Dinuclear Pd^I Catalysts in Equilibrium Isomerizations: Mechanistic Understanding, *in Silico* Casting, and Catalyst Development

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ABSTRACT: The unique reactivity profile of the dinuclear Pd^I complex [Pd^I(μ-Br)Bu₃P]₂ as an isomerization co-catalyst has enabled orthogonal tandem processes ranging from styrene syntheses to biodiesel refining. We have now elucidated the mechanistic basis of its distinct catalytic profile by DFT calculations and experimental studies. Activation of the catalyst proceeds intramolecularly, giving rise to a dinuclear complex composed of a reactive palladium hydride and an inert palladacycle. This complex mediates double-bond migrations with an energy span of 9.5 kcal/mol, which is well below those calculated for known catalysts. Its dissociation leads to an even more active monophosphinopalladium hydride catalyst and an inert dinuclear bispalladacycle. In the main deactivation pathway, two mononuclear Pd species react with each other, liberating a hydrogenation product and regenerating the catalyst precursor [Pd^I(μ-Br)Bu₃P]₂. The experimentally observed build-up of dinuclear palladacycles during the catalysis is, thus, the result of a conversion of binuclear into mononuclear Pd–H catalyst. Phosphines, which would deactivate metathesis co-catalysts, are not liberated at any stage. This explains the unique suitability of [Pd^I(μ-Br)Bu₃P]₂ for isomerizing metatheses. The mechanistic insights were used for the *in silico* casting of a catalyst generation, targeting complexes with a reduced barrier towards the formation of dinuclear Pd–H species, a low energy span of the catalytic cycles, and increased barriers either towards deactivation or, alternatively, towards dissociation to short-lived mononuclear complexes. Complexes with bisadamantyl-*n*-butylphosphine ligands were identified as lead structures. Experimental studies with model catalysts confirmed the validity of the predicted structure-activity relationship.

INTRODUCTION

Metal-catalyzed double-bond isomerizations are widely used in chemical value creation.¹ A prominent example is the Takasago process for the production of menthol, which features a ruthenium/Tol-BINAP-catalyzed asymmetric isomerization of a prochiral enamine.² The discovery of synthetically meaningful isomerizing functionalizations has further boosted the significance of isomerization catalysis.³ The general reaction concept is that a widely available C–C double-bond isomer with limited synthetic potential is converted *in situ* into a mixture of double-bond isomers from which one is drawn forth by follow-up functionalization, leading to a value-added product. It has been widely implemented, e.g., in isomerizing hydroformylations,⁴ hydroborations,⁵ alkoxycarbonylations,⁶ and hydroaminomethylations (Scheme 1).⁷ Striking examples include the synthesis of valeraldehyde from 2-butene,⁸ and of ω-functionalized aliphatic carboxylates from unsaturated fatty acids.⁹ The latter products are of great interest for accessing bio-based long-chain polyesters, i.e. “nature’s polyethylene”.¹⁰ In most of these processes, double-bond migration is promoted by the same catalyst that mediates the functionalization step, e.g. a rhodium, palladium or iridium system.

The latest development in this field is the incorporation of catalytic double-bond migrations into bimetallic orthogonal tandem catalyses.¹¹ In this reaction concept, two different catalysts are independently yet cooperatively active within a single reaction vessel. It is an enabling technology for the valorization of natural products or waste streams, often leading to compounds that would be inaccessible by consecutive action of the same catalysts. Hydration/dehydration olefin metatheses¹² and isomerizing olefin metatheses¹³ showcase its innovative potential.

Scheme 1. Isomerizing hydroaminomethylation or hydroformylation of internal olefins.

Isomerizing metatheses work by the simultaneous action of an isomerization catalyst, which constantly moves double bonds up and down along the alkyl chains of the substrate molecules, and an olefin metathesis co-catalyst, which continually shuffles

the alkyl substituents of each double bond.¹⁴ This iterative, cooperative action of two orthogonal catalysts can be used to convert single olefins or olefin mixtures into defined product blends with carbon-chain lengths evenly distributed around the mean chain length of the starting materials. Pioneering experiments were performed already in the 1990s by Porri and Grubbs, later by Consorti and Dupont, who combined a modified Hoveyda-Grubbs metathesis catalyst with a ruthenium-hydride isomerization catalyst.^{13,15} The key requirement for transforming such isomerizing metatheses from a laboratory curiosity into a powerful synthetic methodology was the development of a set of highly active metathesis and isomerization catalysts that operate under identical conditions with neither catalyst deactivating the other. This mutual compatibility is difficult to achieve for isomerizations, since most catalyst systems call for strong acid or base additives, which are incompatible with sensitive co-catalysts Schrock et al. have demonstrated the utility of product-specific isomerizing metathesis processes with a Ru/W system that allows to selectively produce (*Z*)-5-decene from (*E*)-3-hexene.¹⁶ In the context of equilibrium isomerizing olefin metathesis technology, the discovery of $[\text{Pd}^{\text{I}}(\mu\text{-Br})\text{Bu}_3\text{P}]_2$ (**Pd1^{Br}**) as highly reactive, one-component isomerization catalyst that is mutually compatible with ruthenium metathesis catalysts has led to a major advance (Figure 1). In the context of equilibrium isomerizing olefin metathesis technology, the discovery of $[\text{Pd}^{\text{I}}(\mu\text{-Br})\text{Bu}_3\text{P}]_2$ (**Pd1^{Br}**) as a highly reactive, one-component isomerization catalyst that is mutually compatible with ruthenium metathesis catalysts has led to a major advance (Figure 1). It is not only a highly active catalyst for single bond flips,¹⁷ but is able to continuously move double bonds up and down long carbon chains, allowing metathesis reactions to take place at any time.^{14a}

Figure 1. Structure and optimized geometry of dinuclear Pd^{I} catalyst $[\text{Pd}^{\text{I}}(\mu\text{-Br})\text{Bu}_3\text{P}]_2$ (**Pd1^{Br}**).

Isomerizing metatheses using **Pd1^{Br}** along with Grubbs- or Hoveyda-type catalysts have been implemented in the synthesis of dicarboxylic acid blends from fatty acids for applications in polymers and coatings,¹⁸ of valuable vinylarenes from naturally abundant allylarenes,¹⁹ of tsetse-fly attractants from cashew nutshell liquid,²⁰ and of non-estrogenic bisphenol A surrogates from clove oil (Scheme 2, top).²¹ A Pd/Pd/Ru three-component isomerization/ethenolysis/metathesis catalyst has enabled the one-pot, low-energy, solvent- and waste-free refining of rapeseed oil methyl ester (RME) and (bio)ethylene into a biofuel for conventional diesel engines.²² Its evenly rising boiling point curve fulfils the strict specifications prescribed by the fuel standard EN 590 for modern (petrol) diesel engines. This refining via isomerizing cross-metathesis requires negligible energy input (60 °C), no solvents, and does not produce waste (Scheme 2, bottom). Simulations revealed that around 30 alternating isomerization and metathesis steps have to occur for every substrate molecule to bring the reaction mixture close to equilibrium composition. Many state-of-the-art isomerization catalysts have been tested in extensive studies, but for processes that require multiple double-bond migrations

under conditions that are compatible with sensitive ruthenium complexes, **Pd1^{Br}** was the sole catalyst to give promising results.^{14a}

Scheme 2. Synthetic utility of isomerizing metathesis processes catalyzed by Ru/Pd systems.

The $[\text{Pd}^{\text{I}}(\mu\text{-Br})\text{Bu}_3\text{P}]_2$ isomerization catalyst at the basis of these recent developments in equilibrium isomerizing metathesis¹⁸⁻²² was first reported by Mingos,²³ Prasad,²⁴ and Hartwig,²⁵ who first utilized the Pd^{I} dimer as precatalyst in Pd^0 -promoted cross-couplings. They found it to be an excellent catalyst for couplings of aryl chlorides and bromides e.g. with hindered anilines. Hartwig also demonstrated the applicability of this catalyst in Suzuki couplings. Additionally, **Pd1^{Br}** was used in a variety of reactions including α -arylations of esters and amides,²⁶⁻²⁸ α -vinylation of carbonyl compounds,²⁹ C–CN,³⁰ C–S,³¹ and C–Si bond-forming reactions,³² Kumada couplings,³³ and the amination of heterocyclic halides.³⁴ Schoenebeck et al. reported its use for catalytic aromatic halide-exchange reactions³⁵ and also presented trifluoromethylthiolations of aryl iodides using the iodo analogue **Pd1^I**.³⁶

Several mechanistic studies were undertaken to understand why the catalytic activity of Pd^{I} dimers goes beyond that of mononuclear Pd species in cross-coupling reactions. Hartwig et al. reasoned that the Pd^{I} dimers are rapidly converted into the 12-electron species $\text{Pd}^0\text{-P}^{\text{I}}\text{Bu}_3$.²⁵ Different mechanisms have been proposed for the conversion of Pd^{I} dimers³⁷ into active mononuclear catalysts, including e.g. disproportionation,^{23,38} reduction,³⁹ or homolytic bond scission followed by reduction of the radical species (Scheme 3).⁴⁰ Schoenebeck et al. also considered a homolytic bond cleavage with reduction of a Pd^{I} radical to Pd^0 , but ruled this out in a follow-up publication in favor of a nucleophile-assisted fragmentation.^{33,41} In only few cases, preservation of the Pd – Pd bond during the catalytic process is proposed, but this is not further elaborated or proven.⁴² However, for $[\text{Pd}^{\text{I}}(\mu\text{-I})\text{Bu}_3\text{P}]_2$, it has been shown that the dinuclear structure stays intact e.g. in aromatic substitution reactions with weak nucleophiles.⁴³ These mechanistic investigations focus on the role of the Pd^{I} dimer in cross-coupling and halide exchange reactions. With the present work, it was our aim to elucidate the mechanistic pathways of $[\text{Pd}^{\text{I}}(\mu\text{-Br})\text{Bu}_3\text{P}]_2$ in the equilibrium isomerization part of isomerizing

olefin metathesis processes, and ultimately use the results to improve the efficiency of these orthogonal tandem processes.

Scheme 3. Proposed pathways for the formation of catalytically active species from Pd1^{Br} .

The use of Pd complexes as isomerization catalysts is well established.⁴⁴ State-of-the-art systems such as Brookhart's 2,9-dimethylphenanthroline-palladium catalyst promote isomerizations over several carbon atoms under rather mild conditions, usually in the presence of acids or hydride sources.⁴⁵ In the context of isomerizations of allyl- to vinylbenzenes, catalysts and isomerization mechanisms have recently been reviewed comprehensively.^{46,47} For Pd catalysts, two main pathways are proposed, one of which is initiated by insertion of alkenes into Pd-H catalysts,⁴⁸ the other by allylic C-H cleavage.⁴⁹ Preformed diphosphinopalladium hydride species show high catalytic activities only at 80 °C or above. Mechanistic investigations by Mazet et al. have confirmed the intermediacy of such $(\text{PR}_3)_2\text{Pd-H}$ species in an addition/ β -hydride elimination pathway with an energy span of 20 kcal/mol.⁵⁰ Studies by Hartwig et al. revealed that during the autocatalytic oxidative addition of aryl bromides to $\text{Pd}^0(\text{P}^t\text{Bu}_3)_2$, various species are formed, amongst which the side product $\text{Pd}(\text{P}^t\text{Bu}_3)_2(\text{H})(\text{Br})$ has also shown catalytic activity.⁵¹ However, Skrydstrup et al. found that $(\text{t-Bu}_3\text{P})_2\text{PdHCl}$ systems selectively flip terminal double bonds into the adjacent, thermodynamically favored position, but do not catalyze chain-walking processes.⁵²

In contrast to such $(\text{PR}_3)_2\text{Pd-H}$ species, Pd1^{Br} catalyzes isomerizations over any number of positions along a carbon chain already at room temperature. Its specific activity is so high that it isomerizes even allyl to vinyl esters, rather than inserting into their allyl-carboxylate bond.¹⁸ This is quite counterintuitive in view of the proverbial stability of Pd-allyl complexes. No mechanistic studies have yet been performed to explain the unique isomerizing profile of Pd1^{Br} . It is entirely unclear why Pd1^{Br} is so effective in mixtures with sensitive ruthenium metathesis catalysts, with both catalysts retaining their full activity. It is also uncertain what makes the *tert*-butyl phosphine ligands so exceptionally efficient in this context. Finally, it is not understood what causes Pd1^{Br} to degrade within only several hours, and how this may be avoided.

The present mechanistic study addresses these questions, thus providing a blueprint for the development of isomerization catalysts with new levels of activity and durability in orthogonal tandem catalysis. It delivers in-depth understanding of the catalyst activation, double-bond migration, and catalyst degradation processes, and provides a rational basis for further catalyst development with the goal of advancing isomerizing olefin metathesis towards industrial application. Propene was used as the model substrate because substrate and isomerization product are identical. This makes it a good model for equilibrium isomerizing metatheses e.g. of rapeseed methyl ester, in which the individual steps have almost no thermodynamic driving force (Scheme 4).²² The key findings

are counterintuitive and will support improvement in catalyst design: The build-up of palladacycles in the reaction medium in the course of the reaction was confirmed to be an indispensable part of catalyst activation rather than a result of its degradation.¹⁷ Hence, ligand design must be directed towards facilitating rather than avoiding cyclometalation.

Scheme 4. Isomerizing ethenolysis of rapeseed methyl ester.

COMPUTATIONAL METHODS

All theoretical calculations were carried out using the Gaussian03⁵³ and Gaussian09 program packages.⁵⁴ All geometries of reactants, products, intermediates, and transition states were optimized with the B3LYP exchange-correlation functional⁵⁵ including the Grimme empirical dispersion correction D3.⁵⁶ In the geometrical optimizations, the 6-31+G(d) basis set⁵⁷ was considered for the lighter atoms H, C, N, O, P and Br, Cl. For the heavier Pd, I atoms, we employed the double- ζ -quality basis set with the relativistic effective core potential of Hay and Wadt (LANL2DZ).⁵⁸ Each optimized structure was subsequently analyzed by harmonic vibration frequencies to characterize the stationary point as minima or saddle point. Geometries were fully optimized without symmetry constraints. The intermediates were verified as true minima by the absence of negative eigenvalue, whereas the transition states were characterized by a single imaginary frequency corresponding to the reaction coordinate. The rigid-rotator harmonic oscillator approximation was applied for evaluating the thermal and entropic contributions that are needed to derive the enthalpies H and Gibbs free energies G at 323.15 K. All transition states were located using the linear synchronous transit (LST) method,⁵⁹ in which the reaction coordinate was kept fixed at different distances while all other degrees of freedom were relaxed. After the linear transit search, the transition states were optimized using the default Berny algorithm implemented in the Gaussian09 code.⁵⁴ All transition states were confirmed by Intrinsic Reaction Coordinate (IRC) calculations.⁶⁰ To obtain more reliable relative energies, the single-point calculations of optimized geometries were carried out at the level of B3LYP-D3/6-311++G(d)* (H, C, N, O, P, Br, Cl), SDD (I), LANL2TZ(f) Pd, taking into account the solvation effect of toluene ($\epsilon = 2.374$). Solvation energies (E_{L}^{S}) were evaluated by a self-consistent reaction field (SCRF) approach for all intermediates and transition states using the

SMD continuum solvation model⁶¹ implemented in Gaussian09. To reduce computational cost, the two-layer ONIOM(MO:MO)⁶² method was employed for the adamantyl substituents. The ONIOM high level was designated to the whole molecules except for the adamantyl fragments from phosphines. The high level was treated at the B3LYP-D3/6-31+G*(H, C, N, O, P, Br), LANL2DZ(Pd, I) level, whereas the ONIOM low level has been described using the B3LYP-D3/3-21G method. Natural bond orbital (NBO)⁶³ analysis was performed on the optimized geometry using the NBO Version 3.1 program. Quantum Theory of Atoms in Molecules (QTAIM) calculations were also performed to characterize the electronic distribution around some selected bonds in the chemical species applying Bader's atoms-in-molecule (AIM) theory.⁶⁴

In the Gaussian program, the concentration can be specified by adjusting the pressure value based on the ideal gas law $P_i = RTn_i/V$, where P_i , R , T , n_i and V signify pressure, universal gas constant, absolute temperature, molar quantity, and reaction volume, respectively. The experimental concentrations of catalyst and reactants at the reaction temperature (323.15 K) are approximated by setting the partial pressures of the substrates as follows: propene (**1**) and propane (**2**): 1.0×10^{-3} mol = 13.2 atm; and of the intermediates of the catalytic cycle as follows: catalyst (**Pd1^{Br}**): 2.5×10^{-6} mol = 0.033 atm (for details, see Scheme S1).

In the present study, we considered two energy values: $G_{323.15K}^{S-L}$ and $H_{323.15K}^{S-L}$, which represent Gibbs free energy and the enthalpy, respectively, in the solution phase at the higher basis set mentioned earlier. The solution-phase Gibbs free energy was calculated as $G_{323.15K}^{S-L} = H_{323.15K}^{S-L} - TS_{323.15K}^{S-L}$, where $H_{323.15K}^{S-L}$ represents the solution-phase enthalpy calculated from $E_{323.15K}^{S-L}$ and the enthalpy corrections at the lower basis set, whereas the solvation entropy ($S_{323.15K}^{S-L}$) was estimated as 2/3 of the gas-phase value.⁶⁵ All single-point calculations were performed with tight wave-function convergence criteria, and an "ultrafine" (99950) grid was used in numerical integration. Throughout the text, all bond lengths are given in Ångström, and relative energies are expressed in kcal/mol. The values discussed throughout the manuscript are $\Delta G_{323.15K}^{S-L}$ values, unless otherwise specified. All pictures are rendered with ChemDraw Ultra 16.0 and CYLview software.⁶⁶

RESULTS AND DISCUSSION

Several facts known from experimental results form the boundaries for the DFT study. (1) Double-bond isomerizations with **Pd1^{Br}** as the catalyst proceed rapidly at room temperature with a negligible induction period, whereas **Pd^{II}** and **Pd⁰** phosphine complexes do not display any reactivity under the optimized conditions.¹⁷ (2) In isomerizing metathesis reactions, the activity of ruthenium catalysts is diminished upon addition of *tert*-butyl phosphine or its oxide, whereas the presence of **Pd1^{Br}** does not adversely affect the performance of Ru-based metathesis co-catalysts.^{14a} This means that during catalyst activation, neither P^tBu_3 nor the corresponding phosphine oxide are released. (3) The dinuclear palladacycle **Pd2^{Br}** is the predominant Pd species detected after completion of isomerizing metatheses. One might speculate that this doubly cyclometalated product forms via consecutive cyclometalation steps via a dinuclear palladium monohydride intermediate (Scheme 5). (4) Upon addition of phosphines, mononuclear Pd–

H species were detected in NMR investigations of reaction solutions, presumably $(^tBu_3P)_2PdHBr$ (**Pd5^{Br}**). (5) Diphosphinopalladium hydride species show isomerizing activity beyond single bond flips only above 80° C, so that they are unlikely to play a role.⁵² The energy span of the actual catalytic cycle starting from **Pd1^{Br}** must be smaller than the 20 kcal/mol calculated by Mazet and coworkers for L_2Pd^{II} –H cycles.⁶⁷

Scheme 5. Top: Degradation of **Pd1^{Br} to **Pd2^{Br}** with possible intermediates; bottom: optimized **Pd2^{Br}** geometry.**

Based on these observations, numerous pathways were computed starting from **Pd1^{Br}**, of which the most relevant are depicted in Scheme 6. All pathways were calculated along the pathway from propene (**1**) to the isomerized product (**1i**), as well as the other way around, to cross-validate all values and ensure that they represent the actual energy minimum. **Pathway A** is representative of catalytic double-bond isomerization cycles that are initiated by the reaction of an alkene directly with the dinuclear Pd^I complex. It features carbene intermediates similar to those proposed by Iluc et al. for mononuclear Pd^{II} catalysis.⁶⁷ This pathway has an energy span of 54.4 kcal/mol, much too high for a reaction that proceeds rapidly at RT (For further details: see SI, Pathway A: dinuclear Pd^I catalysis).

Several alternative pathways starting from **Pd1^{Br}** were investigated, but were all ruled out based on unrealistically high-energy steps. No energetically feasible entry to established allylpalladium pathways⁶⁸ opened up when shortening the distance between the alkene **1** and the dinuclear Pd^I complex **Pd1^{Br}**. The formation of dinuclear allyl hydride complexes was found to be endergonic by 26.2 and 23.7 kcal/mol, depending on whether the hydride ends up at the same Pd atom as the allyl group (**A1a^{Br}**) or at the neighboring one (**A1b^{Br}**, Scheme S2, I and II). We also probed whether a base-assisted allylic C–H activation starting directly from **Pd1^{Br}** was conceivable. However, the transfer of an allylic proton to a bridging bromine atom resulting in the formation of a dinuclear allyl–Pd complex (**A1c^{Br}**), along with HBr, is endergonic by 32.2 kcal (Scheme S2, III). All these investigations render a dinuclear allylic isomerization mechanism even less likely than the carbene mechanism outlined as Pathway A.

Pathway B is representative of catalytic cycles starting from the dinuclear Pd–H species **B1^{Br}** generated from **Pd1^{Br}** via intramolecular C–H activation, *en route* to the experimentally observed bis-palladacycle **Pd2^{Br}**. Among them, the depicted pathway was found to be by far the most energetically favorable, with an energy span of 9.5 kcal/mol.

Pathway C is initiated by formation of the monophosphine Pd–H species **C1^{Br}** with release of the stable palladacycle **Pd2^{Br}** from **B1^{Br}**. The actual catalytic cycle consists of a Pd–H insertion/ β -hydride elimination sequence analogous to that proposed for diphosphinopalladium hydride catalysts,^{48,50,69} but

with one less phosphine ligand. It has an energy span of only 5.4 kcal/mol.

In direct comparison to these three pathways involving monoligated Pd, we also investigated several catalytic pathways starting from the bisphosphine complex ($t\text{Bu}_3\text{P}$)₂PdHBr (**Pd5^{Br}**, Scheme S2, IV–VI). However, the addition of propene to coordinatively saturated **Pd5^{Br}** is endergonic by 20.3 kcal/mol (**Pd5^{Br}** → **A1d^{Br}**). Base-assisted allylic C–H activations in which the bromide or phosphine act as the base also turned out to be

unfavorable. A reaction leading to the cationic bisphosphine complex (**A1e^{Br}**) is endergonic by $\Delta G_{323.15\text{K}}^{\text{S-L}} = 45.5$ kcal/mol. Mechanisms involving temporary liberation and re-coordination of phosphines in exchange for propene ligands were ruled out, since they must also be expected to result in phosphine transfer, thereby inevitably deactivating the ruthenium co-catalyst (Scheme S2, IV–VI). This would be in contrast to experimental findings.

Scheme 6. Selected isomerization pathways starting from pre-catalyst [Pd($\mu\text{-Br}$)Bu₃P]₂ Pd1^{Br}.

Pathway B: dinuclear Pd–H catalysis

Formation of dinuclear Pd–H species

Exploration of pathway A has made clear that the isomerization activity of dinuclear Pd^I complex **Pd1^{Br}** is not a consequence of its ability to directly activate alkenes. Another possible reason for this catalytic activity is that **Pd1^{Br}** easily transforms into Pd–H species, which are widely postulated to be the active species in double-bond isomerizations. The conversion of **Pd1^{Br}** to doubly cyclometalated Pd^{II} dimer **Pd2^{Br}** is well documented experimentally, and takes place already at room temperature in solution.¹⁷ It is reasonable to assume that it proceeds stepwise, and the first cyclometalation may well give rise to a Pd–H intermediate capable of catalyzing double-bond isomerizations.

Figure 2. Energy profile diagram ($\Delta G_{323.15\text{K}}^{\text{S-L}}$ in kcal/mol) for potential catalyst activation pathways.

Indeed, when investigating potential pathways for the intramolecular C–H activation of the *tert*-butyl ligand, we found two energetically favorable pathways in which the hydride liberated during Pd²–C bond formation transfers to Pd^I (Figure 2; structures and relevant geometrical parameters on the potential energy surface along the reaction coordinates depicted in Figure S3). The optimal pathway involves concerted C–H bond activation of the tri(*tert*-butyl)phosphine ligand and hydride transfer, leading to the dinuclear Pd–H complex **B1^{Br}** via a single transition state [**Pd1^{Br}–B1^{Br}**][‡]. Species **B1^{Br}** is thermodynamically less stable than **Pd1^{Br}** by only 2.3 kcal/mol. The activation barrier of 20.8 kcal/mol for **Pd1^{Br}** → **B1^{Br}** is rather low, which is in agreement with the experimental observation that the cyclopalladation proceeds swiftly at room temperature (Table S1). Based on simplified model studies,⁷⁰ the dissociation of a phosphine from **Pd1^{Br}** also appeared feasible. However, a comparative study revealed that the dissociation of a phosphine from **Pd1^{Br}**, which might also have opened up a viable catalyst activation pathway, is strongly endergonic (33.4 kcal/mol) and therefore less favorable (Scheme S3).

In **B1^{Br}**, the two Pd centers adopt distorted square planar geometries, the phosphorous atoms are oriented *syn* to each other, and both the Pd^I and Pd^{II} nuclei are in oxidation state II (Figures 2 and S3). Whereas in **Pd1^{Br}**, a Pd–Pd bond was manifested by an electron density maximum ($\rho(r) = 0.051$) between the two atoms and a short Pd–Pd distance of 2.636 Å, this bond is absent in **B1^{Br}**. This leads to a Pd–Pd distance longer by 0.815 Å. The calculated electron density of Pd^I–Br²/Pd^{II}–Br² bonds at (3,–1) bond critical points (BCPs) in **Pd1^{Br}** and **B1^{Br}** (**Pd1^{Br}**: 0.057/0.057; **B1^{Br}**: 0.054/0.054) indicates bridging Pd–Br bonds in both complexes.

In the transition state $[\text{Pd}^{\text{I}}\text{Br}-\text{B}^{\text{I}}\text{Br}]^{\ddagger}$, both of these bridging Pd–Br bonds are temporarily cleaved, resulting in increased electron densities (0.069/0.068) for the terminal Pd–Br bonds as well as increased negative NPA charges on the Br^I and Br² atoms (−0.349/−0.361 e for $\text{Pd}^{\text{I}}\text{Br}$ vs −0.439/−0.501 e in $[\text{Pd}^{\text{I}}\text{Br}-\text{B}^{\text{I}}\text{Br}]^{\ddagger}$). In the transition state $[\text{Pd}^{\text{I}}\text{Br}-\text{B}^{\text{I}}\text{Br}]^{\ddagger}$, the Pd^I–H and Pd²–C⁴ bond distances are shortened to 1.805 Å and 2.256 Å, whereas the C⁴–H bond is elongated to 1.585 Å (Figure S3). The single imaginary frequency (867.8i cm^{−1}) of $[\text{Pd}^{\text{I}}\text{Br}-\text{B}^{\text{I}}\text{Br}]^{\ddagger}$ reflects the concerted formation of the Pd^I–H and Pd²–C⁴ bonds and concomitant cleavage of the Pd^{I/2}–Br^{I/2} and C⁴–H bonds (Figure S3).

Comparative studies revealed that the *anti*-isomer of $\text{B}^{\text{I}}\text{Br}$ is less stable than $\text{B}^{\text{I}}\text{Br}$ by only 0.1 kcal/mol. We thus probed whether it is accessible with similar ease. Indeed, $\text{D}^{\text{I}}\text{Br}$ can be generated through a distinct reaction channel in which initial activation of the tri(*tert*-butyl)phosphine C–H bond takes place at a single Pd nucleus. However, the transition state $[\text{Pd}^{\text{I}}\text{Br}-\text{D}^{\text{I}}\text{Br}]^{\ddagger}$ has a substantially higher activation barrier of 32.9 kcal/mol (Figure 2). The resulting intermediate $\text{D}^{\text{I}}\text{Br}$ features bridging hydride and bromide atoms and a Pd^I–Pd² distance of 2.799 Å. Its formation is endergonic by 16.5 kcal/mol. The *anti*-configured dinuclear Pd–H species $\text{D}^{\text{I}}\text{Br}$ can be accessed by cleavage of the bridging hydrogen bond and subsequent conformational rearrangement reinstating the bridging bromide. This barrierless two-step process ($\text{D}^{\text{I}}\text{Br} \rightarrow \text{D}^{\text{I}}\text{Br}$; $\Delta G_{323.15\text{K}}^{\text{S-L}} = -14.1$ kcal/mol) occurs *via* a transient intermediate $\text{D}^{\text{I}}\text{Br}$. The overall formation of active species $\text{D}^{\text{I}}\text{Br}$ is endergonic by only 2.4 kcal/mol, but due to the high barrier of the first reaction step, this alternative pathway can be ruled out.

Catalytic cycles involving a dinuclear Pd–H species

In principle, the alkene **1** can coordinate to either Pd atom of the dinuclear Pd–H species $\text{B}^{\text{I}}\text{Br}$, but only its coordination to the hydride-bearing Pd^I opened up an energetically reasonable pathway for double-bond isomerization. Following a coordination of **1** to Pd², the only isomerization pathway that could be identified was calculated to have an excessive activation energy barrier of 79.3 kcal/mol (Figures S4 and S5), so that it was not considered to be relevant.

Figure 3. Energy profile diagram ($\Delta G_{323.15\text{K}}^{\text{S-L}}$ in kcal/mol) for dinuclear Pd–H catalysis (pathway B).

Coordination of propene to the Pd^I center within complex $\text{B}^{\text{I}}\text{Br}$ affords the intermediate $\text{B}^{\text{I}}\text{Br}$. It is endergonic by 6.5 kcal/mol, which is a reasonable value for an entropically disfavored adduct formation ($\Delta S_{323.15\text{K}}^{\text{S-L}} = -0.022$ kcal/mol-K). In $\text{B}^{\text{I}}\text{Br}$,

Br² has left the coordination sphere of Pd^I, creating a distorted trigonal-pyramidal geometry at (Pd^I)^{II}, while (Pd²)^{II} remains square planar (Figure 3). The ensuing insertion of the coordinated olefin into the Pd^I–H bond with formation of the alkyl-Pd complex $\text{B}^{\text{I}}\text{Br}$ is almost thermoneutral, and involves an activation barrier of only 3.0 kcal/mol. It proceeds via the four-membered transition state $[\text{B}^{\text{I}}\text{Br}-\text{B}^{\text{I}}\text{Br}]^{\ddagger}$ (Figure 3, see Figure S6 for details). In $[\text{B}^{\text{I}}\text{Br}-\text{B}^{\text{I}}\text{Br}]^{\ddagger}$, the Pd^I–H bond is elongated to 1.589 Å and the C¹–H distance is shortened to 1.641 Å. Progressing from intermediate $\text{B}^{\text{I}}\text{Br}$ to $[\text{B}^{\text{I}}\text{Br}-\text{B}^{\text{I}}\text{Br}]^{\ddagger}$, the NPA charge on the hydrogen atom is significantly increased by 0.121 e ($\text{B}^{\text{I}}\text{Br}/[\text{B}^{\text{I}}\text{Br}-\text{B}^{\text{I}}\text{Br}]^{\ddagger} = -0.002/0.119$ e), reflecting a reversal in charge during its migration from Pd^I to C¹. Importantly, the C¹–C² bond length is slightly elongated in $[\text{B}^{\text{I}}\text{Br}-\text{B}^{\text{I}}\text{Br}]^{\ddagger}$ compared to that in $\text{B}^{\text{I}}\text{Br}$ ($[\text{B}^{\text{I}}\text{Br}-\text{B}^{\text{I}}\text{Br}]^{\ddagger}/\text{B}^{\text{I}}\text{Br} = 1.402/1.359$ Å), indicating a change in hybridization. The successful conversion of double to single bond in the propene fragment is evident from the comparison of the calculated C¹–C² bond length in $\text{B}^{\text{I}}\text{Br}$ with that of free propene ($\text{B}^{\text{I}}\text{Br}/1 = 1.518/1.337$ Å).

The double-bond migration is achieved by β -hydride elimination from the C³ atom. Elongation of C³–H bond leads to transition state $[\text{B}^{\text{I}}\text{Br}-\text{B}^{\text{I}}\text{Br}]^{\ddagger}$, which is only 1.6 kcal/mol higher in energy than $\text{B}^{\text{I}}\text{Br}$. The transition vector in $[\text{B}^{\text{I}}\text{Br}-\text{B}^{\text{I}}\text{Br}]^{\ddagger}$ represents the simultaneous formation of the Pd^I–H bond and cleavage of the C³–H bond (Pd^I–H: 2.852/1.588 Å; C³–H: 1.102/1.641 Å in $\text{B}^{\text{I}}\text{Br}$ vs. $[\text{B}^{\text{I}}\text{Br}-\text{B}^{\text{I}}\text{Br}]^{\ddagger}$). Furthermore, the C²–C³ bond shortens (1.518/1.401 Å in $\text{B}^{\text{I}}\text{Br}/[\text{B}^{\text{I}}\text{Br}-\text{B}^{\text{I}}\text{Br}]^{\ddagger}$), suggesting an increase in double-bond character. Finally, the double-bond migration product **1i** (which in this case is also propene) is released from $\text{B}^{\text{I}}\text{Br}$ in a barrierless process, thereby regenerating the isomerization catalyst $\text{B}^{\text{I}}\text{Br}$.

The energy profile of the double-bond isomerization via dinuclear Pd–H catalysis (pathway B, Figure 3) has an overall energy span of only 9.5 kcal/mol, which is realistic for a reaction that proceeds rapidly at room temperature. In order to benchmark $\text{Pd}^{\text{I}}\text{Br}$ against state-of-the-art systems, we calculated the isomerization of allyl alcohol in analogy to pathway B (Table S2). For this reaction, Mazet et al. have computed an energy span of 20.0 kcal/mol for cationic bis(di-*tert*-butylphosphino)ethane palladium hydride.⁵⁰ For $\text{Pd}^{\text{I}}\text{Br}$, we found an energy span of only 11.9 kcal/mol.

Pathway C: mononuclear Pd–H catalysis

Formation of mononuclear Pd–H species

Rather than acting as an isomerization catalyst itself, the dinuclear Pd–H species $\text{B}^{\text{I}}\text{Br}$ might also function as a key intermediate *en route* to a catalytically highly active mononuclear Pd–H species. However, when we investigated potential pathways leading from $\text{Pd}^{\text{I}}\text{Br}$ to various Pd–H species (Schemes 3 and 6; Figure 4), we initially came across excessive energetic barriers. For example, while the homolytic dissociation of $\text{Pd}^{\text{I}}\text{Br}$ with generation of the coordinatively unsaturated doublet Pd^I species $\text{Pd}^{\text{I}}\text{Br}$ requires only moderate energy input (20.7 kcal/mol), a subsequent cyclopalladation step with formation of a Pd^{III}–H species ($\text{Pd}^{\text{III}}\text{H}$) turned out to be extremely endergonic (91.7 kcal/mol, Figure 4).

Figure 4. Energy profile diagram ($\Delta G_{323.15\text{K}}^{\text{S-L}}$ in kcal/mol) for the formation of mononuclear Pd-H species.

Finally, we identified an energetically favorable dissociation mechanism. The dissociation of the dinuclear Pd-H species **B1Br** to give the mononuclear Pd-H species **C1Br** along with the coordinatively unsaturated palladacycle **Pd3Br** requires a reasonable energy input of 19.4 kcal/mol (Figure 4). The exergonic dimerization of **Pd3Br** to give the dimeric bispalladacycle **Pd2Br** (-11.2 kcal/mol) further reduces the overall energy demand of the overall reaction of two molecules of **B1Br** to two molecules of mononuclear Pd^{II}-H (**C1Br**) along with one molecule of the bispalladacycle **Pd2Br** ($\Delta G_{323.15\text{K}}^{\text{S-L}} = 4.1$ kcal/mol per Pd-H species). The strong enthalpic driving force ($\Delta H_{323.15\text{K}}^{\text{S-L}} = -16.7$ kcal/mol) overrides the loss in entropy for the dimerization of **Pd3Br** to **Pd2Br** ($T\Delta S_{323.15\text{K}}^{\text{S-L}} = -5.6$ kcal/mol). The simultaneous formation of an active Pd-H catalyst along with inert **Pd2Br** is in excellent agreement with the experimentally observed build-up of the latter over the course of catalytic double-bond isomerizations. The presence of a coordinatively unsaturated monophosphinopalladium hydride **C1Br** would also explain why the known diphosphinopalladium hydride complex **Pd5Br** was experimentally observed when excess phosphine was added to a catalytic isomerization reaction medium.¹⁷

The mononuclear Pd-H species **C1Br** has a Pd oxidation state of II, and the d-electrons are localized in four lone pairs (Figure S7). The addition of another phosphine to **C1Br** was calculated to be energetically downhill by $\Delta G_{323.15\text{K}}^{\text{S-L}}$ (**C1Br** → **Pd5Br**) = -15.2 kcal/mol (see Scheme S4). However, even if free phosphine was available for this step – which is unlikely since the surplus ligand is irreversibly incorporated within palladacycle **Pd2Br** – the coordination of a propene substrate to the bisposphino complex **Pd5Br** was calculated to lead preferentially to the release of a $\text{P}(\text{tBu})_3$ ligand rather than of a bromide counterion (Scheme S2, IV). This is another indication that the mononuclear catalytic cycle is likely to proceed via monophosphine-Pd species. Additional ligand, as is present in the Skrydstrup system, is predicted to retard the isomerization due to the abovementioned competitive coordination to Pd, which would explain why the $\text{Pd}(\text{P}(\text{tBu})_3)_2\text{HBr}$ system is selective for single bond flips whereas catalysts generated from **Pd1Br** lead to full equilibration of double-bond isomers.⁵²

Catalytic cycle involving mononuclear Pd-H species

Since the Pd-H species **C1Br** is higher in free energy than the precatalyst **Pd1Br** by only 8.2 kcal/mol and accessible via an activation pathway with an overall barrier of only 20.8

kcal/mol, it is conceivable that it forms spontaneously from **Pd1Br** in organic solvents at room temperature. Further calculations revealed that **C1Br** is an excellent isomerization catalyst. Figure 5 shows structures and energies of the most favorable catalytic cycle starting from Pd-H species **C1Br**. It is initiated by η^2 -coordination of propene to **C1Br**, which is isoenergetic ($\Delta G_{323.15\text{K}}^{\text{S-L}} = -0.5$ kcal/mol). The bond angle of H-Pd^I-Br^I widens from 94.9° in **C1Br** to 172.6° when propene approaches the Pd^I center between the H and Br ligands. In the resulting complex **C2Br**, the Pd^I-C¹ and Pd^I-C² bonds have comparable lengths (Pd^I-C^{1/2} = 2.345/2.395 Å). Starting from **C2Br**, migratory insertion of the coordinated alkene into the Pd^I-H bond with formation of the palladium isopropyl intermediate **C3Br** is almost thermoneutral (1.8 kcal/mol). Complex **C3Br** has a T-shaped geometry with $\angle \text{P}^{\text{I}}\text{-Pd}^{\text{I}}\text{-Br}^{\text{I}}$ and $\angle \text{C}^2\text{-Pd}^{\text{I}}\text{-Br}^{\text{I}}$ bond angles of 104.8° and 88.0°, respectively (Figure S8). The elongation of the C¹-C² bond in intermediate **C3Br** with respect to **C2Br** (C¹-C² (**C3Br**/**C2Br**) = 1.498/1.368 Å) resembles the conversion of the C-C double bond to a single bond.

Figure 5. Energy profile diagram ($\Delta G_{323.15\text{K}}^{\text{S-L}}$ in kcal/mol) for mononuclear Pd-H catalysis (pathway C).

Formation of **C3Br** requires a small activation barrier of 5.1 kcal/mol. It occurs *via* a four-membered transition state $[\text{C2Br-C3Br}]^\ddagger$, in which the Pd^I-H and C¹-C² bond distances increase to 1.600 Å and 1.406 Å, respectively, indicating the transfer of the hydride from Pd^I to C¹ and the conversion of the C-C double bond to a single bond. This process is also reflected in the imaginary frequency of -662.9i cm⁻¹. In order to shift the double bond from C¹-C² to C²-C³, the isopropyl residue can be rotated by 180° for the pathway from **C1Br** to **C3Br** to be traced backwards to **C1Br** and the isomerized propene **1i**. When omitting the rotation step and shortening the Pd-H¹ distance, an alternative pathway with marginally divergent structures and energies was identified. The presence of two pathways for the double-bond isomerization with energy spans below 10.0 kcal/mol suggests that **C1Br** is a catalytic species with tremendous isomerization activity.

Catalyst deactivation

Deactivation of the isomerization catalyst within several hours at room temperature even under strictly anaerobic and anhydrous conditions has become the limiting factor in the development of Pd/Ru bimetallic isomerizing metathesis. Since the bispalladacycle **Pd2Br** has been found to accumulate in the reaction mixture over the course of the reaction, it was

Scheme 7. Catalyst deactivation pathways. Energy values ($\Delta G_{323\text{ K}}^{\text{S-L}}$) are in kcal/mol.

In most cases, this adduct will dissociate, and the majority of the catalyst molecules will continue their productive turnover

Thus, it is the conversion of the catalytically active, dinuclear Pd–H species **B1^{Br}** into the even more active but rather unstable mononuclear Pd–H species **C1^{Br}** that leads to the continuous buildup of **Pd2^{Br}**, and ultimately to the decay of catalytic activity.

The calculations reflect the chief characteristics of this catalyst system: Once the catalyst passes the low barrier from dinuclear to mononuclear Pd–H species, it is tremendously active due to the energy span of only 5.4 kcal/mol for the isomerization cycle. However, catalyst propagation and deactivation pathways

bifurcate at intermediate $\mathbf{C3^{Br}}$. Whereas the remaining energy barrier for propagation $[\mathbf{C3^{Br}-C4^{Br}}]^\ddagger$ is only 3.2 kcal/mol, a barrier of 20.5 kcal/mol for $[\mathbf{Pd4^{Br}-Pd1^{Br}}]^\ddagger$ relative to $\mathbf{C3^{Br}}$ (30.0 kcal/mol overall) is associated with catalyst deactivation. This is in good agreement with the experimental finding that the catalyst is highly active but has a rather short lifetime.

The calculations also explain the unique ability of the dinuclear Pd^{I} species $\mathbf{Pd1^{Br}}$ to act as a co-catalyst in orthogonal tandem catalysis: (1) a highly efficient dinuclear Pd–H isomerization catalyst is formed by an intramolecular process that does not release any byproduct; (2) its dissociation gives rise to an even

more active mononuclear Pd–H catalyst along with a chemically inert bispalladacyclic byproduct; and (3) the predominating pathway for catalyst deactivation, which starts at the mononuclear species, actually leads back to the pre-catalyst. Consequently, in none of these steps, byproducts are released that might interfere with sensitive ruthenium co-catalysts. This rather unusual overall network of activation and deactivation processes is in excellent agreement with the experimental observations, and its elucidation will be of decisive importance for a rational catalyst development.

Figure 7. Comparative energy profiles (ΔG_{323.15K}^{S-L} in kcal/mol). The energy levels are labelled only with the most relevant species; other species included in the energy calculations are omitted for clarity.

In silico casting of isomerization catalysts

These insights into the catalytic pathway provide a solid basis for establishing structure-activity relationships for ligands and counterions. Systematic experimental studies using different ligands had so far been impossible, because the synthesis of dinuclear Pd^{I} species critically depends on their selective crystallization from the reaction medium. Whereas this works very well for tris-*tert*-butylphosphine ligands, even small changes in the ligand structure lead to the formation of inseparable mixtures of Pd^{I} , Pd^{II} , and Pd^0 complexes, unsuitable for reliable comparative kinetic studies. After much fruitless effort aimed at synthesizing structural variants for which it was unclear whether they would be better or worse catalysts, we decided to perform an *in silico* screening for promising catalysts upfront. This way, we hoped to be able to direct our synthetic efforts towards the most relevant catalyst targets.

Based on the energy profiles presented above, the ideal ligand would result in a catalyst with a low catalyst activation barrier (A), a low energy span (S_d and S_m) for the dinuclear and/or

mononuclear catalytic cycles, and as high as possible a catalyst deactivation barrier (D). For catalysts with a low energy span for the dinuclear cycle (S_d), another viable strategy to increase their lifetime would be to increase the barrier (A_m) between the mononuclear and dinuclear catalytic cycles, which would also block access to deactivation. Any complex under investigation scoring better than $\mathbf{Pd1^{Br}}$ in these categories would be a promising lead structure for rational catalyst development.

The catalyst activation barrier (A) corresponds to the energetic difference between $\mathbf{Pd1x^I}$ and $[\mathbf{Pd1x^I-B1x^I}]^\ddagger$. The energy span for the dinuclear catalytic cycle (S_d) consists of the energy difference between the lowest intermediate and highest transition state. The barrier for entering the mononuclear catalytic cycle (A_m) is the difference between $\mathbf{B1x^I}$ and $\mathbf{C1x^I}$. The energy span of the mononuclear catalytic cycle (S_m) is the difference between its lowest intermediate and highest transition state. The catalyst deactivation barrier (D) is somewhat harder to pin down. As can be seen from Figure 7, the first step towards catalyst deactivation is exergonic, and a

high energy span for the deactivation pathway may not necessarily point towards a long-lived catalyst, since it may be caused by the particularly exergonic formation of intermediate **Pd4^{Br}**. We thus used the energy difference between intermediate **C3^{Br}** and the highest transition state [**Pd4^{Br}**-**Pd1^{Br}**][‡] as a measure to assess catalyst longevity.

The above measures for various catalyst candidates are summarized in Figure 8. Out of the complexes shown in Figure 8, **Pd1^{Br}**,^{34, 35} **Pd1ⁱ**,^{43b} and **Pd1c^{Br}**²⁵ have been synthesized before, whereas all others are purely speculative (marked with * in Figure 8). The full data for each structure are listed in Table S6, and the energy profiles for the most relevant structures are displayed in Figure 9.

Figure 8. Catalyst structures screened *in silico*, and key descriptors of their catalytic performance. Literature references of known **Pd1xⁱ** dimers are provided in parentheses. (*) identifies purely speculative structures. A: catalyst activation barrier **Pd1xⁱ** → [**Pd1xⁱ**-**B1xⁱ**][‡]; S_{d,m}: energy spans of the catalytic isomerization cycles, A_m: activation barrier towards mononuclear isomerization cycle **B1xⁱ** → **C1xⁱ**; D: highest barrier of catalyst deactivation **C3xⁱ** → [**Pd4xⁱ**-**Pd1xⁱ**][‡]. ^aRelativistic corrected value.

isopropyl groups (**Pd1a^{Br}** and **Pd1b^{Br}**) led to a decrease of the energy spans S_d and S_m , which points towards increased catalytic activity. However, the activation barriers A for the isopropylphosphine complexes are very high and, in combination with the low deactivation barriers D , suggest that such catalysts would be ineffective.

Replacing one or two *tert*-butyl substituents by bulky adamantyl substituents (**Pd1c^{Br}** and **Pd1d^{Br}**) had a beneficial effect.⁷² Hartwig has already synthesized one bromo-bridged adamantyl derivative (**Pd1c^{Br}**) of **Pd1^{Br}**, and applied it in cross coupling reactions.²⁵ It thus appeared likely that such systems could also be used for isomerization reactions. Complex **Pd1d^{Br}**, which bears two adamantyl groups, was calculated to have a similar energy spans for both catalytic cycles ($S_d = 9.2$ kcal/mol and $S_m = 4.8$ kcal/mol), the same deactivation ($D = 20.5$ kcal/mol), but a lower activation barrier ($A = 18.6$ kcal/mol). Thus, we kept two adamantyl groups, and varied the third substituent at phosphorus. The resulting complexes with *n*-butyl (**Pd1e^{Br}**) or benzyl substituents (**Pd1f^{Br}**) had dramatically lower activation barriers ($A = 13.4$ and 2.1 kcal/mol, respectively), and reduced energy spans for the dinuclear catalytic cycle ($S_d = 8.0$ and 8.1 kcal/mol, respectively). However, in both cases, the deactivation barriers were substantially lower. For **Pd1f^{Br}**, the barrier from the dinuclear to the mononuclear cycle is so much increased that it should effectively suppress catalyst deactivation. Still, the activation barrier is so low for this precatalyst that it is doubtful whether it will be possible to synthesize and isolate it.

In contrast to the *tert*-butyl group, the benzyl substituent is able to cyclometalate via an aromatic position. The advantageous 5-ring geometry of the transition state explains the low barrier A. The *n*-butyl substituent can cyclometalate in the α -, β -, and γ -positions. Comparative studies revealed that activation in the γ -position is most favorable (Table S4).

Next, we evaluated unsymmetrical complexes with the intention of independently optimizing the ligand at Pd² for cyclometalation and the ligand at Pd¹ for stabilizing the mononuclear Pd–H species. Unsymmetrical dinuclear species would be hard to access experimentally, and such calculations would reveal upfront whether it could be worthwhile to attempt their selective synthesis.

A comparison of the activation barriers for **Pd1g^{Br}**, which bears a benzyl-*bis*-adamantylphosphine ligand (PAd₂Bn) on Pd² (A_g = 7.0 kcal/mol) with the two corresponding symmetrical complexes **Pd1^{Br}** (A = 20.8 kcal/mol) and **Pd1f^{Br}** (A = 2.1 kcal/mol) revealed that the singled-out effect of the ligand that undergoes cyclometalation is visible, but not as strong as one could have expected.

An excellent overall profile is presented by **Pd1h^{Br}**, which combines a PAd₂Bn ligand at Pd² with a PAd₂Bu ligand at Pd¹, with a reasonable activation barrier (A = 9.1 kcal/mol) that should allow isolating the precatalyst, a low energy span for the dinuclear pathway (S_d = 10.6 kcal/mol), and a high barrier A_m that should keep it from forming highly active but short-lived mononuclear Pd–H species (A_m = 22.9 kcal/mol).

Because one of the ligands in unsymmetrical complexes does not need to be able to undergo cyclometalation, we also calculated complexes with *tris*-adamantylphosphine (PAd₃) or NHC ligands at Pd². For **Pd1i^{Br}**, the activation barrier is almost identical to that of **Pd1^{Br}**, and PAd₃ improved neither the energy spans (S_d, S_m) nor the deactivation barrier. Mixed dinuclear complexes bearing one phosphine and one NHC ligand (**Pd1j^{Br}** and **Pd1k^{Br}**) also gave similar activation energies and energy spans to their symmetrical diphosphine analogs (**Pd1^{Br}** and **Pd1e^{Br}**, respectively). However, the barriers A_m between the dinuclear and mononuclear cycles are lower than the corresponding activation energies. Worst of all, the initial step of ligand deactivation, i.e. the formation of the dinuclear adduct, is strongly exergonic and renders catalyst deactivation more favorable than propagation of the catalytic cycle (D = 7.9 and -0.5 kcal/mol, respectively). Moreover, the catalytically active species cannot easily be regenerated from the symmetrical complexes resulting from catalyst deactivation, because the usual activation pathway is blocked for dinuclear Pd¹ species bearing two ligands incapable of undergoing cyclometalation (Scheme S6). Based on these evaluations, the use of NHC ligands is unfavorable both in symmetrical and unsymmetrical complexes.

Overall, these comparative studies show that the experimentally observed, unique isomerization activity of **Pd1^{Br}** results from the fact that this complex almost ideally strikes the delicate balance between good synthetic accessibility, easy catalyst activation, a smooth energy profile for the catalysis, and a reasonably high barrier towards catalyst deactivation. Even small changes in the ligand structures were found to have adverse effects on at least one of these characteristics. Nevertheless, the symmetrical PAd₂Bu complex **Pd1e^{Br}** emerged as an interesting lead structure due to its low catalyst activation barrier (A = 13.4 vs 20.8 kcal/mol for **Pd1^{Br}**) and its low energy spans for the catalysis (S_d = 8.0 vs 9.5 kcal/mol and S_m = 4.8 vs 5.4 kcal/mol). However, the calculations also predict a rather low barrier towards catalyst deactivation. It seems worthwhile to experimentally target complexes with two different phosphine ligands such as **Pd1h^{Br}**, whereas NHC-ligated complexes were predicted to be inferior catalysts.

Experimental studies on the isomerization activity

We next set out to synthesize a set of dinuclear Pd¹ complexes with other counterions and ligands other than P^tBu₃, with the aim to validate the results of the *in silico* casting. The iodo analog to **Pd1^{Br}** proved to be stable and easily accessible. In contrast, the chloro analog did not selectively crystallize and was too unstable to allow purification e.g. by chromatography. Similar problems were also encountered for some bromo-bridged complexes. The main challenge was that the known synthetic strategies critically depend on the selective crystallization of the Pd¹ dimers from the reaction mixtures, and this step must be elaborately optimized for every single structure so that the products can be obtained in pure form. In order to be able to establish a structure-activity relationship for the ligand, an entire series of otherwise analogous complexes was required. We thus decided to conduct a systematic comparative catalytic study of ligand activity using the more accessible iodo- rather than the calculated bromo-bridged Pd¹ dimers.

Extensive experimental work led to the successful synthesis of a set of phosphine complexes, namely (P^tBu₃)₂Pd¹₂I₂ (**Pd1^I**)^{43b} and (P^tBu₂Pr)₂Pd¹₂I₂ (**Pd1a^I**)⁴¹ following literature protocols, and of the new complex (PAd₂Bu)₂Pd¹₂I₂ (**Pd1e^I**). During the course of these studies, we managed to synthesize an iodo-bridged NHC-ligated complex [(IPr)Pd¹I]₂ (**Pd1l^I**), which we have since applied in cross-coupling reactions.⁷² The catalytic performance of these complexes was investigated using the isomerization of allylbenzene as a model reaction (Scheme 8). In the presence of 1 mol% of our reference complex **Pd1^{Br}**, the allylbenzene is fully converted into the equilibrium mixture of allyl- (3%) and vinylarenes (97%) within 2 hours at 40°C. In direct comparison, the iodo-bridged catalyst **Pd1^I** is markedly less active, and gave a conversion of only 13%. Only at 50°C, full conversion is reached. This corresponds well with the calculations obtained at the QZP-DKH level, which indicate that this complex has a substantially higher activation barrier than **Pd1^{Br}**. As predicted by the calculations, replacing one of the *tert*-butyl groups by an isopropyl substituent (**Pd1a^I**) led to substantially lower catalytic activity. PAd₂Bu ligands (**Pd1e^I**), for which a superior profile with regard to activation barrier and energy span had been calculated, were confirmed to be better ligands than ^tBu₃P.

It was not possible to synthesize PAd₂Bn complexes **Pd1f^{Br}** with either bromo or iodo substituents in pure form. This is in line with the calculations, which predicted such a low barrier towards palladacycle formation that it appeared unlikely that the pre-catalyst would be stable under the condition of its synthesis.

Almost no conversion was observed for **Pd1l^I**, which bears an NHC ligand. This is in line with the computational studies that had shown that the lowest-energy pathway towards catalytically active Pd–H species requires an intramolecular cyclometalation step. This activation pathway is impossible for the NHC ligands. As this work focuses on the application of Pd¹ dimers in equilibrium isomerizing metathesis, the optimal synthetically accessible catalyst **Pd1e^I** was ultimately tested experimentally in a tandem reaction. We used the isomerizing metathesis of methyl oleate as a model, and found that **Pd1e^I** showed an isomerization activity superior to **Pd1^I** and on a comparable level to **Pd1^{Br}**. This result confirms that performances observed in our test isomerization can be extrapolated to isomerizing metathesis (for further experimental details, see the SI).

Scheme 8. Experimental study of isomerization activity.

In order to verify the reliability of our calculations, we calculated the energy profile for the complex **Pd1e**^l, which showed the highest activity of all iodo-Pd complexes in this experimental study. As one can see from the data in Figure 8 and the profile in Figure 9, the energy spans of both catalytic cycles are almost identical, but the iodo complex has a slightly higher activation and lower deactivation barrier. This is in excellent agreement with the experimental finding that the iodo complex **Pd1e**^l almost, but not quite, reaches the performance of the unmodified bromo complex **Pd1Br**.

CONCLUSION

The unique activity profile of dinuclear Pd^I complex (P^tBu₃)₂Pd^I₂Br₂ as an isomerization catalyst in orthogonal tandem processes is explained by the following factors:

(1) A bimetallic activation pathway with a moderate barrier allows the formation of a highly reactive monophosphinopalladium hydride species. The hydride atom at Pd^I originates from the phosphine ligand at Pd^{II}, which in the C–H insertion process gets tightly bound to Pd with formation of a chemically largely inert palladacycle. This activation mechanism suppresses the liberation of phosphine ligands, which would deactivate sensitive co-catalysts such as Grubbs-type olefin metathesis catalysts.

(2) The actual double-bond migration at the mononuclear Pd–H species has a remarkably low energy span, which is in line with the high activity observed for the dinuclear Pd^I precatalyst.

(3) The rapid loss of catalytic activity and the experimentally observed build-up of a bispalladacycle (**Pd2Br**) is caused by a low barrier pathway leading to a mononuclear Pd–H species along with 1/2 **Pd2Br**. This mononuclear species **C1Br** has tremendous catalytic activity but easily decomposes with formation of the dimeric Pd^I precatalyst.

The key characteristics of an efficient catalyst are thus a low catalyst activation barrier (A), a low energy span (S_d and S_m) for the dinuclear and/or mononuclear catalytic cycles, and as high as possible a catalyst deactivation barrier (D). Catalysts that have a low energy span for the dinuclear cycle (S_d) and a large barrier (A_m) between the dinuclear and mononuclear catalytic cycles would also be highly effective and long-lived.

The comparative evaluation of various structures showed how well (P^tBu₃)₂Pd^I₂Br₂ strikes the delicate balance between good synthetic accessibility, easy catalyst activation, a smooth energy profile for the catalysis, and a sufficiently high barrier

towards catalyst deactivation. Most changes in the ligand structures had adverse effects on at least one of these characteristics.

These calculations were successfully used as a predictive tool for rational catalyst development. By *in silico* casting, the influence of various structural variations of the precatalysts on the activation barrier, the energy span of the catalytic cycles, and the catalyst deactivation barrier were probed. Based on the results, an experimentally inaccessible dinuclear complex **Pd1e**^{Br} with bisadamantyl-*n*-butylphosphine ligands was identified as a lead structure for an easily activated, highly active catalyst. The validity of this lead was confirmed by a comparative experimental study of stable but overall less reactive iodo analogues of the target complexes, in which the bisadamantyl-*n*-butylphosphine complexes by far outperform the established tris-*tert*-butylphosphine complexes.

This research can serve as a showpiece that illustrates how DFT calculations can be embedded directly into the rational development of new catalyst generations rather than being used to provide mechanistic explanation *post hoc* for results that have already been achieved using experimental screening techniques. The experimentally observed build-up of palladacycles **Pd2x**^l during the catalytic isomerization had suggested that their formation is a result of catalyst deactivation. It had appeared to be a logical conclusion that the catalyst deactivation should be suppressed by using ligands that cannot undergo *ortho*-metalation. Based on this, NHC and tris-adamantylphosphine based complexes had been targeted. The DFT calculations became the basis for a paradigm change: They have established cyclometalation as an integral part of catalyst activation, not of its deactivation. This is why NHC complexes can be expected to be rather poor catalysts. This prediction was confirmed by our experimental studies.

The results derived from *in silico* casting and their experimental verification give confidence that tackling the preparative challenge is worth the amount of synthetic work that can be expected in order to develop a selective synthesis of new catalyst lead structures. We are convinced that new complexes designed according to the structure-activity relationships uncovered by the DFT calculations will bring major advances in activity and longevity of isomerizing metathesis catalysts.

SUPPORTING INFORMATION

The Supporting Information is available free of charge on the ACS Publications website at DOI: xx.xxxx/jacs.xxxxxxx.

- Further mechanistic routes and energy profiles
- Full experimental and computational details

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(71) For better comparison, all structures from the catalytic cycle of Pd1c^{Br}, in which the ONIOM method is used, were also exemplarily calculated without it. The energies obtained in both sets of calculations are very similar, see the SI; Table S5.

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For Table of Contents Only

Figure 1. Structure and optimized geometry of dinuclear Pd^I catalyst [Pd^I(μ-Br)Bu₃P]₂ (**Pd1Br**).

40x19mm (600 x 600 DPI)

Scheme 1. Isomerizing hydroaminomethylation or hydroformylation of internal olefins.

120x33mm (600 x 600 DPI)

Scheme 2. Synthetic utility of isomerizing metathesis processes catalyzed by Ru/Pd systems.

141x116mm (600 x 600 DPI)

Scheme 3. Proposed pathways for the formation of catalytically active species from $\text{Pd}^{\text{I}}\text{Br}$.

140x40mm (600 x 600 DPI)

Scheme 6. Selected isomerization pathways starting from pre-catalyst $[\text{Pd}^{\text{I}}(\mu\text{-Br})(\text{Bu}_3\text{P})]_2 \text{Pd}^{\text{I}}\text{Br}$.

414x148mm (600 x 600 DPI)

Scheme 7. Catalyst deactivation pathways. Energy values ($\Delta G_{323.15K}^{S-L}$) are in kcal/mol.

228x130mm (600 x 600 DPI)

Reaction conditions: 0.5 mmol of allylbenzene, 1 mol% of **Pd1x^y**, 1 ml of THF, conversion determined *via* GC-analysis using 25 μl *n*-dodecane as internal standard.

Scheme 8. Experimental study of isomerization activity.

108x96mm (600 x 600 DPI)

Figure 8. Catalyst structures screened in silico, and key descriptors of their catalytic performance. Literature references of known **Pd1xⁱ** dimers are provided in parentheses. (*) identifies purely speculative structures. A: catalyst activation barrier **Pd1xⁱ** → [**Pd1xⁱ-B1xⁱ**][‡], S_{d,m}: energy spans of the catalytic isomerization cycles, A_m: activation barrier towards mononuclear isomerization cycle **B1xⁱ** → **C1xⁱ**; D: highest barrier of catalyst deactivation **C3xⁱ** → [**Pd4xⁱ-Pd1xⁱ**][‡]. ^aRelativistic corrected value.

309x192mm (600 x 600 DPI)

Figure 9. Overlay of selected energy profiles for all catalytic systems. The energy levels are labelled only with the most relevant species; other species included in the energy calculations (Table S6) are omitted for clarity.

490x221mm (96 x 96 DPI)

Scheme 4. Isomerizing ethenolysis of rapeseed methyl ester.

131x112mm (300 x 300 DPI)