \rightarrow 1)^c$	1	5	TS6-7	38.0
A (partial $1a \rightarrow 1a$ ) <sup>d</sup>	$4.9 \times 10^{4}$	5a	TS6a-7a	31.2
$B \; (\text{full } 8 \to 8a \to 8)^{\text{c}}$	$1.3 \times 10^{-11}$	11	TS12-13	54.2
<b>B</b> (partial $8a \rightarrow 8a$ ) <sup>d</sup>	$2.3 \times 10^{-4}$	11a	TS12a-13a	42.5
C-II	$3.8 \times 10^{9}$	14	TS16-17	24.5
D	$4.5 \times 10^{10}$	25	TS26-27	22.9
D-6Me	$1.2 \times 10^{11}$	26	TS26-27	22.4
D-Dication	$4.9 \times 10^{12}$	25	TS26-27	20.1

<sup>*a*</sup>Computed at T = 298.15 K. <sup>*b*</sup>Free-energy difference in kcal/mol between the MARI (most abundant reaction intermediate) and HETS (highest energy transition state). <sup>*c*</sup>Full cycle producing 2 equiv of MMA. <sup>*d*</sup>Half-cycle with lower energy span producing 1 equiv of MMA and assuming rapid interconversion between 1 and 1a or 8 and 8a as applicable.

computed profiles, taken against mechanism **A**, and additionally identifies the MARIs and HETS for each reaction channel. **A** (full) and **B** (full) have had their TOFs multiplied by 2, as these cycles produce two equivalents of MMA.

In keeping with the free-energy barriers discussed previously, the computed TOFs cover a large span, more than 23 orders of magnitude. Compared to the highest TOF obtained for the dicationic variant of pathway **D** (last entry in Table 2), mechanisms **A** and **B** show negligible turnover. This conclusion is relevant regardless of whether the full paths have to be completed or shortcuts are available that could bypass the highest barriers (cf. the discussion in sections 1 and 2 above). Mechanism **C-II**, like **D-Dication**, a dicationic pathway, is barely

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competitive with the latter, with relative turnover predicted to be 3 orders of magnitude lower.

Pathway **D**, with its 10-fold increase in TOF over **C-II** and the correct selectivity, is clearly the most plausible mechanism. Crucially, **D** and **D-6Me** remain within an order of magnitude, which is inline with experiment. The TOF of pathway **D** is still 2 orders of magnitude below that of **D-Dication**, but in practice both will operate simultaneously, depending on the precise position of the protonation equilibria, and an intermediate TOF will be observed. Therefore, an in situ base mechanism is the most likely one at this point, and the key intermediates and transition states, prime targets for rational catalyst design, are identified as 25/26 and TS26–27 respectively.

# CONCLUSIONS

We have studied four of the most likely mechanisms for MMA production at Pd catalysts with P,N ligand systems. Our computations show that a typical carbomethoxy mechanism (A) cannot account for selectivity or turnover. Likewise, a hydride mechanism (B) can be excluded because it would suffer deactivation as a result of a particularly high barrier for intra-molecular methanolysis.

Drent's original messenger carbomethoxy route (C) was proposed to operate via the same selectivity-determining transition state as that of A, which we have shown exhibits a preference for MC over MMA, and we are confident in excluding this route. Dervisi proposed a similar mechanism that we have adapted to operate through a dicationic pathway. This mechanism, C-II, always contains two 2-PyPPh<sub>2</sub> units and displays promising barriers and reasonable selectivity should the Pd-OMe species be available under turnover conditions. However, this mechanism fails to reproduce the observed increase in selectivity for the 6-methylated analogue and can thus be discounted.

The preferable pathway is **D**, a Pd(0) in situ base mechanism with hemilabile and cocatalytic 2-PyPPh<sub>2</sub> ligands and/or a dicationic variant thereof (Scheme 12). While we could not confirm a concerted protonation and migratory insertion step that had been proposed recently,<sup>1</sup> we were able to characterize a stepwise pathway, beginning with a regioselective and irrever-

### Scheme 12. Catalytic Cycle of Mechanism D Involving an in Situ Base, As Emerging from Our DFT Calculations



sible protonation of coordinated propyne and terminating via P<sub>1</sub>N-assisted methanolysis. With both 2-PyPPh<sub>2</sub> and 2-(6-Me)-PyPPh<sub>2</sub> ligand systems, this catalytic cycle exhibits a selectivity for the branched-forming route that is completely congruent with experimental observations. Calculations show that the P,N system is strikingly different from other ligands used in catalytic carbonylation at Pd. Typically, these concern bidentate diphosphine backbones and give high selectivities toward *linear* (alkoxy)carbonylation products.<sup>35,91–93</sup> By contrast, 2-PyPPh<sub>2</sub> and congeners undergo an alternative "Pd-H" cycle, and it is the unique mechanistic inclusion of the cocatalytic pyridyl moiety in regioselective proton transfer that enables this framework to conduct an alternative selectivity and favor branched products over linear. We have been able to identify the subtle ligand effects that dictate why the 6-methylated analogue exhibits enhanced selectivity and can trace the requirement of acidic conditions back to the involvement of at least one, but possibly two, hemilabile 2-PyPPh<sub>2</sub> ligands protonated at the free nitrogen atoms during a monocoordinating mode.

A diprotonated dicationic system is indicated to have the lowest overall barrier (for rate-determining methanolysis), and improving the accessibility of the solvolysis transition state has been outlined as a potential target for directed design.

We are hopeful that our detailed computational insights, which account for reactivities and selectivities at an atomistic level, will spur the development of new generations of more active and more selective catalyst systems for this important feedstock molecule. We have already proposed a simple ligand modification that should lower the turnover-determining barrier,<sup>51</sup> and further studies along these lines are in progress.

# ASSOCIATED CONTENT

#### **S** Supporting Information

Model studies, additional energies for variants of mechanisms A-D, XYZ coordinates of all complexes and small molecules, and keywords employed are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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#### Notes

The authors declare no competing financial interest.

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- (75) We computed barriers for the reaction of  $21 \rightarrow TS21-22$  and  $25 \rightarrow TS26-27$  with an alternative methodology of B3PW91-D2/ECP2/ PCM//B3PW91-D2/ECP1. The barriers optimized at the level of B3PW91-D3 are lower by 0.3 and 0.4 kcal/mol, respectively. As such, we do not anticipate that optimization with a dispersion inclusive functional or method would drastically change or alter our conclusions with regard to the overall preferred mechanism. These dispersion-corrected geometries are provided in the SI.
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(78) Both 1 and 3 may bind methanol instead of carbon monoxide and propyne, respectively. In both cases, coordination of MeOH is found to be less favorable than the route illustrated in Scheme 5. Against CO uptake to form 2 from 1, binding of MeOH is 2.9 kcal/mol ( $\Delta G$  B3PW91-D3/ECP2/SDD PCM) uphill. Coordination of propyne to form 4 from 3 has a driving force of 15.9 kcal/mol, which is greater than MeOH coordination with 3, which has a gain of 9.1 kcal/mol. Solvent inhibition of catalytic cycle A is therefore unlikely and has no noticeable impact on either the selectivity- or rate-determining steps.

(79) Similar to mechanism **A**, complexes with MeOH coordinated in the vacant site of **8** and **8a** have been located. Such intermediates are approximately 9 and 3 kcal/mol more stable in free energy (vs 8/8a, respectively) though do not perturb the overall profile energetics. Associative transition states for propyne undergoing hydride transfer may thus be present, but we have not located such in light of the challenging barrier for solvolysis. These solvated intermediates do not alter predicted TOF values for cycle **B**.

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(82) Much debate still surrounds the exact mechanism of such methanolysis processes,  $^{31-34,76,77,85-88}$  and we note that one commonly proposed route is the loss of a proton from Pd(II)-coordinated methanol into bulk, forming a high-lying methoxide species and allowing for subsequent reductive elimination. Such a mechanism has been studied by Zuidema<sup>77</sup> and has been found to be considerably uphill. Therefore, more efficient methanolysis routes may well be present, but these would do little to resolve the lack of selectivity we find for mechanism **B**.

(83) Due to the small difference in kinetic energy between TS18–19 and TS18L–19L and the inclusion of moieties that contribute noticeably to dispersive interactions (i.e., phenyl rings), we additionally optimized these complexes at the level of B3PW91-D2/ECP1. At this level, and following minimization on a dispersion-inclusive potential energy surface, we find that the gross structure of these complexes is retained. However,  $\Delta\Delta G^{\ddagger}$  between these transition states drops from 1.6 kcal/mol (B3PW91/ECP1) to 0.6 kcal/mol at the aforementioned level, with TS18–19 being more accessible in both cases. Upon refinement at B3PW91-D2/ECP2/PCM//B3PW91-D2/ECP1, we find that  $\Delta\Delta G^{\ddagger}$  decreases further to less than 0.1 kcal/mol. A  $\Delta\Delta G^{\ddagger}$  of 0.1 kcal/mol is also computed at B3PW91-D2/ECP2/PCM//B3PW91-D2/ECP1 between TS18–19 6-Me and TS18L–19L 6-Me. This level of theory, therefore, also discounts mechanism C-II from operating.

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