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Binuclear Pd(I)–Pd(I) Catalysis Assisted by Iodide Ligands for Selective Hydroformylation of Alkenes and Alkynes

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thoroughly investigated and broadly applied in industry (>10⁷ metric ton yearly). However, the ability to precisely control its regioselectivity with well-established Rh- or Co-catalysts has thus far proven elusive, thereby limiting access to many synthetically valuable aldehydes. Pd-catalysts represent an appealing alternative, yet their use remains sparse due to undesired side-processes. Here, we report a highly selective and exceptionally active catalyst system that is driven by a novel activation strategy and features a unique Pd(I)– Pd(I) mechanism, involving an iodide-assisted binuclear step to



release the product. This method enables β -selective hydroformylation of a large range of alkenes and alkynes, including sensitive starting materials. Its utility is demonstrated in the synthesis of antiobesity drug Rimonabant and anti-HIV agent PNU-32945. In a broader context, the new mechanistic understanding enables the development of other carbonylation reactions of high importance to chemical industry.

■ INTRODUCTION

Hydroformylation of alkenes and alkynes is the method of choice for the synthesis of versatile aldehydes.¹⁻⁴ Since the reactions typically yield mixtures of regioisomeric products, finechemical synthesis requires the ability to control precisely the regioselectivity of these processes, founding a compelling but often unaddressed problem.^{5–7} Because of inherent selectivity preferences, Pd-based catalysts^{8–11} could complement wellestablished Rh-based catalysts for reactions with alkenes such as vinyl arenes, enamides or acrylates (Figure 1a).¹²⁻¹⁸ However, the utility of these protocols is limited due to requirement of a strong Brønsted acid cocatalyst and high temperatures (e.g., ptoluenesulfonic acid at 100-125 °C). Such conditions are not suitable for numerous substrates, including oligomerizationprone (electron-rich) vinyl arenes or substrates containing acidsensitive functional groups (e.g., acetal, silyl, and N-Boc). Furthermore, the formation of aldehydes is typically accompanied by undesired formation of ketones, CO/alkene copolymerization, and hydrogenation processes.^{8,9}

Because of limited experimental and theoretical insight,¹⁹ the mechanistic proposals for Pd-catalyzed hydroformylation remain to a large degree speculative, hampering further rational development of new protocols (Figure 1b). For instance, the empirically determined requirement for a Brønsted acid cocatalyst is typically attributed to precatalyst activation,^{8–10} while excess phosphine ligand is applied as the reductant for catalyst activation. In contrast, related Pd-catalyzed carbonylation reactions were reported to occur in the absence of a Brønsted acid,²⁰ and a number of other pathways to generate the catalytically active species have been suggested.²¹ Common to

all proposed catalytic cycles is the involvement of Pd-acyl species, observed as intermediates in several carbonylation reactions.²² These Pd-acyl species are typically suggested to undergo hydrogenolysis with dihydrogen to release the aldehyde product.^{8,9,23} Nonetheless, Beller and colleagues reported that such an elementary step might be challenging and requires specific ligands and basic additives.²⁴

In order to address the reasons for low catalyst activity and the need for elevated reaction temperatures, we initiated our study with the following proposals:

- (1) We speculated that the acidic conditions of previous hydroformylation protocols might not only limit the substrate scope, but also partially deactivate the catalytically active palladium hydrido complex ($L_2Pd(II)HX + HX \rightarrow L_2Pd(II)X_2 + H_2$; Figure 1b).²⁵
- (2) Additionally, we surmised that excess phosphine ligand, typically used as the reductant during catalyst activation, might inhibit certain elementary steps of the catalytic cycle²⁶ or favor the formation of off-cycle dormant complexes.^{24,27}
- (3) Therefore, we envisioned an alternative pathway for generation of the palladium hydrido species through

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Figure 1. Hydroformylation of functionalized alkenes. (a) State of the art for Rh- and Pd-catalysis. (b) Plausible mechanism of Pd-catalyzed reactions. (c) Summary of this work.

heterolytic H_2 cleavage assisted by anions (Figure 1c),²⁵ a mechanism that would render the presence of a Brønsted acid and excess phosphine obsolete. We surmised that such a process would on one hand depend on the basicity of the anion (thought to facilitate heterolytic H_2 cleavage), and on the other hand be influenced by the ability of the anion to coordinate to Pd, which could potentially block the active Pd site.

Herein we present, guided by the above design criteria, a broadly applicable iodide-dependent Pd-based protocol that enables β -selective hydroformylation of alkenes and alkynes, including starting materials that contain a range of (acid-sensitive) functional groups. Our mechanistic studies further reveal the origin for the high catalytic activity, which is attributed to both, the facile precatalyst activation with dihydrogen and an unconventional binuclear mechanism assisted by iodide ligands to release the product.

RESULTS AND DISCUSSION

Formulation of the Catalyst. Evaluation of Effect of Different Anions. We commenced our studies by probing the activity of bisphosphine-Pd-complexes containing different anions in the absence of cocatalysts or protic solvents. We selected xantphos (4,5-bis(diphenylphosphino)-9,9-dimethyl-xanthene) as the model ligand, previously reported to form highly active Rh-based hydroformylation²⁸ and Pd-based carbonylation catalysts.^{29,30} 1-Decene served as the initial robust model substrate (Figure 2a). No reaction (<2%) was observed

with complexes containing an acetate, a trifluoroacetate, an acetylacetonate, a triflate, or a tetrafluoroborate counterion. In contrast, in the presence of complexes bearing a chloride, a bromide, or an iodide, the aldehyde products were generated readily and with complete chemoselectivity (Figure 2a); none of the commonly generated side-products, such as (poly)ketones, alcohols, or alkanes were detected.⁸ Reaction in the presence of iodide as counterion was most efficient, affording the aldehydes exclusively (>99%; 58% regioselectivity for n-aldehyde). It should be noted that the Shell laboratories have reported an increase in rate and selectivity of Pd-catalyzed hydroformylation-hydrogenation tandem reactions of simple internal $C_8 - C_{10}$ alkenes to linear alcohols under syngas upon addition of sodium halide salts, but that Brønsted acids and high temperatures were still required. The rate increased up to 6-7-fold (sodium iodide < bromide \approx chloride), whereas the regioselectivity for the linear product increased from 65% to 82% in the reverse order (sodium chloride < bromide < iodide).⁹ A halide anion was speculated to bind a proton during heterolytic dissociation of H₂, leading to formation of a Pd-acyl-hydride species. No experimental or theoretical data were reported to support such a hypothesis. Similarly, Shi and co-workers reported the accelerating effect of tetrabutylammonium iodide in Pdcatalyzed hydroformylation of alkenes with formic acid (used instead of syngas).¹¹ In the latter case, the iodide anion was proposed to facilitate ligand exchange to form a Pd-acyl-formate complex, which would release CO₂ and the aldehyde product. Again, no data were reported to support such a claim.

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b. Reaction development for sensitive substrates^b



Figure 2. Hydroformylation of alkenes. (a) Reactions with 1 mmol 1-decene, 1.0 mol % PdX₂, 1.1 mol % xantphos, 20/80 bar of CO/H₂, 2 mL of dioxane, 100 °C, 16 h. For the results of reactions in other solvents or with other ligands in place of xantphos, see section 3 of the Supporting Information. (b) Reactions with 0.125 mM alkene in toluene. (c) 2.0 mol % xanpthos–PdI₂. (d) Reactions with 0.125 mM alkene, 1.0 mol % xanpthos–PdI₂, 0.2 mol % Pd(OAc)₂, 20/80 bar of CO/H₂, toluene, 70 °C, 16 h. (e) 5-fold catalyst loading. (f) 100 °C. (g) 0.5 mM alkene in 1,4-dioxane, CO/H₂ 20/80 bar, 1 mol % PdI₂, 1.1 mol % xantphos, 100 °C. Conversion, yield, and regioselectivity determined by analyses of GC traces and ¹H NMR spectra with a standard (1,3,5-trimethoxybenzene or 1,4-dimethoxybenzene).

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a. Unprecedented simultanous control of chemo-, regio-, and stereoselectivity



Figure 3. Hydroformylation of alkynes (a and b) and synthesis of bisarylpyrazoles (c). (a) Reactions with 0.125 mM alkyne. (b) 2.0% cat. (c) 82% conv. Yield and regioselectivity determined by analysis of ¹H NMR spectra with an internal standard (1,3,5-trimethoxybenzene or 1,4-dimethoxybenzene). (d) Conditions: (a) For 1.2 g of methylphenylacetylene (4a), PdI₂ (1.0 mol %), xantphos (1.0 mol %), Pd(OAc)₂ (0.2 mol %), CO/H₂ (20/80 bar), toluene, 70 °C, 18 h, 83% yield; (b) Ar'NHNH₂*HCl (1.5 equiv), I₂ (1.5 equiv), EtOH, reflux, 18 h; 74% yield for R = CH₃, Ar = Ph, Ar' = 2,4-Cl₂Ph; 41% yield for R = CH₃, Ar = Ph; (c) NBS (1.1 equiv), AlCl₃ (10 mol %), CH₃CN, 80 °C, 80% yield for R = CH₃, Ar = Ph, Ar' = 2,4-Cl₂Ph; (d) 1-aminopiperidine (1.5 equiv), Pd(OAc)₂ (2 mol %), P(*t*-Bu)₃ (6 mol %), tetramethylethylenediamine (TMEDA, 0.75 equiv), CO (40 bar), dioxane (0.125 M), 120 °C, 58% yield; (e) NBS (1.1 equiv), azobis(isobutyronitrile) (AIBN, 5 mol %), CCl₄, reflux, overnight; (f) KCN (1.1 equiv), DMSO, 22 °C, 30 min, 45% yield (over 2 steps).

Evaluation of Phosphine Ligands. Because the activity and chemoselectivity (i.e., selectivity for hydroformylation over other side-reactions) have been reported to be sensitive to basicity, bite- and cone-angle of a phosphine,^{8,10} we tested

several other mono- and bidentate ligands in the presence of PdI_2 . For all of them the model reaction occurred with full chemoselectivity toward the aldehyde (e.g., with PCy_3 , PPh_3 , MePhos, dppf, rac-BINAP, DPEphos as ligands; Table S3),

although regioselectivity and yields varied. For instance, the reactions in the presence of dppf–PdI₂ or DPEphos–PdI₂ provided similar regioselectivity and yields as the reaction with xantphos–PdI₂ (95–99% yield, 54–58% n-regioselectivity), while regioselectivity was higher with rac-BINAP–PdI₂ (82%), albeit at lower alkene conversion (21%). Noteworthy, monodentate PPh₃ and PdI₂ formed an active catalyst that furnished the model aldehydes in 93% yield and 49% n-selectivity.

Optimization of Reaction Conditions. We then evaluated reactions of functionalized alkenes that are prone to undergo side reactions (e.g., (co)polymerization, hydrogenation processes).⁸ In the presence of 1 mol % xantphos–PdI₂ and syngas, styrene (1a) was consumed completely (>99% conv.), but there was only 11% of aldehyde 2a formed with 76:24 β : α selectivity (Figure 2b). The remaining starting material was converted to a complex mixture of products as the result of oligomerization and hydrogenation side reactions. Varying the reaction conditions (e.g., solvent, temperature, or pressure) did not lead to a significant improvement of the yield of 2a.³¹

Next we turned to Lewis acid additives, which have been demonstrated by Dobereiner and Becica to accelerate amide Naryl formation catalyzed by a xantphos–Pd complex.³² The rate enhancement was proposed to originate from reversible ligand abstraction to create an open ligation site for substrate coordination. We indeed observed an increase in activity of xantphos–PdI₂ in the presence of 0.2 mol % Al(OTf)₃ or In(OTf)₃ (Figure 2b). In sharp contrast, and in line with our mechanistic assumptions, the addition of 0.2 mol % PPh₄+I⁻ or excess xantphos (0.2 mol %) slowed down or completely inhibited the reaction. Furthermore, the addition of Brønsted acids lowered yields of aldehydes to <10% and promoted hydrogenation processes (66% or 71% yield of ethylbenzene formed, in the presence of AcOH or TsOH, respectively).

To eliminate the need for the presence of a strong Lewis acid that may trigger side reactions, we tested whether excess PdI₂ (without dative ligands) could also serve to reversibly abstract ligands. Indeed, with 0.2 mol % PdI₂ instead of a Lewis acid, the reaction was also accelerated (Figure 2b). Similar enhancement was observed by the addition of Pd(OAc)₂ (the latter is soluble in organic solvents, alike xantphos–PdI₂, allowing for ease of manipulation in solution). In addition, 1 mol % xantphos–PdI₂ and 0.2 mol % Pd(OAc)₂ also allow for the transformations to be carried out efficiently at lower temperature. At 70 °C, **1a** was converted to the aldehydes in nearly quantitative yield, with 78% β selectivity. At 50 °C, the reaction was slower (65% conversion, using double the standard catalyst loading), but the aldehyde was formed with higher regioselectivity (85% β -aldehyde).

Evaluation of Substrate Scope of Alkenes. The method proved to be broadly applicable (Figure 2c). Styrene derivatives containing an electron-withdrawing (1b–1f) or an electrondonating group (1g–1j), as well as those with a sizable aromatic moiety (1k) were compatible substrates, generating the product with up to 90% β selectivity. Reactions with 1,1-disubstituted olefins (11–1n) were similarly efficient and highly regioselective (93–99% β). A range of vinyl and allyl substrates 1q–1u also underwent hydroformylation to form aldehydes with high β selectivities (90%–99%). Notably, acrylates 1v-1w, which have been reported to copolymerize with CO in the presence of Pdbased hydroformylation catalysts,³³ reacted smoothly (94–99% β selectivity and 81–99% yield). Remarkable are also transformations involving acid-sensitive N-Boc-N-vinylformamide 1u and acetal 1x, which are incompatible with the acidic conditions of previous Pd-based hydroformylation protocols, but are compatible with the new method $(81-94\% \beta$ selectivity and 33-81% yields). Linear and cyclic aliphatic alkenes (1y-1z) were compatible as well; albeit the reactions required higher temperature (100 °C). Notably, alkene substrates containing unprotected N-H or O-H bonds or strongly coordinating groups, such as pyridyl moiety, failed to deliver the aldehyde product, illustrating current limitations of the method (Scheme S1).

Because 1,2-disubstituted aryl olefins, such as transisomethyleugenol 10 or trans- β -methylstyrene 1p are prone to undergo isomerization, especially at elevated temperatures, hydroformylation typically results in a mixture of aldehydes with either the α or γ isomer being the main product.³⁴ With the new conditions, however, 10-1p reacted to form β aldehydes predominantly (62–69% β selectivity; Figure 2d). Remarkably, β selectivity was partially maintained at higher temperatures, albeit hydrogenation diminished the yield of aldehydes. Interestingly, methyleugenol 1o' and allylbenzene 1p', the terminal alkene analogues of 10-1p, reacted to form aldehyde products with similar regioselectivity, suggesting facile isomerization and an inherent (moderate) β -selectivity under these conditions. Likewise, hydroformylation reactions of monosubstituted 1aa as well as Z-1,2-disubstituted aliphatic olefin 1ab produce the same linear aldehyde product (Figure 2e).

Hydroformylation of Alkynes. Next, we turned our attention to alkynes. The hydroformylation of alkynes constitutes an appealing strategy to produce enals, which are valuable building blocks in synthesis and occur as structural motives in natural or synthetic products (e.g., fragrances or flavors). However, despite many efforts, the hydroformylation protocols for their generation remain largely undeveloped.^{35–41} Besides controlling regioselectivity, a key challenge is to prevent undesired side reactions, which mainly include hydrogenation of both starting materials and products. Previous efforts have shown that the chemoselectivity of the reaction can be adjusted by carefully designed catalysts and optimized reaction conditions;³⁵⁻ however, control over regioselectivity remains largely unsolved. For instance, under state-of-the-art Rh-based³⁵ or Pd-based³⁶ protocols, methylphenylacetylene (4a) reacted to form a mixture of regioisomeric aldehydes 5a:6a in 62:38 ratio, 78% combined yield along with 10% hydrogenation products, or in 21:79 ratio, 70% combined yield at 100% conversion of starting material, respectively (Figure 3a).

We found that in the presence of xantphos–PdI₂ and Pd(OAc)₂, the reaction of **4a** furnished enals with an unprecedented selectivity of **5a:6a** 95:5, 99:1 *E:Z* (**5a**), and 96% yield (Figure 3a). Control experiments confirmed that the presence of an iodide as well as the use of Pd(OAc)₂ as a cocatalyst are critical for activity and chemoselectivity. No reaction occurred when xantphos–PdI₂ was substituted by an analogue containing a different anion, or when Pd(OAc)₂ (or PdI₂) was absent.³¹ Furthermore, the iodide also appears to be instrumental in controlling regioselectivity. This feature is highlighted by the control reaction in the presence of xantphos–Pd(acac)₂ and *p*-TsOH, which only led to formation of enals in low regioselectivity and yield (**5a:6a** 68:32, 14% yield). These results suggest an active role of the iodide in the product-forming step.

Evaluation of Substrate Scope of Alkynes. The catalytic protocol can be applied to a broad range of alkynes to form β -aryl enals, which were inaccessible through previous hydro-formylation protocols (Figure 3b). Reactions with alkynes **4b**-

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Formation of Pd2-deuteride & DX with D2/CO confirms H2 activation





- As initially hypothesised, Pd-hydride species can be formed in reaction with H₂ without any Brønsted acid co-catalyst

- All xantphos–Pd(II) complexes bearing *weakly-coordinating anions* form dinuclear Pd-hydrido-carbonyl species under syngas

- Presence of base shifts the equilibrium towards Pd₂-hydride⁺ (H₂/CO)

or PdHI species (H₂), but excess base leads to Pd(0) species

c. Many xantphos-Pd(II) complexes and an alkene form Pd-acyl species under syngas, but their further reactivity depends on the counterion present



Figure 4. Investigation of reactivity of xantphos–Pd(II) complexes under syngas–influence of anions and additives. Reactions were performed in $CD_2Cl_2 6$ bar H_2/CO (or 1 bar CO) using 2 equiv. alkene 1q; the progress was monitored by the NMR spectroscopy. * The hydride atom was located from the Fourier difference map and then refined with the AFIX1 constraint; anions in both structures are disordered; one position of BF_4^- is shown for clarity; thermal ellipsoids are drawn at 20% level; for ORTEP presentations at 50% level and further details, see the SI.

4e, containing longer aliphatic moieties than 4a, produced the aldehydes with high β regioselectivities (88–91%) and yields (83–92%). Derivatives bearing larger benzyl (4f) or iso-butyl (4g) groups also reacted with high β regioselectivities (89% and 84%) and yields (79% and 88%, respectively). In contrast to the

former examples, an alkyne containing a sterically demanding cyclohexyl (4h) group reacted to form α -aldehyde 6h as the major isomer (70%). Alkyne derivatives with an electron-donating or an electron-withdrawing group in the para-, meta-, or ortho-position of the phenyl ring (4i–4s), as well as those

with a sizable aryl moiety (4t-4u) were effective substrates, furnishing the product with up to 90% selectivity for β isomer. Particularly noteworthy are the transformations involving heteroaryl alkynes, bearing sensitive N-Boc-indole (4v), benzothiophene (4w), or (benzo)furan (4x-4y), which delivered β aldehydes in 82–86% regioselectivity and yields up to 98%. Selectivity issues aside, starting materials containing these sensitive moieties have previously not been reported to be compatible with Pd-based hydroformylation protocols. Notably, similar to the scope of alkenes, alkyne substrates bearing unprotected N–H, a strongly coordinating pyridine ring, or a terminal alkyne bond were not compatible, defining the limitations of the method (Chart S1).

Synthesis of Bisarylpyrazoles. With an efficient β selective hydroformylation method for alkynes in hand, we devised a 4-step modular synthesis of 1,5-bisarylpyrazole derivatives (Figure 3c), which are at the core of many pharmaceuticals and agrochemicals.⁴²⁻⁴⁵ The sequence starts with the hydroformylation of alkynes (either commercially available or easily accessible⁴⁶) followed by I_2 -mediated oxidative condensation of enal **5** with an arylhydrazine to assemble pyrazole derivative 7.⁴⁷ The subsequent selective electrophilic bromination of the pyrazole ring in 7 with Nbromosuccinimide (NBS) to form 8 enables diversification of the 5-position. For instance, 5-bromopyrazole 8 reacted with 1aminopiperidine under a CO atmosphere in the presence of a palladium complex to furnish 9, a Rimonabant derivative, i.e., a cannabinoid-1 receptor antagonist previously used as an appetite suppressant.⁴⁸ Alternatively, in the presence of a radical initiator (azobis(isobutyronitrile), AIBN), 7 reacted with NBS at its alkyl site to form 4-(bromomethyl) derivative 10, which was reacted directly (in one-pot) with KCN⁴⁹ to form 11, PNU-32945, a HIV-1 reverse transcriptase inhibitor.⁵⁰ The above examples showcase that, starting from simple commercial building blocks, numerous derivatives of such biologically active molecules can be rapidly accessed.

Mechanistic Studies. Having demonstrated utility of the method, open questions remained regarding the mechanistic aspects of this reaction. In particular we wondered whether activation of the precatalyst occurred as hypothesized (see above) and whether the activation process would determine the overall activity of the catalyst or whether other factors would be rate-limiting. Equally unclear was the unique role the halide anions played in the reaction and why the addition of free $Pd(OAc)_2$ (or PdI_2) had an accelerating effect. When and how the regioselectivity was established remained to be solved as well. To shed light onto the above questions, we performed detailed experimental studies, which we further corroborated with DFT calculations.

Activation of the Palladium-Complex (Generation of Pd-Hydride Species). In agreement with our initial hypothesis, a series of xantphos–Pd(II) complexes bearing weakly coordinating anions readily formed Pd-hydride species under syngas without the need for any Brønsted acid cocatalyst (Figure 4a). In particular, the formation of fluxional cationic binuclear Pd(I)– Pd(I) hydridocarbonyl complex $[(xantphos)_2Pd_2(\mu-H)(\mu CO)]^+$ (Pd₂–hydride⁺) was indicated by the characteristic quintet hydride signal in the ¹H NMR spectrum as well as doublet and singlet signals in the proton-coupled and protondecoupled ³¹P NMR spectra, respectively. ^{19,51–56} The structure was further confirmed by X-ray analysis for Pd₂–hydride⁺ bearing a trifluoroacetate counterion. Additionally conducted isotope-labeling experiments with D₂ confirmed the source of the hydride atom; reaction of xantphos-Pd(II) trifluoroacetate and D_2/CO in CH_2Cl_2 furnished [(xantphos)_2Pd_2(\mu-D)(\mu-D))/(\mu-D) (CO)]⁺, Pd₂-deuteride⁺ complex, with a characteristic quintet deuteride signal in the ²H NMR spectrum and a triplet signal in the proton-decoupled ³¹P NMR spectrum (Figures S30-S31).³¹ A plausible mechanism for formation of the binuclear Pd(I)-Pd(I) complexes, consistent with the observations of the activation reactions under dihydrogen (Figures S35–S36),³¹ is depicted in Figure 4b. Notably, because formation of the Pdhydride is accompanied by formation of a molecule of Brønsted acid that favors the reverse reaction,^{25,53} the process remains reversible. It appears that the base is not required for the activation, but its presence (Et₃N) can profoundly impact the equilibrium of the various Pd species (most noticeable in case of HI generation). In the absence of a base xantphos-PdI₂ dominates the equilibrium, while in the presence of a stochiometric amount of base Pd2-hydride+ or xantphos-PdHI are formed (under syngas or dihydrogen, respectively). Furthermore, an excess of base drives these reactions toward the Pd(0) species.³¹ It should be pointed out that under catalytic conditions, the strong acid (e.g., HI) can be quenched by the alkene (e.g., hydrohalogenation of alkene 1q, Figure S65). We also found that the formation of Pd₂-hydride⁺ is fully inhibited for the complexes bearing an acetate or an acetylacetonate (anions of typical catalyst precursors).^{8,10,36} Notably, Poli, Drent and co-workers reported the formation of a mixture of a related binuclear Pd(I)-Pd(I) carbonyl hydride complex and a binuclear Pd(I)-Pd(I) biscarbonyl complex in the reaction of preformed BCOPE–Pd(OTf)₂ with syngas (BCOPE = $(c-C_8H_{14}-1,5)PCH_2CH_2P(c-C_8H_{14}-1,5))$.¹⁹ Although, a mixture of Pd(OAc)₂, excess BCOPE, and TfOH and water was catalytically active in hydroformylation-hydrogenation tandem reactions,⁹ neither the catalytic competency of binuclear Pd(I)-Pd(I) species bearing BCOPE nor their formation under the actual catalytic conditions were reported.¹

Reaction Intermediates (Pd-acyl vs Pd-alkyl). Our initial focus was directed toward the structure and stability of prospective Pd-acyl intermediates, both in solution and in the solid state. Reaction of a xantphos-Pd(II) complex bearing a weakly coordinating anion, alkene 1q, and syngas leads to formation of the cationic Pd- β -acyl species, Pd- β -acyl⁺ (Figure 4c). 1q was chosen as a substrate due to its easy to monitor NMR signatures. The same cationic Pd- β -acyl species was formed in direct reactions of 1q with isolated Pd₂-hydride⁺ in the presence or absence of iodide anions (under inert conditions). The structure of **Pd-\beta-acyl⁺** was confirmed through X-ray analysis of the tetrafluoroborate complex, wherein the fourth site of the square-planar complex is occupied by the oxygen of trans-chelating xantphos. Analysis of the Pd-acyl species in solution at room temperature (NMR) reveals no dependence on the identity of the anion.³¹ At temperatures below -20 °C, however, the NMR signals change significantly for the iodide complex, suggesting the existence of a pronounced degree of Pd-I interaction. Furthermore, control experiments for analogues of Pd-alkyl species bearing different anions (Pd $alkyl_{Me}^{+}$), that is, the prospective intermediates connecting the Pd-hydride and the Pd-acyl species, confirmed that CO insertion into the Pd-alkyl bond is rapid in all cases (Figure 4d).^{31,57} The latter results are consistent with nondetectable amounts of Pdalkyl species during the NMR studies under syngas.

Release of the Aldehyde Product. Although the treatment of 1q and a series of xantphos-Pd(II) complexes under syngas leads to formation of Pd- β -acyl⁺, release of the aldehyde product

H₃CCN

X-rav of

[(xantphos)2-Pd(I)2(NCCH3)2](BF4)2*

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Figure 5. Investigation of reactivity of Pd(II)-acyl intermediates and binuclear Pd(I)-Pd(I) species. (a) Reactions were performed in CD₂Cl₂ under N₂ (or 6 bar H₂/CO) using 1 equiv. Pd-acyl bearing a tetrafluoroborate; 1 equiv. Pd-hydride bearing a trifluoroacetate; 1 equiv. PPh₄+I⁻ (per each Pd-complex); 1 equiv. HI; 1 equiv. **1qB**. The incubation of Pd-acyl species at higher temperatures led to decomposition. (b) Reaction mixture of xantphos-PdI₂ with alkene **1q** under syngas (6 bar) in CD₂Cl₂, at 50 °C for 6 h, was analyzed by ESI-TOF-HRMS; # – signals of [xantphos-Pd-H+O₂+]. (c) Reactions in CD₂Cl₂. * Structure of Pd-acyl complex is disordered in the methyl group of the acyl ligand; structure of [(xantphos)₂-Pd(I)₂(NCCH₃)₂](BF₄)₂ is disordered in one phenyl group and one BF₄⁻⁻, disorder and cocrystallized CH₂Cl₂ are omitted for clarity; thermal ellipsoids are drawn at 20% level, except for the tetramer (50% level); for ORTEP presentations at 50% level, see the SI. For full experimental details, see the SI.

X-ray of tetramer of

(xantphos)–Pd(l)₂l₂*

2q occurs only in the presence of halides, most readily iodide (Figure 4c). This step, which appears to be the bottleneck of the reaction, is further inhibited by excess xantphos or accelerated by catalytic $Pd(OAc)_2$ or PdI_2 additives.³¹

A series of stochiometric experiments with independently prepared $Pd-\beta-acyl^+$ complexes indicated that, in contrast to former proposals,²³ $Pd-\beta-acyl^+$ does not react directly with dihydrogen (Figure 5a).³¹ Notably, the presence of iodide anions did not promote the reaction with dihydrogen, which is in contrast with the previous hypothesis on the role of halide anions by Leñero, Drent, and colleagues.⁹ Moreover, $Pd-\beta-acyl^+$ did not undergo protonolysis with the Brønsted acids (HI, HCl, or TsOH), a process that would represent an alternative pathway to the formation of aldehydes.

Further experiments demonstrated that formation of the aldehyde occurs through a process involving Pd-hydride species and iodide anions (Figure 5a). Specifically, $Pd-\beta-acyl^+$ reacted readily with Pd_2 —hydride⁺ at room temperature in the presence of iodide forming aldehyde 2q in 83% yield. No aldehyde was formed in the absence of iodide. This process was also accelerated by catalytic amounts of $Pd(OAc)_2$, but the presence of iodide ions was critical for the reaction to occur. These studies provide clear evidence for the critical role of iodide, which is not to promote dihydrogen activation⁹ but to promote the reaction of $Pd-\beta$ -acyl⁺ with Pd_2 —hydride⁺.

Resting State and Selectivity-Determining Step (Stochio*metric Experiments*). Although the pathways toward α - and β aldehydes bifurcate already at the insertion of the alkene into the Pd-H bond, we established that this step does not control the regioselectivity of the reaction (as it does for a majority of Rhcatalyzed hydroformylation reactions).¹ Because the alkene and CO insertion steps are reversible, the regioselectivity is determined during conversion of Pd-acyls to aldehydes. The following two experiments were conducted to support such a scenario. (a) Reaction of $Pd-\beta$ -acyl⁺ (derived from alkene 1q) in the presence of alkene $1q_B$ led to the formation of a new Pd- β acyl species (Pd- β -acyl_B⁺ bearing incorporated 1q_B) and the free alkene 1q (Figure 5b). (b) Alternatively, the independently prepared $Pd-\alpha$ -acyl⁺ species was first converted into $Pd-\beta$ -acyl⁺ in the presence of **Pd**₂**-hydride**⁺ and iodide before it reacted to form β -aldehyde **2q** in 84% yield; again, no α -aldehyde **3q** was generated (Figure 5c). These results suggest that (i) not only does formation of both Pd-acyl species occur reversibly but that (ii) **Pd-\beta-acyl**⁺ is thermodynamically more stable and (iii) most importantly also more reactive than $Pd-\alpha-acyl^+$ during reaction with Pd₂-hydride⁺ and iodide. The catalytic experiments with substrates containing electronically altered aryl groups with similar steric contribution (cf. Figure 2) further provide deeper insight into the relevance of electronic effects. It appears that the β selectivity in 2a-2i as well as 2o-2o' and 2p-2p' correlate roughly with thermodynamic stabilities of the corresponding α and β aldehydes (i.e., electron-donating groups stabilize the electron-withdrawing formyl group),⁵⁸ consistent with a regioselectivity-determining transition state of the step in which the product is released. In short, it is therefore likely that both, higher thermodynamic stability, and higher reactivity of $Pd-\beta-acyl^+$ originate from a combination of steric and electronic effects. First, because of diminished steric requirements of the β -acyl ligand, with the steric bulk in Pd- β -acyl⁺ being further away from the Pd site vs in $Pd-\alpha-acyl^+$, and second, because the key transition state partly has the character of the product, electronic effects favor the thermodynamically more favored aldehyde product.

Identification of Binuclear Pd Complexes. Based on the stochiometric experiments between $Pd_{-\beta}-acyl^{+}$ and Pd_{2} hydride⁺, we hypothesized that the prospective productforming step could be a halide-mediated binuclear elimination reaction⁵⁹ between a Pd(II)-acyl species and a mononuclear Pd(II)-hydrido species; a step so far not considered for Pdcatalyzed hydroformylation.²³ The process would lead to the formation of a binuclear Pd(I)-Pd(I) complex (Figure 5d, insert). Initial support for such a mechanism was obtained through high-resolution mass-spectrometry of a reaction mixture between xantphos-PdI₂ and 1q under syngas, which revealed a series of binuclear Pd(I)-Pd(I) complexes. Signals corresponding to $[xantphos-Pd_2I]^+$, $[(xantphos)_2-Pd_2I]^+$, and $[(xantphos)_2 - Pd_2I(CO)]^+$ along with signals of other intermediates, i.e., mononuclear Pd-hydride⁺ ([xantphos-PdH]⁺), Pd-alkyl⁺, and Pd-acyl⁺ were observed (Figure 5d). Further, reaction of an independently prepared binuclear Pd(I)-Pd(I) complex, $[(xantphos)_2 - Pd_2](BF_4)_2$, with syngas led to facile formation of the above-mentioned catalytically active binuclear Pd_2 -hydride⁺ complex (Figure 5e), in accordance with the involvement of binuclear Pd(I)-Pd(I) complexes in the catalytic cycle. Most interestingly, binuclear complex [(xantphos)₂-Pd₂](BF₄)₂ reacts with syngas to form Pd₂-hydride⁺ much faster than mononuclear complex xantphos $-Pd(BF_4)_2$ does (<10 min at 22 $^{\circ}$ C vs >2 h at 60 $^{\circ}$ C).

X-ray analyses of several binuclear xantphos-Pd(I)–Pd(I) complexes gave insight into their structural features. While, in Pd_2 -hydride⁺, each xantphos is bound to the same Pd-center (in a cis fashion), each ligand is coordinated to both Pd-centers (in a bridging fashion) in cationic complex [(xantphos)₂– Pd₂(NCCH₃)₂]²⁺ and in neutral complex xantphos–Pd₂I₂ (Figure 5e). In the latter case, 4 binuclear units are arranged in a tetrameric macrocycle, stabilized by bridging iodide anions. Noteworthy, the square planar geometries of the neighboring Pd centers are perpendicular to each other (vide infra).

Kinetic Studies and Rate-Determining Step (Catalytic Experiments). To provide insight into the mechanism under actual catalytic conditions, we conducted detailed kinetic studies. First, by using a 5:1 mixture of xanptphos-PdI₂ to $Pd(OAc)_2$ to maintain the ratio of xantphos-ligated and nonligated Pd species, we determined a reaction order of 2.0 (± 0.1) in Pd, which is in agreement with a binuclear ratelimiting step involving Pd-acyl and Pd-hydride species. Next, we established the reaction to be of negative order in alkene 1q $(-1.0 (\pm 0.1))$, which is in accordance with the alkene and the **Pd-\beta-acyl⁺** resting state competing for the reaction with Pdhydride species. Because the catalytic activity is sensitive to the Pd:xantphos ratio, we also studied the stoichiometry of the catalyst in the turnover-limiting step by the method of continuous variations of concentrations of PdI₂ and xantphos, often referred to as a Job analysis.⁶⁰ The highest activity was observed at ~0.67 molar fraction of PdI₂ (Figure S99), indicating a catalytic species (or a transition state) with a 2:1 Pd: xantphos ratio in the turnover-limiting step. Additionally, the experiments with varied amount of iodide at constant concentrations of Pd and xantphos (fixed 2:1 ratio) indicated the highest activity in the presence of 2-4 equiv of the anion (vs xantphos), while the activity was significantly reduced outside of that range (Figure S100). Together, the above data imply a $\sim 2-$ 4:2:1 iodide/Pd/xantphos molecularity in the turnover-limiting

Resting State under Catalytic Conditions. To get insight into the reaction intermediates under catalytic conditions, we

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Figure 6. DFT investigation for binuclear reaction of $Pd-acyl^+$ with various Pd-hydride species. Calculations have been performed at the $\omega B97MV/$ def2-QZVPP//M06L/def2-SVP level of theory in dichloromethane as solvent (SMD solvation model); SMD, solvation model based on density; INT1 and INT2, intermediates, TS, transition state. For full discussions, further details, and structures of all transition states and intermediates, see the SI.

monitored the reaction progress in situ with the aid of highpressure NMR spectroscopy. It was revealed that conversion of alkene **1q** was accompanied by the transient formation of one major intermediate, **Pd-\beta-acyl⁺**, which is finally converted to the single product **2q** (Figure S101).³¹ Analogous experiments with **Pd-\alpha-acyl⁺**, **Pd-\beta-acyl⁺**, or **Pd₂-\beta-hydride**⁺ and PPh₄I (iodide source) as catalysts in place of xantphos–PdI₂, painted a similar picture (Figure S102). Irrespective of the initial complex, conversion of 1q to product 2q was observed, along with the presence of the same Pd- β -acyl⁺ intermediate.⁶¹

Lastly, when the catalytic reaction using alkene 1q and a mixture of deuterium and CO was monitored in situ with ²H NMR spectroscopy, fast incorporation of deuterium into 1q, at both α - and β -C–H sites of the vinyl bond, prior to formation of

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Figure 7. DFT investigation for mononuclear reaction of Pd-acyl⁺ with H_2 or HI. Calculations have been performed at the ω B97MV/def2-QZVPP// M06L/def2-SVP level of theory in dichloromethane as solvent (SMD solvation model); SMD, solvation model based on density; **INT1**, **INT2**, and **INT3**, intermediates, **TS**, transition state. For full discussions, further details, and structures of all transition states and intermediates, see the SI.

any observable amount of aldehyde **2q**, was observed (within <10 min; Figure 103).³¹ These data indicate that the alkene insertion into the Pd-hydride bond occurs both quickly and reversibly to form both Pd- α -alkyl and Pd- β -alkyl species.

Density Functional Theory (DFT) Studies. The experimental findings were further corroborated by DFT calculations at the ω B97MV/def2-QZVPP//M06L/def2-SVP level of theory,^{62,63} which indicate that a binuclear reductive elimination step is the most likely scenario for the reaction (Figure 6). Initial formation of a mononuclear xantphos–Pd-hydride species LPdHX (along

with xantphos–Pd⁰(CO))⁶⁴ from the binuclear Pd₂–hydride⁺ ground state is predicted to be less endergonic in the presence of iodide vs a weakly coordinating triflate anion ($\Delta G_{rel} = +11.6$ kcal/mol vs +16.4 kcal/mol for LPdHI vs LPdHOTf, respectively). In addition, reaction of these mononuclear Pdhydride species with the Pd–acyl⁺ ground state via binuclear reductive elimination (transition states A and B) is significantly favored in the presence of the stronger coordinating halide anion ($\Delta G_{rel} = +27.4$ kcal/mol for X = iodide vs +36.8 kcal/mol for X = triflate; Figure 6a). Since the presence of two xantphos ligands in

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Figure 8. Full proposal of the mechanism of halide-assisted Pd-catalyzed hydroformylation of alkenes.

transition states A and B might lead to significant steric crowding, we investigated the further activation of LPdHI by additional iodide anions and Pd(II) additives (modeled as $(PdI_2)_n$). While generating I_2Pd-H^- anion is even more endergonic (ΔG_{rel} = +19.5 kcal/mol, Figure 6b), its subsequent reaction with the Pd-acyl⁺ through transition state C is strongly favored most likely due to reduced steric crowding ($\Delta G_{\rm rel}$ = +21.5 kcal/mol). The presence of an additional halide ion, as in anionic transition state D, leads to further stabilization of the coordinatively unsaturated complex C ($\Delta G_{\rm rel}$ = +14.5 kcal/ mol;), identifying the most favored scenario for the reaction.³¹ It is important to stress out that the geometry of transition state D is in excellent agreement with the structure of xantphos-Pd₂I₂ determined through X-ray crystallography (Figure 5e), giving further credence to the computed reaction pathway. Moreover, these computational results are consistent with the facile reaction at room temperature observed during stochiometric experiments (Figure 5a). The stoichiometry of the binuclear transition state complex containing 3 iodide ligands and just one xantphos is further in line with the accelerating effect of free $Pd(OAc)_2$ (or PdI_2), the inhibition by excess xantphos ligand, and the stoichiometry determined by kinetic experiments ($\sim 2-$ 4 iodide : 2 Pd : 1 xantphos). Whether the I_2Pd-H^- anion represents an actual intermediate or if one of the xantphos ligands is lost during the formation of the binuclear complex remains a subject of speculation. However, Hartwig and coworkers showed that related anionic "ligandless" arylpalladium halide species (Br₂PdAr⁻) are catalytic relevant intermediates in the presence of dative phosphines ligands in the Heck reaction,⁶⁵ and the catalytic role of other anionic palladium halide species has been recently elucidated in cross-coupling reactions.^{66–68}

Additional calculations indicate that the energy barriers for aldehyde formation via direct hydrogenolysis of the Pd–acyl⁺ ground state by H₂ (transition state E; Figure 7a) or protonolysis by HI (transition state F; Figure 7b) are energetically more demanding ($\Delta G_{rel} = +27.1$ and +22.6 kcal/mol, respectively). These findings are consistent with the lack of reactivity in the stochiometric experiments involving the Pd-acyl species and H₂ or HI at room temperature (Figure 5a).

It is worth mentioning that due to the presence of sizable xantphos ligands, dispersion forces play a significant contribution to the relative energies of intermediates and transition states A-F (several tens of kcal/mol).⁶⁹ Given that the applied solvation model tends to rather overestimate intermolecular dispersion in solution,^{70,71} easier generation of the monomeric hydride species from dimeric Pd₂-hydride⁺ is predicted when only partial nonlocal dispersion⁶² is accounted for. Simultaneously, transition states C and D are further favored over A, B, E and F (for the discussion of a plausible origin, see section 8.4 of the SI and Figure S108).

Summarized mechanistic proposal. Based on the mechanistic data we propose that the halide-assisted Pd-catalyzed hydroformylation of alkenes occurs as shown in Figure 8. The key mechanistic features are

- (1) Activation of phosphine–Pd(II) complex with dihydrogen–step I, to form the Pd-hydride species is both, facile and reversible, with the binuclear hydrido-carbonyl complex, Pd_2 –hydride⁺, dominating the equilibrium under syngas. The formation of Pd-hydride species does not require the presence of a Brønsted acid as cocatalyst, in contrast to previous speculations.^{8–10}
- (2) Alkene insertion into the Pd-hydride bond-step II, to form cationic Pd-alkyl intermediates, **Pd-alkyl**⁺, followed

by CO insertion-step III, to form the cationic Pd-acyl species, $Pd-acyl^+$, are both fast and reversible.

- (3) $Pd-acyl^+$ is the resting state of the catalytic cycle and does not react directly with dihydrogen, as had been proposed previously.^{8,9,23} Instead, $Pd-acyl^+$ reacts with a Pdhydride species in the rate and selectivity determining step-step IV, via a binuclear elimination reaction⁵⁹ to form a Pd(I)-Pd(I) intermediate and the aldehyde product. The process is assisted by halides as ligands in accordance with the strong dependence of catalytic activity on the counterion. The proposed transition state geometry (3 iodide: 2 Pd: 1 xantphos) strongly correlates with the stoichiometry determined through kinetic experiments (2-4:2:1).
- (4) In the final step the binuclear Pd(I)-Pd(I) intermediate reacts rapidly with H_2 under syngas-step V, to generate $Pd_2-hydride^+$, and HI. The acid then oxidizes this binuclear Pd(I)-Pd(I) hydrido species, furnishing two mononuclear Pd(II)-hydride species required for the catalytic turnover.

Noteworthy, binuclear cooperativity has been reported for some Co- and Rh-catalyzed hydroformylation processes;^{13,59,72,73} however, a mechanistic proposal involving binuclear cooperativity in Pd-catalyzed hydroformylation as well as its dependence on the halide anions are unprecedented.

The herein proposed binuclear mechanism (Figure 6b) and the previously and more commonly invoked mononuclear process involving direct reaction of the Pd-acyl intermediate with H_2 (Figure 7a) are distinct from one another. Specifically, although the overall outcome is the same, the order of events appears to be altered. While it is an activated hydride species (a Pd(II)-hydride) that reacts with the Pd-acyl resting state in the binuclear mechanism (Figure 6b), heterolytic cleavage of H_2 across the Pd-acyl bond (as in Figure 7a) can be regarded as a protonation event of the acyl ligand (plus a hydride transfer to the Pd(II) cation). Why exactly such a reversal of events leads to a lowering of free energy is unclear at present, particularly given that direct comparison of transition states of significantly different nature is challenging. It is plausible to regard the Pd(II)-hydride species as a masked Brønsted acid that releases the proton upon donation of its d electrons to the Pd(II)-acyl species during formation of the Pd(I)-Pd(I) bond, while the proton protonates the acyl ligand to form the aldehyde. Further efforts directed toward deeper understanding of the herein proposed unique mechanism and evaluation of its validity in other Pd-catalyzed hydroformylation protocols with varied monodentate and bidentate ligands, as well as, its comparison to other more common metal catalyzed hydroformylation mechanisms (including Rh-based ones) are underway.

CONCLUSIONS

In conclusion, the herein disclosed hydroformylation strategy enables the production of a broad range of valuable aldehyde building blocks and products from feedstock materials and relies on an unconventional approach for activation of a palladium precatalyst. Additionally, our investigations elucidated a unique binuclear reaction mechanism and provide new insights regarding the positive influence of halide anions, a feature that had previously only been reported empirically in various palladium-catalyzed transformations.^{9,11,74,75} Our preliminary data of high-yielding and highly selective alkoxy-, thio- and aminocarbonylation transformations (Figure S1) foreshadow extension of our methodology to lift existing limitations in other industrially important palladium-catalyzed carbonylation reactions used in the synthesis of highly valuable carbonyl compounds such as carboxylic acids, esters, thioesters, or amides.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09254.

- Details on experimental procedures for the catalytic reactions, the mechanistic experiments, crystallographic analysis, detailed DFT data, and spectroscopic data for the starting materials and the products (PDF) Crystallographic data discussed in the text (CIF)
- DFT computed geometries in .xyz file format discussed in the text (XYZ)

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Notes

The authors declare no competing financial interest.

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