Ligand Effects in Pd-Catalyzed Intermolecular Alkyne Hydroarylations

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Supporting Information

ABSTRACT: The use of palladium(II) catalysts for the synthesis of aryl alkenes by addition of aromatic C–H bonds to alkynes has received a great interest in the literature. The mechanistic features of the reaction have been largely discussed, but no systematic study has been reported so far, particularly for what concerns the role of ligands. In this work, we performed a detailed theoretical study in order to fill this gap. To this extent, three different systems have been considered, with the aim to emphasize how the steric and electronic metal environment affects the catalytic activity and, most notably, steers the reaction selectivity toward the two main products of single and double alkyne insertion into the aromatic C–H bond. Moreover, given the crucial role of the acid media, two acids have been considered, namely, trifluoroacetic acid and tetrafluoroboric acid, to understand the effect of the acid strength and coordinative power on the competition between the different pathways.

INTRODUCTION

The addition of an aromatic C–H bond to the triple bond of an alkyne is a very practical route for the introduction of alkenyl groups into aromatic compounds.^{1–4} Such a reaction, commonly termed “hydroarylation”,⁵ presents indeed several advantages, such as perfect atom economy and potentially high chemo-, regio-, and stereoselectivity. For example, the regioselectivity of the C–H addition depends primarily on the electronic properties of the substituents at the alkyne, particularly in the case of terminal alkynes: electron-donating as well as aromatic substituents promote the formation of a Markovnikov addition product, whereas *anti*-Markovnikov selectivity is generally recorded in the presence of electron-withdrawing substituents.^{1–4} The stereoselectivity of the reaction is also remarkable: in the majority of cases, formal *trans*-addition of the C–H bond to the alkyne is observed, which, in the case of electron-poor terminal alkynes, typically yields *Z*-1,2-disubstituted olefins, i.e., the less thermodynamically stable stereoisomer. As consequence, in this context, the hydroarylation reaction efficiently complements more traditional cross-coupling methodologies for the preparation of 1,2-disubstituted olefins, most notably the Heck reaction,⁶ which generally yields the more stable *E* isomer as product. Finally, the chemoselectivity of the reaction can vary as well, from standard single hydroarylation products (type 1, Scheme 1) to

Scheme 1. Potential Chemoselectivity of a Hydroarylation Reaction^{7–9}

products of multiple alkyne insertion into the same C–H bond (type 2)^{7,8} or of multiple hydroarylation of the same triple bond (type 3);⁹ the last one generally arises only with the most electrophilic arenes and heteroarenes.

Both the regio- and stereoselectivity of the reaction are influenced by the actual occurring mechanism. This, in turn, depends on the catalyst that is employed, whose role is mainly to convert either the arene or the alkyne into a more nucleophilic/electrophilic species, thus lowering the activation barrier for the reaction. The two possible mechanisms (Scheme 2) have been largely discussed in the literature,^{10,11} and they differ not only in the activation step but also in the stereochemical consequences. For example, when the reaction proceeds in a Friedel–Crafts fashion (Scheme 2, at the top), the catalyst, possessing soft Lewis acid character, coordinates

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Scheme 2. Possible Reaction Mechanisms Proposed for the Direct Alkyne Hydroarylation Reaction: Friedel–Crafts (at the Top) and Arene Metalation (at the Bottom)^{3,27}

the alkyne, which attacks the arene, forming a Wheland-type intermediate (in *anti* fashion); upon subsequent proton dissociation and protonolysis of the metal–vinyl bond, this intermediate liberates the *Z* product and the catalyst for another reaction cycle. A variant of this mechanism concerns terminal alkynes or alkynes functionalized with a leaving group at one end (halide, carboxylate...), which might isomerize to vinylidenes in the metal coordination sphere prior to electrophilic attack on the arene. However, the incidence of this mechanistic variant in the case of alkyne hydroarylation reactions is rather low, and it has been validated mostly in the case of intramolecular hydroarylation reactions, and particularly when metal centers prone to vinylidene formation (e.g., ruthenium) are used as catalysts.¹² Alternatively, the catalyst can first metalate the arene and subsequently insert the alkyne into the metal–aryl bond (in *syn* fashion); subsequent protonolysis of the intermediate regenerates the catalyst and produces the reaction product as the *E* stereoisomer (Scheme 2, at the bottom). This second possibility is generally limited to arenes featuring directing groups (which can precoordinate to the catalyst directing and promoting its attack to a specific position of the arene),^{13,14} or to intramolecular reactions (in which the alkyne tethered to the arene may itself act as a directing group and insert in a second moment into the metal–aryl bond).¹⁵

Less electrophilic metal centers generally prefer the arene metalation route,^{16–19} which, however, is less straightforward

(requires prior installation of the directing group or the synthesis of the arene–alkyne adduct) and also less efficient (requires higher temperatures to reach a satisfactory reaction rate). On the other hand, more electrophilic metal centers such as late transition metals in medium to high oxidation states, early transition metals, rare earths, and main group elements of the p block, do promote the Friedel–Crafts route.^{20–24} Interestingly, Pd(II) has been reported to exploit both reaction mechanisms, depending on the substrates and the reaction conditions.^{15,25–31} Thanks to this flexibility and to the great efficiency in promoting the reaction, Pd(II) is undoubtedly the metal center that, up to now, has been most commonly employed as catalyst for intermolecular alkyne hydroarylation reactions.

The first investigation on the mechanism of action of palladium centers was provided by the group of Fujiwara in their pioneering work on cationic Pd(II) species formed *in situ* under acid conditions in the intermolecular alkyne hydroarylation reaction with unfunctionalized substrates.^{25,26} On one hand, Fujiwara detected a vinylpalladium species as crucial intermediate of the reaction, but, on the other hand, he postulated a mechanism based on arene metalation (Scheme 2, at the bottom) based on experimental data that could be equivocal. Indeed, this proposal was shortly thereafter disputed by Tunge and Foresee,²⁷ who performed a thorough mechanistic study based on the kinetic isotope effect for an intramolecular hydroarylation reaction. They found the reaction mechanism based on alkyne π -activation (without isomerization to vinylidene species) much more compatible with their experimental data, and they proposed the final protonolysis step as the rate-determining step of the reaction. This result was further corroborated by theoretical investigation by Soriano and Marco-Contelles²⁸ and Strassner,²⁹ and, more recently, by mass spectroscopic investigation on the reaction intermediates by the group of Correia.³⁰ Only recently, an arene metalation route was again proposed for an intermolecular Pd-catalyzed alkyne hydroarylation reaction under acid conditions,³¹ but the DFT calculations performed to support the mechanistic proposal could not locate all the key intermediates.

While the essential features of the mechanism seem quite well established by these studies, the role of the ancillary ligands coordinated to Pd(II) has received very scarce attention up to now. Actually, this role appears crucial for many aspects. For example, chelating di-N-heterocyclic carbene (NHCs) ligands significantly increase the reactivity of Pd(II) in the reaction.³⁴ Furthermore, modifying the ligand allows to steering the reaction selectivity, for example, toward the formation of products of formal double alkyne insertion into the arene C–H bond.⁷ In this study, we aim at filling this gap and at rationalizing the active role of the ligand as well as of the acid by a theoretical approach.

RESULTS AND DISCUSSION

A comprehensive theoretical DFT study of the hydroarylation of ethyl propiolate (S1) via C–H activation of pentamethylbenzene (S2) has been performed (Figure 1). To have a detailed understanding of the mechanistic aspects and of the impact of the metal ancillary ligands on the reaction rate and on the selectivity, we investigated the behavior of three palladium(II) catalysts (Figure 1), namely, Pd(OAc)₂ (OAc = acetate, Fujiwara catalyst 1A), (di-NHC)PdX₂ (X = halide and NHC = methylenebis(*N*-methylbenzimidazolin-2-ylidene),

Figure 1. Schematic structures of the investigated reaction and of the employed catalysts.

Biffis catalyst **2A**), and (dppe)Pd(OAc)₂ (dppe = 1,2-bis(diphenylphosphino)ethane, Kitamura catalyst **3A**). Moreover, since the experimental conditions require the presence of an excess of acid in the environment, we modeled the reaction in the presence of trifluoroacetic acid (HTFA) and tetrafluoroboric acid (HBF₄) in order to rationalize also the effect of the acid nature on the obtained products.

All energies reported are Gibbs free energies (kcal/mol) evaluated at 298.15 K and 1.0 atm in CH₂Cl₂ as solvent. The presence of HTFA/TFA (or HBF₄/BF₄) in the reaction media was considered in agreement with the experimental conditions used for the reported reactions of pentamethylbenzene with ethyl propiolate (mixed solvent TFA/CH₂Cl₂, 4/1 by volume, at 25 °C).^{3,7,25}

Catalytically Active Species and Ethyl Propiolate (S1) Coordination. At first, we focused on the formation of the catalytically active species. For all the three catalysts, the active species consists in the cationic square planar complex **B** in which Pd coordinates one molecule of trifluoroacetate (TFA) and one molecule of HTFA in addition to the ancillary ligands of the precatalysts, i.e., two molecules of HTFA, the di-NHC, and the DPPE for **1A**, **2A**, and **3A**, respectively; see Figure 2. The two OAc ligands coordinated initially to Pd in **1A** and **3A** are promptly replaced by (H)TFA in the reaction mixture.³² Similarly, the two halides in **2A** are also replaced by (H)TFA as shown by the DFT calculations reported by Strassner et al.,³³ and also for the almost identical catalytic performance recorded for systems with the same di-NHC ligand and different halides.³⁴ In all cases, complexes **B** show a stabilizing hydrogen interaction between the TFA and the HTFA.

Starting from **B**, **S1** coordinates to the metal by replacing the HTFA molecule. For this step we explored both the one-step (**B**→**C**) and the stepwise (**B**→**B2**→**C**) mechanism; see Figure 2.

The one-step pathway consists in a simultaneous decoordination of HTFA and η^2 coordination of **S1** to the Pd in the position *cis* to TFA.³⁵ In the transition state, the complex assumes a trigonal bipyramid geometry with **S1** and HTFA lying in the equatorial plane (the alternative square pyramidal TS is calculated higher in energy). The energy barrier for this step is 12.6, 13.7, and 7.4 kcal/mol for **1A**, **2A** and **3A**, respectively. Such a lower energy barrier for **3A** is ascribed to the lower positive charge on Pd (see Table S1) that weakens the interaction with HTFA, favoring its decoordination.^{36,37}

Figure 2. **S1** coordination to Pd via one-step (**B**→**C**) and two-step (**B**→**B2**→**C**) pathways for the three investigated catalysts. Numbers are free energies in CH₂Cl₂ in kcal/mol.

On the other side, the stepwise pathway involves the decoordination of HTFA and the formation of a temporary κ^2 -carboxylate species (**B2**). Starting from **B2**, **S1** coordinates to the metal by breaking this chelate interaction. For all the three systems, the one-step **B**→**C** pathway is favored over the two-step pathway. However, while, for **2A** and **3A**, the **C** intermediate is slightly higher in energy relative to **B** + **S1** (ΔG = 3.7 and 4.1 kcal/mol for **2A** and **3A**, respectively), for **1A**, it is favored by 10.6 kcal/mol. This difference is ascribed to the electronic effects of the ancillary ligand lying in a position *trans* to the coordinated alkyne. In details, the di-NHC and the DPPE ligands have a stronger *trans* effect and therefore they weaken the Pd–**S1** bond to a greater extent (Pd–C_{S1} distances are 2.14/2.15, 2.25/2.31, and 2.26/2.35 Å for **1A**, **2A**, and **3A**, respectively).

Formation of the *Z*-Arylalkene (P1) Catalyzed by **1A**.

In this section, we discuss the complete catalytic cycle starting from intermediate **C** in the case of precatalyst **1A**; see Figure 3.

The nucleophilic addition of pentamethylbenzene (**S2**) to **S1** to form the vinyl-Pd complex **E** proceeds in two steps. At first, a *syn/anti* nucleophilic attack of **S2** to the C–C triple bond involving a low energy barrier leads to a very stable σ arylalkenyl-Pd complex **D** (at least 25 kcal/mol more stable than **C**), namely, the Wheland intermediate, as reported by Tunge et al.²⁷

As in Figure 3, although the **D-anti** product is 3.6 kcal/mol less stable than the **D-syn** product, the energy barrier for its formation is favored by almost 6 kcal/mol. From **D**, a proton transfer from the C_{ipso} atom of the arenium to the oxygen of the TFA ligand leads to the formation of **E** with a barrier of 19.7 and 26.8 kcal/mol from the **D-anti** and **D-syn**, respectively.

Both results are in agreement with the experimentally favored formation of **P1** rather than the corresponding isomer *E*-arylalkenyl, as reported by Fujiwara et al.^{26,27,38}

Figure 3. Catalytic cycle, at the top, and energy profiles (free energies in kcal/mol), at the bottom, for the hydroarylation of **S1** (*anti* and *syn* **S2** addition pathway in red and blue in the energy profile, respectively) in the presence of **1A**. All the species in the catalytic cycle are cationic.

Even though the barriers involved in the first step are at least 15 kcal/mol lower than those calculated for the latter, the selectivity between the two isomers occurs mainly in the **C-D** transition state: the much lower energy barrier for **C-D-anti** is ascribed to the approach of **S2** occurring *trans* to Pd, which reduces the steric stress between the aromatic ring and the alkenyl-Pd (see **Figure 4**). Conversely, in **C-D-syn**, short distances (2.90 and 2.80 Å) between the **S1** and **S2** carbon atoms are found.

On the basis of the computed energy barriers, we excluded the formation of **E-syn** and, thus, we investigated the following steps of the catalytic cycle only for the formation of **P1**. It is worth to note that the formation of the neutral intermediate proposed by Tunge et al.²⁷ (see **E'** in **Scheme 2**) is calculated to be unfavored by 30 kcal/mol over intermediate **E**.

From **E**, at −24.8 kcal/mol from the starting species **C** + **S2** considered at infinite distance, the system evolves to the next intermediate **F** containing the coordinated olefin product through the protonolysis step **E-F**.

Figure 4. Optimized geometry of transition states **C-D-syn** and **C-D-anti** (**C-D-syn**, C_1-C_2 2.90 Å, C_1-C_4 2.80 Å, C_1-C_3 2.56 Å; **C-D-anti**: C_1-C_2 2.93 Å, C_1-C_4 3.26 Å, C_1-C_3 2.72 Å). The two molecules of HTFA are portrayed as green tubes.³⁹

Different pathways have been investigated for this proton transfer reaction. A one-step and a stepwise reaction, via a six-membered transition state (see **Figure S1a**) or two consecutive [1,2]-H shift steps as proposed by Marco-Contelles et al.²⁸ (see **Figure S1b**), respectively, have been studied as intramolecular pathways. An intermolecular protonolysis reaction involving an external solvent molecule has also been considered, taking into account a one-step proton migration from the arenium to the C of the vinyl-Pd mediated by the external acid molecule (see **Figure S1c**) or a stepwise mechanism as proposed by Tunge et al.²⁷ (**Figure S1d**). The one-step intramolecular protonolysis, with an energy barrier of 7.9 kcal/mol, is favored by 20.0 kcal/mol over the double [1,2]-H shift intramolecular reaction and by 4.0 and 7.0 kcal/mol over the one-step and the stepwise intermolecular reactions, respectively.

The following **P1** dissociation proceeds in two steps; see **Figure 3**. At first, HTFA is displaced by the coordination of a new **S1** molecule through a square pyramid transition state (**F-G**) with the leaving acid occupying the apical position at almost 2.55 Å from the metal and a free energy barrier of 10.7 kcal/mol. After formation of **G**, in equilibrium with **F**, the starting species **C** is regenerated by displacement of **P1** and concomitant recoordination of a HTFA molecule (for **G-C**, $\Delta G^\ddagger = 12.6$ kcal/mol).

Overall, the rate-determining step is the formation of the vinyl-Pd intermediate **E** that is obtained selectively from an *anti*-addition of **S2**. Even though this result is in contrast with the conclusions reported by Tunge and Foresee²⁷ and by Soriano and Marco-Contelles,²⁸ they both investigated intramolecular hydroarylations that can contemplate a more energy demanding protonolysis step becoming, as consequence, rate-determining.

Formation of the Z-Arylalkene (**P1**) Catalyzed by **2A**.

In this section, we focus on the reaction mechanism/energies when system **2A** is used as precatalyst; see **Figure 5**.

Starting from **C**, differently from catalyst **1A**, for **2A**, the formation of intermediate **E** occurs by the *syn/anti*-addition of **S2** to the C–C triple bond, followed by a spontaneous breaking of the aryl C–H bond with the H transferring, at first, on the carboxylate group, and then on the TFA group (see **Figure S2** in the Supporting Information). Transition state **C-E** requires a free energy barrier of 13.2 and 22.7 kcal/mol for the *anti* and *syn*-addition, respectively. The almost 10 kcal/mol in favor of the *anti*-addition, ascribed to the most favorable *trans* orientation between the arene and the alkenyl-Pd, makes this step selective, in agreement with the experimentally preferred

Figure 5. Catalytic cycle, at the top, and energy profiles (free energies in kcal/mol), at the bottom, for the hydroarylation of **S1** (*anti* **S2** addition pathway in red and *syn*-addition pathway in blue in the energy profile, respectively) in the presence of **2A**. [Pd] = diNHC-Pd.

formation of **P1**, as observed for system **1A**. It is worth noting that, for **2A**, the formation of the Wheland intermediate **D** was ruled out since transition state **C-D** is calculated to be kinetically unfavored by 4 kcal/mol over the direct formation of the vinyl intermediate **E**. This decisive difference between **1A** and **2A** is ascribable to the presence of a HTFA ligand in the coordination sphere of the metal for **1A**. As can be noted in **Figure 4**, a hydrogen bond interaction between one HTFA and the ethyl propiolate substituent stabilizes the negative charge delocalized on the ester group after arene addition in the case of **1A**. The absence of this interaction for **2A** brings the ester group to interact with the arenic hydrogen during the nucleophilic attack of **S2** to **S1**, leading to the weakening of the $C_{ipso}-H$ bond and promoting the spontaneous proton transfer in intermediate **E**. It is worth to note that, since the mentioned H transfer in the **E** product involves the anion on Pd, the strength of the acid/base pair is expected to affect this step and the overall reaction rate, as discussed below. As for

1A, the strong kinetic preference for the *anti*-pathway allowed us to exclude the formation of **E-syn** and to investigate the following steps only for the *anti*-pathway.

From **E**, favored by more than 10 kcal/mol with respect to the starting species **C** + **S2** considered at infinite distance, the system undergoes to the protonolysis step **E-F** through the one-step intramolecular pathway with an energy barrier of 13.3 kcal/mol.

From **F**, differently from **1A**, **P1** is displaced by an η^2 coordination of TFA, leading to the formation of the κ^2 -carboxylate species **B2**. In transition state **F-B2**, the complex assumes a distorted square pyramid geometry with the leaving *Z*-aryllkene occupying the apical position at almost 2.8 Å far from the metal and a free energy barrier of 7.9 kcal/mol. After displacement of **P1** (i.e., formation of **B2**), the starting species **C** is regenerated via breaking of the chelate interaction in **B2** by coordination of a new molecule of **S1** (for **B2-C**, $\Delta G^\ddagger = 11.8$ kcal/mol).

Overall, **C-E**, which is the determining step for product selectivity and for the reaction rate, is almost 6 kcal/mol lower with respect to the determining step in the presence of **1A**, in agreement with the higher activity found for **2A** with respect to **1A** under the same experimental conditions.³⁴ It is worth to highlight that, differently from **2A**, for **1A**, the acid is involved in all the steps of the cycle since it acts also as an ancillary ligand on Pd.

Formation of the *Z*-Aryllkene (**P1**) Catalyzed by **3A**.

For system **3A**, only the determining steps in the catalytic cycle have been calculated. Similarly to system **2A**, starting from **C**, the nucleophilic addition of **S2** to the C–C triple bond occurs concomitant with the breaking of the C–H bond and the proton migration from the arene to the TFA, and the *anti*-product is formed selectively. The key energy barrier for the two catalysts differs only by 1–2 kcal/mol, in agreement with their comparable experimental activity.^{3,7}

Formation of the (1*E*,3*Z*)-Butadiene (P2**) Catalyzed by **2A**.** In this section, the competitive catalytic cycle (Cycle 2) leading to the formation of **P2** has been investigated for catalyst **2A**. Both Cycles 1 and 2 with the corresponding energy profiles are reported in **Figure 6** to facilitate the comparison between the two pathways.

Cycle 2 starts from the vinyl-Pd intermediate **E**. Since we have already observed that the formation of **E** occurs selectively by *anti*-addition of **S2** in the step **C-E**, here we only discuss the *anti*-pathway of Cycle 2.

From **E**, the coordination of the second molecule of **S1** leads to the simultaneous decooordination of HTFA through transition state **E-H**. The energy barrier for this step is 13.6 kcal/mol, almost isoenergetic with the competitive protonolysis step in Cycle 1 (**E-F**). Formation of intermediate **H** is thermodynamically unfavored by 8.0 kcal/mol with respect to **E** and by 16.1 kcal/mol with respect to **F**. The following **S1** insertion into the Pd–C bond leads to the formation of the vinyl-Pd intermediate **I** with a free energy barrier of 2.0 kcal/mol. From **I**, the system evolves toward the release of **P2** through low energy barriers and thermodynamically stable intermediates: one external HTFA molecule coordinates to the metal (**I-L**) and transfers the proton during the following protonolysis step with a barrier of only 10.7 kcal/mol (**L-M**). The last two steps of the cycle take place similarly to what is described for Cycle 1, i.e., decooordination of the product with formation of the κ^2 -carboxylate species **B2** and coordination of a new molecule of **S1**.

Figure 6. Catalytic cycle, at the top, and energy profiles (free energies in kcal/mol), at the bottom, for the hydroarylation of S1 to P1 (in red) and to P2 (in green) in the presence of 2A. [Pd] = diNHC-Pd.

The comparison of the two catalytic cycles suggests that the system prefers to evolve toward the protonolysis E-F rather than toward the coordination of a second molecule of S1. In fact, from E, the common intermediate for the two pathways, the thermodynamic favors Cycle 1 by almost 10 kcal/mol, in agreement with the experimentally favored formation of P1 with respect to P2 in the presence of 2A (P1/P2 ratio of 75/2).

Formation of the (1E,3Z)-Butadiene (P2) Catalyzed by 3A. Since the experimental results showed that 3A mainly produces P2 (P1/P2 ratio of 9/82), based on the considerations reported in the previous section, we only discuss the two competitive E-F (Cycle 1) and E-H (Cycle 2) steps.

As for 2A, F is strongly thermodynamically favored with respect to H by almost 10 kcal/mol. However, differently from 2A, starting from E (formed selectively as E-*anti* product), E-H is almost 9 kcal/mol lower than E-F. This kinetic preference for Cycle 2 pushes the system toward the coordination of a further molecule of S1 rather than to the protonolysis, in agreement with the experiments.

Comparison between 2A and 3A. To rationalize the substantial difference between 2A and 3A toward the competition between the two catalytic cycles, we have performed both a steric and an electronic analysis.

From a steric point of view, even though overall the di-NHC ligand is less sterically hindered than the DPPE, the greater tightness of the di-NHC determines a higher steric pressure in the close proximity of the Pd center with the carbenic carbons found at short distances from the aryl-alkenyl bond to the metal. This effect is particularly relevant in the crowded transition state E-H that, as consequence, is unfavored to a larger extent with respect to E-F for 2A than for 3A (see short distances in Figure 7).

Figure 7. Optimized geometries of transition state E-H for 2A (on the left) and 3A (on the right) and key distances (in Å). In green and orange tubes are reported the HTFA and the alkyne molecule, respectively.⁴⁰

From an electronic point of view, all the species along the catalytic cycle show a lower positive charge on Pd for 3A with respect to 2A; see Table S1. As consequence, the Pd-O bond *trans* to the ligand is weaker for 3A than 2A, favoring the release of the acid moiety and decreasing the energy of the E-H transition state. This effect is confirmed also by the decrease of the ΔG between F and H from −16 kcal/mol for 2A to −10 kcal/mol for 3A due to the higher destabilization of the Pd-O bond in 3A.

Formation of the (1E,3Z)-Butadiene (P2) Catalyzed by 2A in the Presence of HBF₄. In order to explain how the acid affects the product selectivity, we performed calculations on the hydroarylation of S1 with S2 for catalyst 2A in the presence of HBF₄ (Figure 8). Indeed, it has been experimentally demonstrated that, under these conditions, the reaction selectivity of 2A switches toward formation of P2.⁴¹

Starting from the formation of the active species, as previously reported, the reaction occurs by coordination of S1 with the concomitant release of one molecule of acid of the precatalyst and formation of intermediate C. Although this reaction turned out to be thermodynamically unfavored in the presence of HTFA, with HBF₄, the formation of intermediate C is favored by almost 6 kcal/mol, suggesting an easier initiation process in agreement with the higher experimental activity in the presence of HBF₄. This difference is ascribed to the greater steric hindrance and lower Lewis basicity of HBF₄ with respect to HTFA that favors the decooordination of the acid and the coordination of S1.

From C, the favored pathway consists in the formation of intermediate E by *syn/anti*-addition of the aryl-hydrogen bond of S2 to the C-C triple bond with concomitant breaking of the C-H bond and H migration from the arene to the ethyl propiolate. The free energy barriers of 19.4 and 27.6 kcal/mol for the *anti*- and *syn*-addition, respectively, make this step

Figure 8. Catalytic cycle, at the top, and energy profiles (free energies in kcal/mol), at the bottom, for the hydroarylation of S1 (*anti* and *syn* S2 addition pathway in red and blue in the energy profile, respectively; S1 second addition pathway in green, protonolysis in purple) in the presence of 2A and HBF₄. [Pd] = diNHC-Pd.

selective, in agreement with the experimentally preferred formation of the product with *Z* stereochemistry (as already observed in the presence of HTFA).

From E, the coordination of the second molecule of S1 with simultaneous decooordination of HBF₄ through transition state E-H requires a barrier of only 10 kcal/mol and, contrary to what was observed in the presence of HTFA, is kinetically favored with respect to the protonolysis reaction. This different behavior is the result of the weaker coordination of HBF₄ to Pd with respect to HTFA. Nevertheless the formation of H is disfavored by almost 6 kcal/mol with respect to E, the

following S1 insertion into the Pd–C bond with a free energy barrier of only 8.5 kcal/mol leads to the formation of the very stable vinyl-Pd intermediate I (at –26.3 kcal/mol with respect to C) driving the reaction toward the release of P2.

Interestingly, starting from H, we located an alternative pathway leading to the release of P1 (forming a new Cycle 1). This pathway consists in an intermolecular proton transfer that takes place through a one-step mechanism (H–C) involving an external HBF₄ molecule. The acid molecule adds to the Pd–C bond, releasing the proton to the carbon and coordinating the anion to the metal center with a barrier of 13 kcal/mol with respect to H. This pathway was ruled out for system 2A in the presence of HTFA for the high energy barrier calculated, i.e., almost 30 kcal/mol with respect to H.

The comparison of the energies of the two catalytic cycles suggests that system 2A in the presence of HBF₄ prefers to evolve toward the coordination/insertion of a second molecule of S1 rather than the formation of P1, in agreement with the experimentally favored formation of P2 (P1/P2 ratio equal to 7/43).³

The meaningful difference of energy between the two competitive transition states H–C and H–I (almost 5 kcal/mol) is ascribed to the inefficient coordination of HBF₄ to the metal that increases the energy of H–C and favors instead the insertion of S1 (H–I).

In conclusion, the different selectivity toward P2 and P1 in the presence of HTFA/TFA and HBF₄/BF₄ for 2A is explained upon considering the different coordination ability of the acid/base pairs, rather than the strength of the acid, in agreement with the experimental results obtained for the system 2A in the presence of various acids with different strength and coordination ability.⁷ However, such a selectivity switch is also critically dependent on the steric hindrance provided by the di-NHC ligand in 2A; this is apparent when one considers that use of the catalytic system 1A with HBF₄ results in a less active catalytic system compared to 2A, and most notably in a reaction selectivity that provides almost exclusively the product of single alkyne insertion.

It is worth to highlight that the rate-determining step in the presence of HBF₄ is almost 6 kcal/mol higher than in the presence of HTFA. This difference is directly related to the strength of the acid involved, as already anticipated above. Since the mentioned determining step implies the transfer of a proton from the arene to the ethyl propiolate substituent assisted by the anion ligand (TFA or BF₄), the higher basicity of TFA (given the lower acidity of HTFA) with respect to BF₄ helps the transition from an alkyne coordinated species (C) to a vinyl-Pd one (E), decreasing the rate-determining barrier C–E.

CONCLUSIONS

The detailed mechanism of the hydroarylation of ethyl propiolate via C–H activation of pentamethylbenzene in the presence of three different palladium complexes and two different acids has been discussed here.

The calculations performed indicate a Friedel–Craft type mechanism as the most likely to occur: the alkyne is activated by coordination to the metal with the following addition of the aromatic ring promoting the proton transfer to the alkyne and the formation of a vinyl-palladium intermediate. The final one-step intramolecular protonolysis of the vinyl-palladium liberates the product and regenerates the catalyst.

The arene addition step is found to be rate-determining, but its precise nature strongly depends on the ligands coordinated to the metal. For instance, for the $\text{Pd}(\text{OAc})_2/\text{HTFA}$ system, a two-step mechanism involving the formation of a Wheland-type intermediate occurs. On the contrary, a one-step mechanism consisting in the arene addition concerted with the hydrogen transfer from the arene to the alkyne assisted by the anionic ligand coordinated to the metal is preferred in the case of $(\text{di-NHC})\text{PdX}_2/\text{HTFA}$ and $(\text{dppe})\text{Pd}(\text{OAc})_2$ systems. This difference is mainly ascribed to the hydrogen bond interactions establishing in the coordination sphere of the metal when the acid molecule acts also as ligand, as in the case of the former system. The one-step addition mechanism features a lower energy barrier and is consequently coherent with the higher catalytic activity exhibited by $(\text{di-NHC})\text{PdX}_2/\text{HTFA}$ and $(\text{dppe})\text{Pd}(\text{OAc})_2$.

The *syn/anti* selectivity of the arene addition step strongly depends on the steric clash between the aromatic ring and the Pd-alkyne π complex, with the *trans*-addition leading to the Z-arylalkene product being favored over the *cis* one for all the catalysts studied.

On the other hand, the selectivity toward the formation of single or double alkyne insertion products depends on a strict combination of both steric and electronic features of the ligands as well as of the employed acid cocatalyst. For instance, from an electronic point of view, strong σ donor ligands, such as dppe, weaken the Pd–acid bond to a greater extent, favoring the release of the acid moiety and the coordination of the second ethyl propiolate. In the case of the di-NHC ligand, the steric factors are predominant: a greater tightness in close proximity of the metal unfavors the space demanding transition state for the addition of another molecule of ethyl propiolate determining the selectivity toward the formation of arylalkenes.

The performed studies allowed also rationalizing the effect of the acid on the catalyst performances. In detail, the experimentally observed higher reaction rate in the presence of HBF_4 is ascribed to the thermodynamically more favored formation of the alkyne coordinating species C, thanks to the easier release of one molecule of HBF_4 with respect to HTFA, which results in a higher concentration of catalytically competent species.

Instead, the actual activation barrier in the catalytic cycle increases by decreasing the acid strength, since the proton transfer from the arene to the ethyl propiolate in the rate-determining step of the reaction is more efficient the more basic is the anionic ligand in the catalyst (i.e., the weaker is the corresponding acid). Finally, the selectivity toward the single and double alkyne insertion is mainly affected by the coordinating power of the acid/base pairs, with a low coordinating acid (as HBF_4) that is more easily displaced by the second alkyne in the Pd coordination sphere, thus favoring the double insertion product.

EXPERIMENTAL SECTION

Computational Details. All the DFT static calculations were performed with the Gaussian 09 quantum chemistry package.⁴² The electronic configuration of the molecular system was described with the standard split-valence basis set with a polarization function of Ahlrichs and co-workers for H, C, N, F, P, and O (SVP keyword in Gaussian 09).⁴³ For Pd, we used the small core, quasi relativistic Stuttgart/Dresden effective core potential, with an associated valence basis set contracted (standard SDD keywords in Gaussian 09).⁴⁴ The geometry optimizations were carried out without symmetry constraints, and the characterization of the located stationary points

was performed by analytical frequency calculations, by using the BP86 functional of Becke and Perdew.^{45,46} Gibbs energies reported in the reported figures, ΔG , were built through single point energy calculations on the BP86/SVP geometries using the M06 functional⁴⁷ and the triple- ζ valence plus polarization on main group atoms (TZVP keyword in Gaussian),⁴⁸ whereas, for Pd, the SDD basis set was employed. Solvent effects were included with the polarizable continuous solvation model PCM using CH_2Cl_2 as the solvent.⁴⁹ To these M06/TZVP electronic energies in solvent (CH_2Cl_2), zero point energy and thermal and entropic corrections, evaluated at 298.15 K and 1.0 atm, were included from the gas phase frequency calculations at the BP86/SVP level of theory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.9b00473.

Alternative pathways investigated and NBO analysis (PDF)

Cartesian coordinates (XYZ)

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) *Catalytic Hydroarylation of Carbon-Carbon Multiple Bonds*; Ackermann, L., Gunnoe, T. B., GojHabgood, L., Eds.; Wiley-VCH: Weinheim, Germany, 2018.
- (2) Boyarskiy, V. P.; Ryabukhin, D. S.; Bokach, N. A.; Vasilyev, A. V. Alkenylation of Arenes and Heteroarenes with Alkynes. *Chem. Rev.* **2016**, *116*, 5894–5986.
- (3) Biffis, A.; Tubaro, C.; Baron, M. Advances in Transition-Metal-Catalysed Alkyne Hydroarylations. *Chem. Rec.* **2016**, *16*, 1742–1760.
- (4) Yamamoto, Y. Synthesis of heterocycles via transition-metal-catalyzed hydroarylation of alkynes. *Chem. Soc. Rev.* **2014**, *43*, 1575–160.
- (5) Perhaps the term “direct hydroarylation” would be more appropriate, as formal alkyne hydroarylation products can be obtained also from other routes starting from, e.g., aryl halides.
- (6) *The Mizoroki-Heck Reaction*; Oestreich, M., Ed.; Wiley: Hoboken, NJ, 2009.
- (7) Oyamada, J.; Kitamura, T. Drastic effect of bidentate phosphine ligands on Pd-catalyzed hydroarylation of ethyl propiolate: a simple route to arylbutadienes. *Chem. Commun.* **2008**, 4992–4994.
- (8) Biffis, A.; Gazzola, L.; Gobbo, P.; Buscemi, G.; Tubaro, C.; Basato, M. Alkyne Hydroarylations with Chelating Dicarbene Palladium(II) Complex Catalysts: Improved and Unexpected

Reactivity Patterns Disclosed Upon Additive Screening. *Eur. J. Org. Chem.* **2009**, 2009, 3189–3198.

(9) Kitamura, T. Transition-Metal-Catalyzed Hydroarylation Reactions of Alkynes Through Direct Functionalization of C-H Bonds: A Convenient Tool for Organic Synthesis. *Eur. J. Org. Chem.* **2009**, 2009, 1111–1125.

(10) Nevado, C.; Echavarren, A. M. Transition Metal-Catalyzed Hydroarylation of Alkynes. *Synthesis* **2005**, 2005, 167–182.

(11) Wang, X.; Zhou, L.; Lu, W. Hydroarylation of Alkynes via Aryl C-H Bond Cleavage. *Curr. Org. Chem.* **2010**, 14, 289–307.

(12) Li, B.; Dixneuf, P. H. Ruthenium (II)-Catalysed sp^2 C-H Bond Functionalization by C-C Bond Formation. *Top. Organomet. Chem.* **2014**, 48, 119–193.

(13) Manikandan, R.; Jeganmohan, M. Recent advances in the ruthenium-catalyzed hydroarylation of alkynes with aromatics: synthesis of trisubstituted alkenes. *Org. Biomol. Chem.* **2015**, 13, 10420–10436.

(14) Santhoshkumar, R.; Cheng, C.-H. Hydroarylations by cobalt-catalyzed C-H activation. *Beilstein J. Org. Chem.* **2018**, 14, 2266–2288.

(15) Chernyak, N.; Gervogyan, V. Exclusive 5-*exo-dig* Hydroarylation of *o*-Alkynylbiaryls Proceeding via C-H Activation Pathway. *J. Am. Chem. Soc.* **2008**, 130, 5636–5637.

(16) Gao, K.; Yoshikai, N. Low-Valent Cobalt Catalysis: New Opportunities for C-H Functionalization. *Acc. Chem. Res.* **2014**, 47, 1208–1219.

(17) Ryu, J.; Cho, S. H.; Chang, S. A Versatile Rhodium(I) Catalyst System for the Addition of Heteroarenes to both Alkenes and Alkynes by a C-H Bond Activation. *Angew. Chem., Int. Ed.* **2012**, 51, 3677–3681.

(18) Schipper, D. J.; Hutchinson, M.; Fagnou, K. Rhodium(III)-Catalyzed Intermolecular Hydroarylation of Alkynes. *J. Am. Chem. Soc.* **2010**, 132, 6910–6911.

(19) Nakao, Y. Hydroarylation of alkynes catalyzed by nickel. *Chem. Rec.* **2011**, 11, 242–251.

(20) Blons, C.; Mallet-Ladeira, S.; Amgoune, A.; Bourissou, D. π Complexes of P-P and P-N chelated gold(I). *Angew. Chem., Int. Ed.* **2018**, 57, 11732–11736.

(21) Nakhi, A.; Archana, S.; Seerapu, G. P. K.; Chennubhotla, K. S.; Kumar, K. L.; Kulkarni, P.; Haldar, D.; Pal, M. AlCl₃-mediated hydroarylation-heteroarylation in a single pot: a direct access to densely functionalized olefins of pharmacological interest. *Chem. Commun.* **2013**, 49, 6268–6270.

(22) Choi, D. S.; Kim, J. H.; Shin, U. S.; Deshmukh, R. R.; Song, C. E. Thermodynamically- and kinetically-controlled Friedel-Crafts alkenylation of arenes with alkynes using an acidic fluoroantimonate(V) ionic liquid as catalyst. *Chem. Commun.* **2007**, 3482–3484.

(23) Song, C. E.; Jung, D.-u.; Choung, S. Y.; Roh, E. J.; Lee, S.-g. Dramatic Enhancement of Catalytic Activity in an Ionic Liquid: Highly Practical Friedel-Crafts Alkenylation of Arenes with Alkynes Catalyzed by Metal Triflates. *Angew. Chem., Int. Ed.* **2004**, 43, 6183–6185.

(24) Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. Friedel-Crafts alkenylation of arenes using alkynes catalysed by metal trifluoromethanesulfonates. *Chem. Commun.* **2000**, 1573–1574.

(25) Jia, C.; Dongguo, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. Efficient Activation of Aromatic C-H Bonds for Addition to C-C Multiple Bonds. *Science* **2000**, 287, 1992–1995.

(26) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. Novel Pd (II)- and Pt (II)-Catalyzed Regio- and Stereoselective *trans*-Hydroarylation of Alkynes by Simple Arenes. *J. Am. Chem. Soc.* **2000**, 122, 7252–7263.

(27) Tunge, J. A.; Foresee, L. N. Mechanistic Studies of Fujiwara Hydroarylation. C-H Activation versus Electrophilic Aromatic Substitution. *Organometallics* **2005**, 24, 6440–6444.

(28) Soriano, E.; Marco-Contelles, J. Mechanisms of the Transition Metal-Mediated Hydroarylation of Alkynes and Allenes. *Organometallics* **2006**, 25, 4542–4553.

(29) Schroeter, F.; Císařová, I.; Soellner, J.; Herdtweck, E.; Strassner, T. Electron-poor hemilabile dicationic palladium NHC complexes -

synthesis, structure and catalytic activity. *Dalton Trans.* **2018**, 47, 16638–16650.

(30) Godoi, M. N.; de Azambuja, F.; Martinez, P. D. G.; Morgon, N. H.; Santos, V. G.; Regiani, T.; Lesage, D.; Dossmann, H.; Cole, R. B.; Eberlin, M. N.; Correia, C. R. D. Revisiting the Intermolecular Fujiwara Hydroarylation of Alkynes. *Eur. J. Org. Chem.* **2017**, 2017, 1794–1803.

(31) Hota, P. K.; Jose, A.; Mandal, S. K. Stereo- and Regioselective Addition of Arene to Alkyne Using Abnormal NHC Based Palladium Catalysts: Elucidating the Role of Trifluoroacetic Acid in Fujiwara Process. *Organometallics* **2017**, 36 (22), 4422–4431.

(32) The acetate ligands substitution occurring in solution was calculated for **1A** following the reaction: $\text{Pd}(\text{OAc})_2 + 4\text{HTFA} = \text{Pd}(\text{HTFA})_2(\text{TFA})_2 + 2\text{HOAc}$. The process is exoergonic by 16.0 kcal/mol.

(33) Muehlhofer, M.; Strassner, T.; Herrmann, W. A. New Catalyst Systems for the Catalytic Conversion of Methane into Methanol. *Angew. Chem., Int. Ed.* **2002**, 41, 1745–1747.

(34) Biffis, A.; Tubaro, C.; Buscemi, G.; Basato, M. Highly Efficient Alkyne Hydroarylation with Chelating Dicarbene Palladium (II) and Platinum (II) Complexes. *Adv. Synth. Catal.* **2008**, 350, 189–196.

(35) All the attempts to optimize the geometry with the **S1** coordinated *trans* to TFA failed as proton transfer between TFA and HTFA occurs, leading to a *cis* coordinated geometry.

(36) Antonova, N. S.; Carbó, J. J.; Poblet, J. M. Quantifying the Donor-Acceptor Properties of Phosphine and N-Heterocyclic Carbene Ligands in Grubbs' Catalysts Using a Modified EDA Procedure Based on Orbital Deletion. *Organometallics* **2009**, 28, 4283–4287.

(37) Getty, K.; Delgado-Jaime, M. U.; Kennepohl, P. An Electronic Rationale for Observed Initiation Rates in Ruthenium-Mediated Olefin Metathesis: Charge Donation in Phosphine and N-Heterocyclic Carbene Ligands. *J. Am. Chem. Soc.* **2007**, 129 (51), 15774–15776.

(38) Jia, C.; Kitamura, T.; Fujiwara, Y. Catalytic Functionalization of Arenes and Alkanes via C-H Bond Activation. *Acc. Chem. Res.* **2001**, 34, 633–639.

(39) The alternative conformers for transition states **C-D-syn** and **C-D-anti** generated through rotation around the $\text{C}_1=\text{C}-\text{CO}_2\text{Et}$ single bond are 6.5 kcal/mol higher in energy with respect to transition state **C-D** reported in the paper; see Figure 4. The formation of an H-bonding between the carbonyl oxygen of **S1** and the acidic hydrogen HTFA is crucial in stabilizing the system.

(40) The alternative conformer for the **E-H** transition state in which the alkyne substrate is rotated 180 °C and the EtO_2C group points towards the alkenyl group is unfavored for steric reasons, and the corresponding following intermediate **H** is 4.0 kcal/mol higher in energy than the one reported in the paper.

(41) We used the simple “ HBF_4 ” model for this acid in order to simplify the calculations. However, we are aware that a more appropriate representation of such acid in solution would be $\text{H}_3\text{O}^+\text{BF}_4^-$. To this extent, we have performed a series of benchmark calculations on key intermediates and transition states using for catalyst **2A** in the presence of $\text{H}_3\text{O}^+\text{BF}_4^-$. On the basis of the considerations reported in the paper, we calculated, starting from intermediate **H**, the competitive **H-C** (Cycle 1) and **H-I** (Cycle 2) transition states. **H-I** is calculated clearly lower in energy than **H-C** as in the presence of the HBF_4 , indicating that the system prefers to evolve towards coordination/insertion of a second molecule of **S1**, leading to the preferential formation of **P2**, instead of undergoing protonolysis of the vinyl-palladium. This is in agreement with the experiments. Therefore, these tests resulted only in minor numerical differences relative to calculations using HBF_4 , and no chemical conclusion is modified.

(42) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; et al. *Gaussian 09*, Revision D.01; Gaussian, Inc.: Wallingford, CT, 2009.

- (43) Schaefer, A.; Horn, H.; Ahlrichs, R. Fully optimized contracted Gaussian basis sets for atoms Li to Kr. *J. Chem. Phys.* **1992**, *97*, 2571–2577.
- (44) Haussermann, U.; Dolg, M.; Stoll, H.; Preuss, H.; Schwerdtfeger, P.; Pitzer, R. M. Accuracy of energy-adjusted quasirelativistic ab initio pseudopotentials. *Mol. Phys.* **1993**, *78*, 1211–1224.
- (45) Becke, A. Density-functional exchange-energy approximation with correct asymptotic behaviour. *Phys. Rev. A: At., Mol., Opt. Phys.* **1988**, *38*, 3098–3100.
- (46) Perdew, J. P. Density-functional approximation for the correlation energy of the in homogeneous electron gas. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1986**, *33*, 8822–8824.
- (47) Zhao, Y.; Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, non-covalent interactions, excited states, and transition elements: Two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2008**, *120*, 215–241.
- (48) Weigend, F.; Ahlrichs, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305.
- (49) Tomasi, J.; Persico, M. Molecular interactions in solution: An overview of methods based on continuous distributions of the solvent. *Chem. Rev.* **1994**, *94*, 2027–2094.