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Article

Remote Functionalization by Pd-Catalyzed Isomerization of Alkynyl Alcohols

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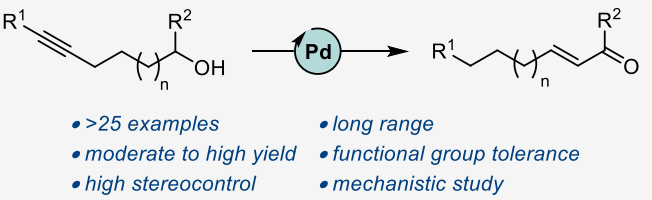
ABSTRACT: In recent years, progress has been made in the development of catalytic methods that allow remote functionalizations based on alkene isomerization. In contrast, protocols based on alkyne isomerization are comparatively rare. Herein, we report a general Pd-catalyzed long-range isomerization of alkynyl alcohols. Starting from aryl-, heteroaryl-, or alkyl-substituted precursors, the optimized system provides access preferentially to the thermodynamically more stable α,β-unsaturated aldehydes and is compatible with potentially sensitive functional groups. We showed that the migration of both π-components of the carbon−carbon triple bond can be sustained over several methylene units. Computational investigations served to shed light on the key elementary steps responsible for the reactivity and selectivity. These include an unorthodox phosphine-assisted deprotonation rather than a more conventional β-hydride elimination in the final tautomerization event.



INTRODUCTION

The field of transition-metal-catalyzed remote functionalizations has grown at an exponential pace over the past decade.[1] In these relay reactions, two distant functional groups can be interconverted by exploiting the reactivity of one function to induce a reaction on the other via a dynamic transmission process, which occurs typically by alkene migration through a hydrocarbon linker (a process referred to as "chain-walking"). With a few exceptions,[2] the current catalytic methods are based on the formation of the thermodynamically most stable product or the most stable organometallic intermediate, before it is intercepted by an appropriate reagent to install a novel functional group.

In contrast to alkenes, the (long-range) isomerization of alkynes has not witnessed the same level of development. Upon isomerization, the integrity of a C≡C bond can be preserved by migration of the two mutually orthogonal π systems ("alkyne isomerization"; Figure 1, **I** → **II** and **II** → **I**). Mechanistically, the formation of a transient allene intermediate is generally invoked to account for such processes.[3,4] Perhaps counterintuitively, the contra-thermodynamic isomerization of internal alkynes to terminal alkynes (often referred to as "alkyne zipper") has been studied in detail and implemented in the synthesis of several complex structures (Figure 1A, isomerization "out").[4,5] A particularly attractive feature of alkyne zipper reactions is their ability to sustain migration over long distances. Nonetheless, the strongly basic conditions employed severely limit functional group tolerance and impose to apply the method at early stages of multistep syntheses or necessitate additional protection/deprotection sequences. Although thermodynamically favored and usually high yielding, the isomerization of terminal alkynes into internal alkynes has received only limited attention, presumably because the use of a superstoichiometric amount of a strong alkali base is required (Figure 1B, isomerization "in").[6] To date, only relocations of the triple bond by one carbon unit have been described. Alkynes can also be isomerized into thermodynamically more stable conjugated 1,3-dienes (Figure 1C; "yne-to-diene" isomerization, **I** → **III**). Even though examples of base and phosphine catalysis have been reported, most of the methods developed rely on the use of late transition metals.[7] In this context, the isomerization of a C≡C bond driven by the conjugation of the diene to an electron-withdrawing substituent is the most documented strategy. The Trost and Lu groups concurrently disclosed highly stereoselective Pd-, Ru-, and Ir-based systems for the isomerization of α,β-ynones, α,β-ynoic esters, and α,β-ynoic amides to the corresponding $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl derivatives.[8,9] In comparison, Yamamoto and Hayashi independently established that complex stereoisomeric mixtures are usually obtained in the absence of a stabilizing functional group.[10,11] More recently, Zhang and co-workers showed that aryl-alkynes and sulfonyl-protected ynamides underwent yne-to-diene isomerization with high levels of stereocontrol under gold catalysis in the presence of an elaborated Buchwald-type monophosphine ligand.[12] While the ruthenium systems employed by Ikawa for the isomerization of propargyl (silyl)ethers and propargyl ethers delivered

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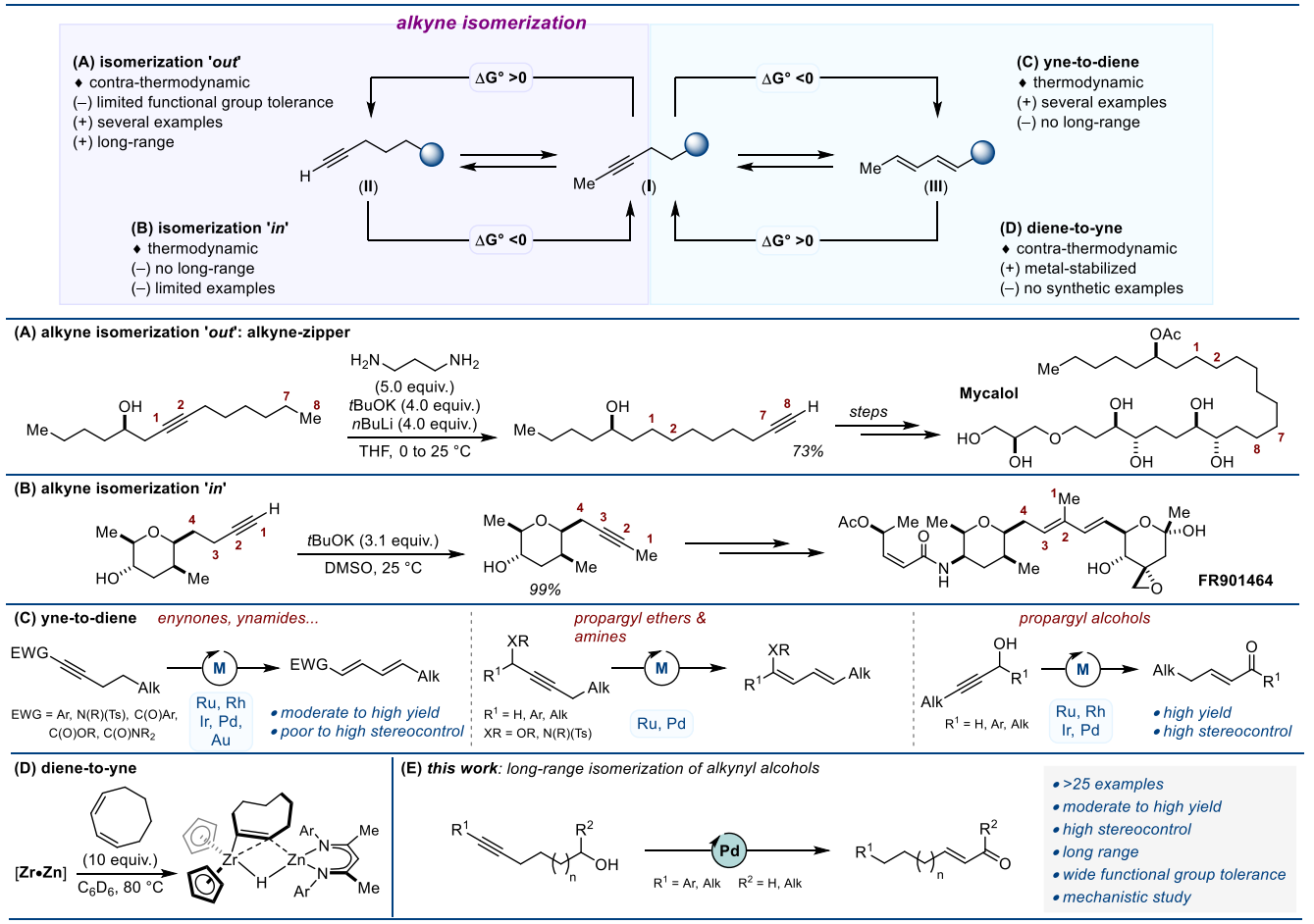

Figure 1. Overview of the thermodynamic factors associated with alkyne isomerizations (A, B) and yne−diene isomerizations (C, D), their challenges, and limitations. (A−D) Examples of alkyne and yne−diene isomerizations. (E) This work: long-range isomerization of alkynyl alcohols into α,β-unsaturated carbonyls.

mixtures of geometrical isomers,[13] Maestri showed that propargyl amines were isomerized with high levels of stereocontrol using simple palladium precursors and a catalytic amount of benzoic acid.[14] The isomerization of primary and secondary propargylic alcohols into α,β-unsaturated aldehydes and ketones has been achieved with several Rh, Ru, Ir, and Pd precursors under thermal conditions.[15] These protocols are frequently highly productive and provide excellent levels of stereocontrol. Finally, examples of catalytic and synthetically useful contra-thermodynamic diene-to-yne isomerizations are yet to be discovered (Figure 1D, **III** → **I**). As a first step in this direction, Crimmin and co-workers have observed an unorthodox "on-metal" diene-to-yne isomerization of cyclooctadiene using a heterodinuclear [Zr/Zn] complex.[16]

As the literature analysis presented above demonstrates, long-range yne-to-diene isomerizations (type C) are conspicuously absent from the current library of remote functionalization strategies. To address this challenge, we hypothesized that alkynes featuring a hydrocarbon chain terminated by an alcohol functionality may impart a sufficient thermodynamic driving force to ensure displacement of the two π components of the C≡C bond.[1,2] The choice of such substrates was equally dictated by the ubiquitous nature of the α,β-unsaturated aldehydes that would ultimately be obtained upon complete isomerization. Nevertheless, in addition to sustaining migration of the two π systems of an alkyne over several carbon atoms, we recognized that the ideal catalyst would have to overcome several challenges. Indeed, the metal-catalyzed intramolecular hydroalkoxylation of alkynes that produces furan or pyran derivatives is well-established and may occur preferentially.[17] Moreover, the transient dienes and/or skipped dienes that are expected to be generated during the reaction are susceptible to act as catalyst poisons by chelation to the metal center or simply to be thermodynamically too stable to undergo further isomerization. Finally, because deconjugation of α,β-unsaturated carbonyls has been achieved using several metal hydride complexes, the ability of the product to act as an effective thermodynamic sink was initially unclear.[2]

As part of our program directed toward the development of remote functionalization strategies, we report herein the identification of a readily available and well-defined palladium hydride for the long-range isomerization of alkynyl alcohols into α,β-unsaturated aldehydes and ketones (Figure 1E). This process is sustainable over several methylene units and is compatible with a variety of functional groups. Preliminary experimental and computational investigations providing information on the mechanism of this transformation are also presented.

RESULTS AND DISCUSSION

We began our study by examining the isomerization of 5-phenylpent-4-ynol **1a** by various transition-metal complexes

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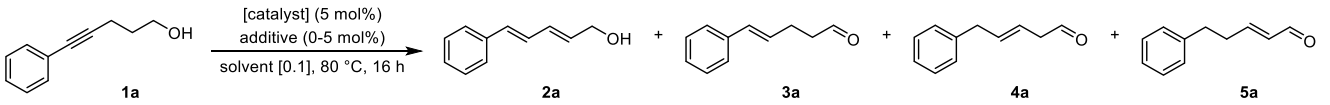
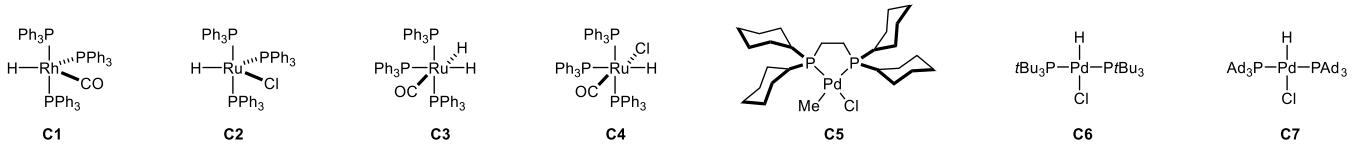
Table 1. Reaction Optimization[a]



entry	catalyst/additive	solvent	conv. **2a** (%)[b]	(*EE*/*EZ*) **2a**[b]	conv. **3a** + **4a** (%)[b,c]	conv. **5a** (%)[b]	(*E*/*Z*) **5a**[b]
1	**C1**	toluene	<5	nd			
2	**C2**	toluene	<5	nd			
3	**C3**	toluene	<5	nd			
4	**C4**	toluene	<5	nd			
5[d]	**C5**/NaBAr^F	toluene	<5	nd			
6	[$(Cy_3P)_2Pd$]	toluene	<5	nd			
7	[$(^tBu_3P)_2Pd$]	toluene	<5	nd			
8	[$(tBu_3P)_2Pd$]/TsOH	toluene	9	>20:1	~5	<5	nd
9	[$(tBu_3P)_2Pd$]/$C_6H_5CO_2H$	toluene	12	>20:1	~5	<5	nd
10	[$(tBu_3P)_2Pd$]/$(EtO)_2P(O)OH$	toluene	32	>20:1	~5	<5	nd
11	[$(tBu_3P)_2Pd$]/HBAr^F	toluene	55	>20:1	~5	<5	nd
12	[$(tBu_3P)_2Pd$]/HCl	toluene	10	9:1	~5	66	>20:1
13	[$(Cy_3P)_2Pd$]/HCl	toluene	<5	nd			
14[e]	**C6**	toluene	6	9:1	~5	77	>20:1
15[e]	**C7**	toluene	14	>20:1	~11	65	>20:1
16[e]	**C6**/NaBAr^F	toluene	48	9:1	~5	34	>20:1
17[e]	**C6**	1,2-DCE	5	7:1	15	68	>20:1
18[e]	**C6**	2-MeTHF	17	9:1	~5	66	>20:1
19[e]	**C6**	CH_3CN	70	7:1	~5	16	>20:1
20[e,f]	**C6**	toluene	>99	>20:1			



[a]Reactions performed on a 0.05 mmol scale. [b]Conversion, stereoselectivity, and stereoisomeric ratio determined by ^{1}H NMR spectroscopy using an internal standard. [c]Complex stereoisomeric mixture. [d]50 mol % cyclohexene. [e]1 h. [f]25 °C.

(**C1**−**C5**) that are effective for the long-range isomerization of C═C bonds (Table 1). In our series of exploratory experiments, no reactivity was observed using the commercially available rhodium and ruthenium hydrides **C1**−**C4** (Table 1, entries 1−4), our homemade bisphosphine palladium precatalyst **C5** (Table 1, entry 5), or the common palladium precursors [$(Cy_3P)_2Pd$] and [$(tBu_3P)_2Pd$] (Table 1, entries 6 and 7). With the idea of generating [Pd−H] species in situ, the latter was used in combination with a variety of protic additives (5 mol %). Isomerization of **1a** into 5-phenylpenta-2,4-dienol (**2a**) was observed using benzoic acid, diethylphosphate, *p*-toluenesulfonic acid, and HBAr^F, with conversions ranging from 9% to 55% and with stereoselectivity systematically >20:1 (Table 1, entries 8−11). These reactions were accompanied by the formation of stereoisomeric mixtures of **3a** and **4a**, several hardly distinguishable internal alkenes, and a trace amount of **5a**. Much to our satisfaction, when hydrochloric acid was employed, the desired *α*,*β*-unsaturated aldehyde was obtained as the major product (66%, *E*/*Z* > 20:1) together with a minor amount of **2a**−**4a** (Table 1, entry 12). No reaction was observed when [$(Cy_3P)_2Pd$] was employed under otherwise identical reaction conditions, underscoring the importance of the ancillary ligand (Table 1, entry 13). We found that the catalytic performances could be improved using the well-defined complex [$(tBu_3P)_2Pd$(H)(Cl)] (**C6**) and, after just 1 h at 80 °C, a 77% conversion to **5a** and a nearly perfect level of stereocontrol (*E*/*Z* > 20:1) were measured (Table 1, entry 14).[18] Even though appreciable catalytic activity was observed with a [Pd−H] precatalyst supported by larger trialkylphosphine ligands (**C7**, L = PAd_3), conversion in **5a** was noticeably lower (Table 1, entry 15).[19] Finally, the use of NaBAr^F as a halide abstractor and a rapid solvent survey did not lead to any better results (Table 1, entries 16−19). Of particular note, when the isomerization reaction was conducted at room temperature with **C6**, dienyl alcohol **2a** was obtained quantitatively with perfect stereoselectivity (*EE*/*EZ* > 20:1) (Table 1, entry 20).[20]

With the conditions described in Table 1, entry 14, we next assessed the generality of the Pd-catalyzed isomerization of alkynyl alcohols (**1**) into *α*,*β*-unsaturated carbonyls (**5**) (24 examples, Figure 2). As a preamble, it should be noted that the products of catalysis (**5**) were systematically obtained with an excellent level of stereocontrol (*E*/*Z* > 20:1) and usually as the major reaction component. Occasionally, the presence of dienyl alcohol (**2**) or other regioisomers (**3**, **4**, and other internal olefins) rendered purification delicate and affected the yield of pure isolated material. Therefore, to reflect catalytic efficiency, the regioisomeric ratio (*rr*) between **5** and all other (stereo)-isomers is indicated in Figure 2. First, we evaluated a series of aryl-substituted substrates where the distance between the C≡C bond and the alcohol functionality was set to three carbon atoms (Figure 2A). We found that the reaction of our model substrate (**1a**) could be conducted on a gram scale without any loss of catalytic efficiency and **5a** was isolated in 61% yield. The use of a secondary alcohol led to a substantially diminished yield and afforded the corresponding *α*,*β*-unsaturated ketone **5b** in 33% yield. The introduction of electron-donating substituents in

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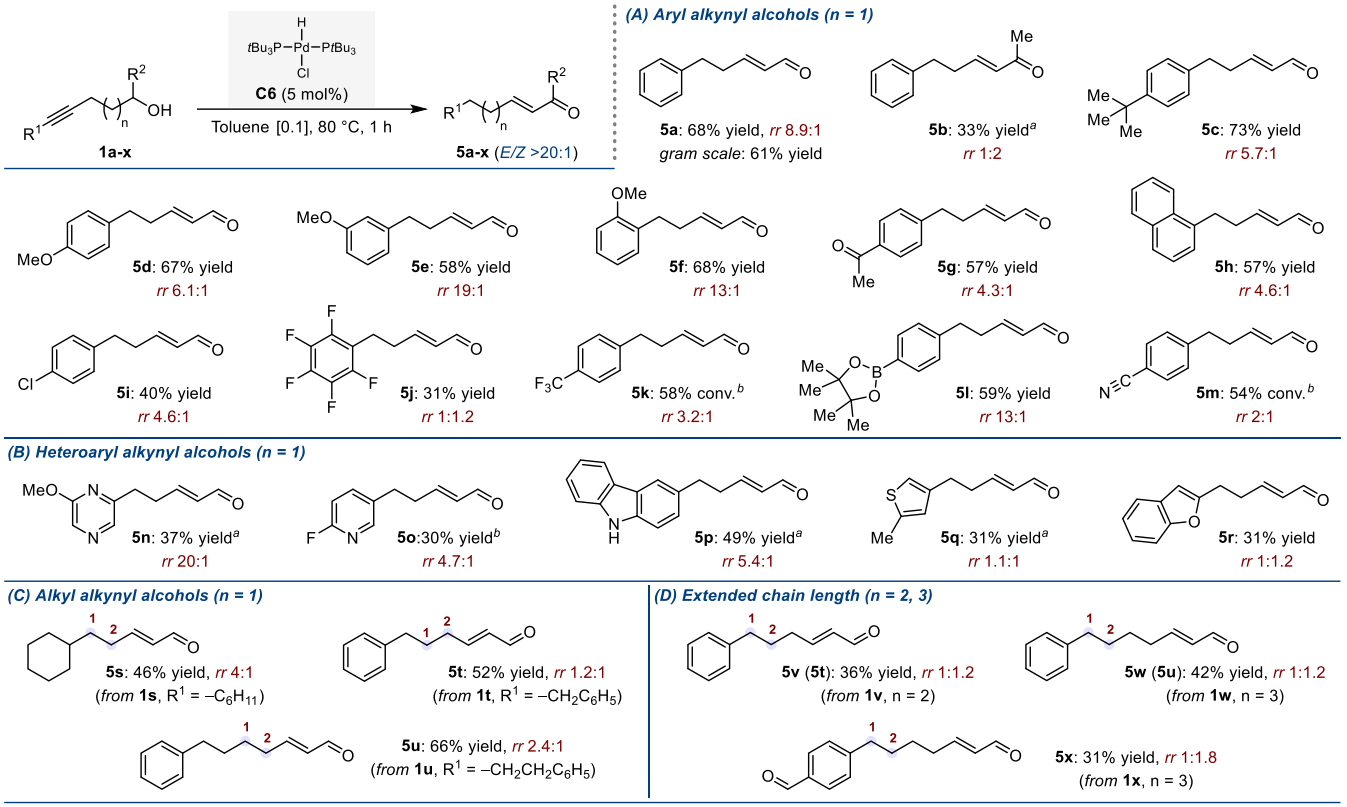

Figure 2. Scope of the Pd-catalyzed isomerization of alkynes into α,β-unsaturated carbonyls. Reaction scale: 0.5 mmol. All products were obtained with $E/Z > 20{:}1$. Regioisomeric ratio (*rr*) measured by ^{1}H NMR of the crude reaction mixture using an internal standard and expressed as the ratio between **5** and all other isomers. (A) Isomerization of aryl alkynyl alcohols. (B) Isomerization of heteroaryl alkynyl alcohols. (C) Isomerization of alkyl alkynyl alcohols. (D) Isomerization with extended chain length. [a]3 h. [b]Isolated together with other regioisomers.

the *para*-, *meta*-, and *ortho*-positions was well-tolerated (**5c**−**5f**) as was the presence of an enolizable methyl ketone (**5g**) or a 1-naphthyl group (**5h**). A reduced catalytic activity was observed for the *p*-chloro (**5i**), pentafluoroaryl (**5j**), and *p*-trifluoromethyl (**5k**) derivatives. Pleasingly, sensitive functional groups such as a boronic ester (**5l**) and a nitrile (**5m**) were found to be compatible with the catalytic process. Even though the yields were diminished, we were pleased to find that pyrazine-, pyridine-, and unprotected carbazole-containing substrates were isomerized to the desired α,β-unsaturated aldehydes (**5n**−**5p**). Similar results were obtained with a thiophene and a benzofuran derivative (**5q**−**5r**) (Figure 2B). The evaluation of alkyl-substituted alkynyl alcohols proved particularly instructive, and the product of remote functionalization was generated preferentially in all cases. While side-products containing an endocyclic double bond were detected using **1s**, no sign of styrenyl derivatives were observed with the benzyl- and phenethyl-containing substrates **1t** and **1u**, suggesting that the formation of the α,β-unsaturated carbonyl is a stronger driving force (Figure 2C). Most notably, we showed that the length of the hydrocarbon chain between the C≡C bond and the alcohol functionality could be extended up to 5 carbon atoms, although this led to slightly reduced catalytic performances (**5v**−**5x**). Attempts to improve these results by re-evaluating standard reaction parameters were not met with success.

Preliminary mechanistic insights were next gleaned experimentally (Figure 3). Resonances attributed to allene intermediates were observed during the monitoring of the catalytic experiment by NMR spectroscopy. The difficulty associated with the purification of these complex mixtures prompted us to independently prepare compound **6w**. In the presence of 5 mol % of $[(t\mathrm{Bu_3P})_2\mathrm{Pd(H)(Cl)}]$ (**C6**) in toluene-d_8, conversion of **6w** into dienyl alcohol **2w** occurred within minutes at room temperature (Figure 3A). Next, placing the same sample at 80 °C led after 3 h to the formation of the α,β-unsaturated aldehyde **5w** (46% conv., $E/Z > 20{:}1$) along with ca. 12% of internal olefins. These experiments support the notion that both allenes and dienyl alcohols are intermediates in the long-range Pd-catalyzed isomerization of alkynyl alcohols and that the process is likely to proceed by iterative migratory insertion/β-hydride elimination sequences.[21] When the α,β-unsaturated aldehyde **5a** was resubjected to catalysis, no reaction occurred. In contrast, related ketone **5b** was partially converted into styrenyl **3b** (Figure 3B). Retrospectively, these results explain the reduced yield obtained in the isomerization of the alkynyl secondary alcohol **1b**. More importantly, they indicate that α,β-unsaturated ketones are susceptible to be deconjugated, while isomerization of primary alkynyl alcohols is not reversible under the optimized reaction conditions. Finally, isomerization of the enantioenriched substrate (*R*)-**1y** (97:3 *er*) yielded a 4:1 mixture of dienyl alcohol **2y** and α,β-unsaturated aldehyde **5y**, albeit in racemic form. This not only indicates that isomerization toward the α,β-unsaturated aldehyde is not completely interrupted by the presence of an alkyl substituent on the hydrocarbon chain but it also implies that the catalyst dissociates during the migration of the two π components of the initial alkyne.[22] When the alkynyl methyl ether derivative **1w.Me** was subjected to the optimized reaction conditions, after 1 h, formation of diene **2w.Me** was observed along with a complex mixture of alkenes in a ca. 2:1 ratio (Figure 3D). Prolonging the

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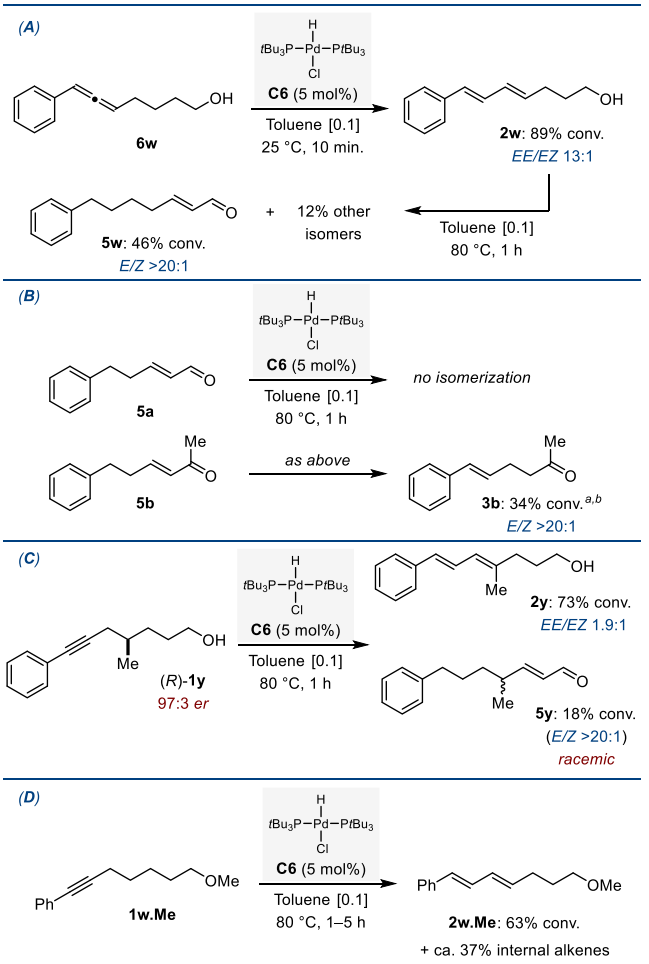

Figure 3. (A) Isomerization of allene **6w**. (B) Evaluation of the reversibility of the catalytic reaction. (C) Isomerization of an enantioenriched substrate. (D) Isomerization of alkynyl methyl ether **1w.Me**. [a]Contains ca. 5% of **4b**. [b]Conversion reaches 37% after 3 and 5 h.

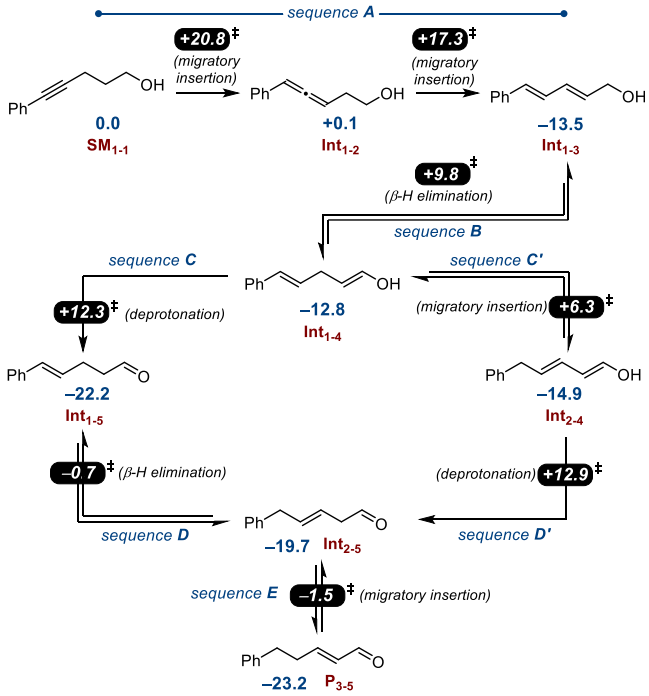

Figure 4. Free energy (kcal/mol) of intermediates along the isomerization pathway relative to substrate **1a**/$\mathbf{SM}_{1-1}$. Calculated at the DLPNO-CCSD(T)/def2-TZVPP//ωB97X-D3(BJ)/def2-mTZVPP level of theory with CPCM (toluene). Black boxes along the arrows indicate the highest-energy transition state between the linked intermediates in the isomerization sequence, with reference to $\mathbf{SM}_{1-1}$ and **C6**. The nature of said transition state is indicated in parentheses.[23]

reaction time to 3 or even 5 h did not change the outcome of the reaction significantly, suggesting that a thermodynamic equilibrium has been reached. This result indicates that although the hydroxyl functionality is not required to trigger the first elementary steps, it is a necessary thermodynamic driving force for the formation of α,β-unsaturated aldehydes.

To obtain additional information on the thermodynamic parameters of the reaction, a computational study based on density functional theory (DFT) combined with post-Hartree–Fock methods was conducted using the ORCA 5.0.4 software package.[24] The relative stabilities of **1a** (thereafter denoted as $\mathbf{SM}_{1-1}$) and its most relevant (stereo)isomers intervening in the isomerization process to **5a** (thereafter denoted as $\mathbf{P}_{3-5}$) are displayed in Figure 4. While initial conversion of the alkyne to the parent allene ($\mathbf{Int}_{1-2}$) does not result in any thermodynamic stabilization, further migration of the π system to afford conjugated diene $\mathbf{Int}_{1-3}$ constitutes a first thermodynamic sink, which lowers the energy of the system by 13.5 kcal/mol. Further delocalization to afford skipped diene $\mathbf{Int}_{1-4}$ or conjugated dienol $\mathbf{Int}_{2-4}$ is essentially isoenergetic (−12.8 and −14.9 kcal/mol, respectively). By contrast, all of the computed aldehydes benefit from an additional stabilization energy of ca. 10 kcal/mol when compared to their enol precursors, whereby the final α,β-unsaturated aldehyde ($\mathbf{P}_{3-5}$) is calculated to be the most thermodynamically stable compound (sequence C → sequence D → sequence E). This is in full agreement with our experimental observations. Our calculations were also in line with the deconjugative isomerization of ketone **5b** into **3b** when subjected to the catalytic conditions (Figure 3B and Section S6.8). Indeed, a $\Delta\Delta G$ of 0.8 kcal/mol was calculated in favor of the styrenyl derivative compared to the α,β-unsaturated ketone. Collectively, these results suggest a degree of reversibility in the isomerization processes occurring between the various aldehydes leading to a thermodynamic mixture.

The entire mechanism of the Pd-catalyzed isomerization of alkynyl alcohol $\mathbf{SM}_{1-1}$ was explored next. Sequence A leading to diene $\mathbf{Int}_{1-3}$ is presented in detail in Figure 5. We found that displacement of a phosphine ligand and binding of the substrate lead to complex **A.1** with an energy penalty calculated at +15.9 kcal/mol. Migratory insertion of the alkyne occurs via $\mathbf{TS}_{\mathbf{A.1-2}}$, which lies at +20.8 kcal/mol. Subsequent β-hydride elimination from **A.2** was calculated to be relatively facile (+19.3 kcal/mol) and yields the π-bound allene (**A.3**). Likewise, further migratory insertion proceeds with a low barrier (+17.3 kcal/mol) to furnish *anti*/*syn* π-allyl palladium complex **A.4**. Because this intermediate lies at −10.3 kcal/mol on the pathway from its parent transition state $\mathbf{TS}_{\mathbf{A.3-4}}$, its formation is likely to be irreversible and therefore prevents forming back either the allene ($\mathbf{Int}_{1-2}$) or the alkyne ($\mathbf{SM}_{1-1}$). From **A.4**, a $\pi-\sigma-\pi$ isomerization sequence results in *anti*–*syn* interconversion of the phenyl substituent by rotation around the σ(C–C) bond in the η^1-Pd-benzyl intermediates **A.5** and **A.6** to finally generate the *syn*/*syn* π-allyl palladium **A.7** (with an associated activation energy of $\Delta G^{\ddagger}$ = 16.2 kcal/mol).

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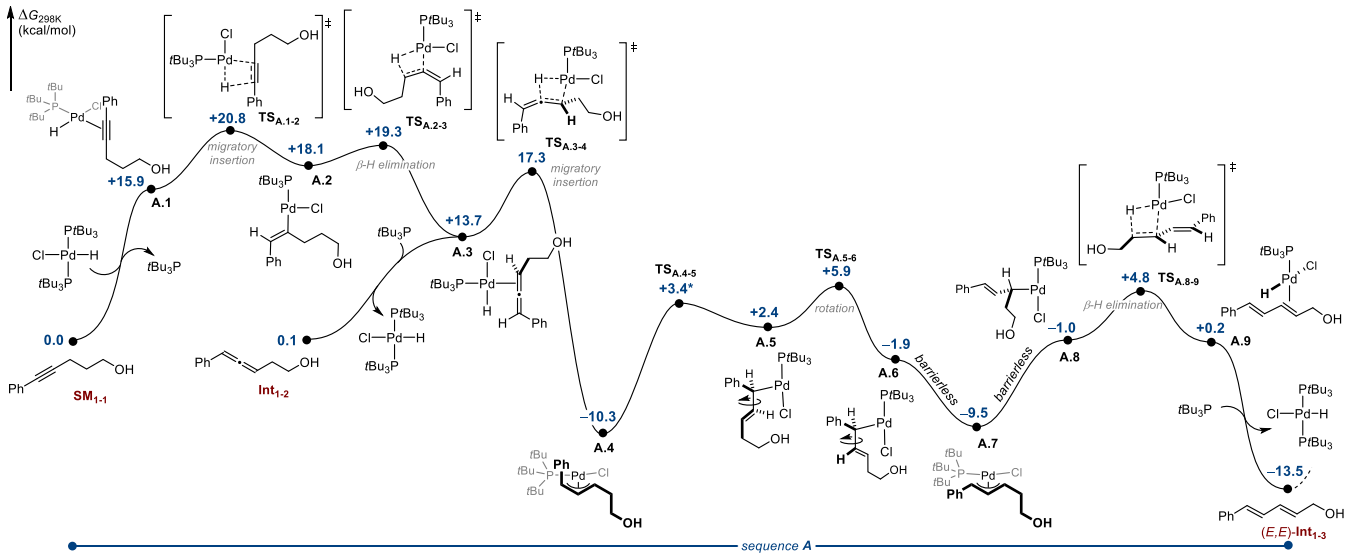

Figure 5. Computed free-energy profile for sequence A of the Pd-catalyzed isomerization of alkynyl alcohol **1a**/$\mathbf{SM}_{1-1}$. Level of theory: DLPNO-CCSD(T)/def2-TZVPP//ωB97X-D3(BJ)/def2-mTZVPP with CPCM(toluene). * $\mathbf{TS}_{A.4-5}$ was located as the climbing image of a nudged elastic band (NEB-CI) calculation.[23]

The only path forward to $\mathbf{Int}_{1-3}$ we could identify consists of a rapid conversion to energetically accessible σ-allyl palladium intermediate **A.8**, which can engage in a subsequent β-hydride elimination with the adjacent methylene unit through a transition state located at +4.8 kcal/mol ($\mathbf{TS}_{A.8-9}$). Overall, with the highest barrier calculated at $\Delta G^{\ddagger}$ = +20.8 kcal/mol for the migratory insertion of the [Pd−H] across the alkyne moiety, our calculations suggest that the allene $\mathbf{Int}_{1-2}$ (although an intermediate) may not be isolable in the presence of the catalytic system. Indeed, rapid conversion to **A.4** is expected even at room temperature. This result is fully consistent with the conversion of allene **6w** into **2w** at room temperature within minutes, as observed experimentally. Moreover, with an activation barrier to revert to **A.7** lying at $\Delta G^{\ddagger}$ = 18.3 kcal/mol, the formation of $\mathbf{Int}_{1-3}$ is likely reversible. Even though they were found to be thermodynamically slightly less stable, all other stereoisomers of (*E,E*)-$\mathbf{Int}_{1-3}$ are theoretically accessible at room temperature (see Section S6.9). Conversion of the conjugated diene $\mathbf{Int}_{1-3}$ into the skipped diene $\mathbf{Int}_{1-4}$ is accomplished through consecutive migratory insertion ($\mathbf{TS}_{B.1-2}$) and β-hydride elimination ($\mathbf{TS}_{B.2-3}$) via the intermediacy of the agostic complex **B.2** (sequence B, Figure 6). The overall barrier of $\Delta G^{\ddagger}$ = 23.3 kcal/mol in sequence B is higher than that in sequence A. This is consistent with the possibility to isolate dienyl alcohol **2**. While no transition state could be successfully optimized between **A.9** and $\mathbf{Int}_{1-3}$ (Figure 5), the accumulation of the latter at room temperature before further isomerization to $\mathbf{Int}_{1-4}$ suggests that decoordination is facile. This hypothesis is in line with the results disclosed in Figure 3C (vide supra). From pivotal intermediate $\mathbf{Int}_{1-4}$, conversion into $\mathbf{Int}_{2-4}$ is energetically facile ($\Delta G^{\ddagger}$ = 19.1 kcal/mol). Of note, this relatively stable dienol lying at −14.9 kcal/mol may act as a temporary reservoir before tautomerization into $\mathbf{Int}_{2-5}$ or may convert back to $\mathbf{Int}_{1-4}$, which subsequently tautomerizes into $\mathbf{Int}_{1-5}$. Retrospectively, $\mathbf{Int}_{1-4}$ and $\mathbf{Int}_{2-4}$ (and stereoisomers thereof) may likely be the various internal alkenes observed experimentally (vide supra). To access the next pivotal intermediate ($\mathbf{Int}_{2-5}$, lying at −19.7 kcal/mol), sequences C → D and C′ → D′ are equally energetically viable and exhibit similar idiosyncrasies.

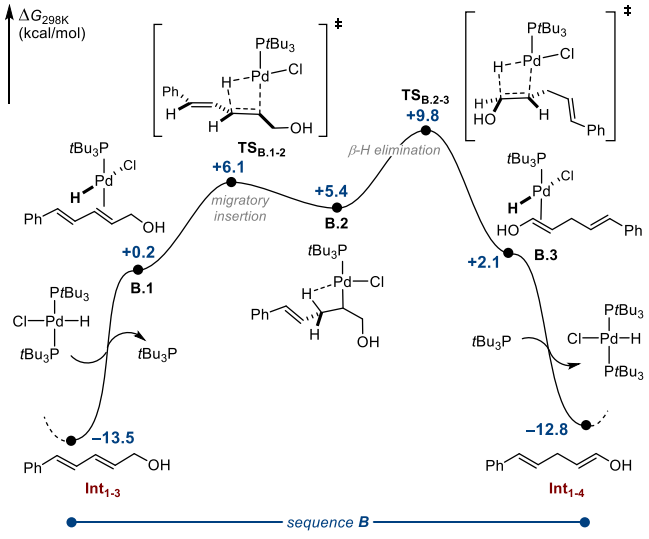

Figure 6. Computed free-energy profile for sequence B of the Pd-catalyzed isomerization of alkynyl alcohol **1a**/$\mathbf{SM}_{1-1}$. Level of theory: DLPNO-CCSD(T)/def2-TZVPP//ωB97X-D3(BJ)/def2-mTZVPP with CPCM(toluene).[23]

Therefore, for the sake of brevity, in the following section, we will only discuss the nature of the intermediates intervening in the slightly favored sequence C → D. The full free-energy profiles of sequences C′ and D′ are available in the Supporting Information.

Tautomerization of $\mathbf{Int}_{1-4}$ into $\mathbf{Int}_{1-5}$ presents some unorthodox features (sequence C, Figure 7). Coordination to the enol followed by migratory insertion is endergonic and occurs with an overall barrier of $\Delta G^{\ddagger}$ = 22.6 kcal/mol. Generation of $\mathbf{Int}_{1-5}$ via a conventional β-hydride elimination from agostic palladium complex **C.2** was found to be kinetically inaccessible for our system ($\mathbf{TS}_{C.3\text{-}Int1-5}$ lies at +27.8 kcal/mol). Instead, a transition state involving the spare equivalent of $t\mathrm{Bu}_3\mathrm{P}$ acting as a base to deprotonate the alcohol proved to be more favorable and constitutes a potential rate-determining step with $\mathbf{TS}_{C4-5}$ at +12.3 kcal/mol. Calculated from $\mathbf{Int}_{2-4}$, this leads to

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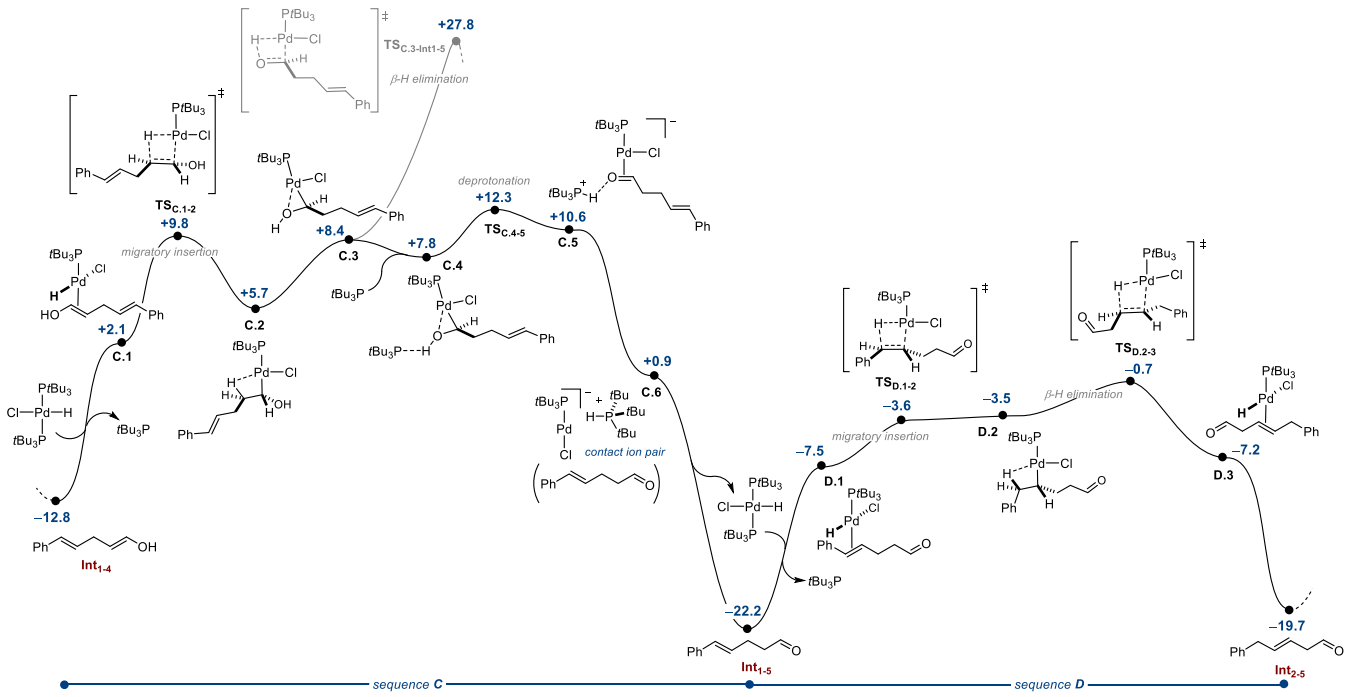

Figure 7. Computed free-energy profile for sequences C and D of the Pd-catalyzed isomerization of alkynyl alcohol **1a**/$\mathbf{SM}_{1-1}$. Level of theory: DLPNO-CCSD(T)/def2-TZVPP//ωB97X-D3(BJ)/def2-mTZVPP with CPCM(toluene).[23]

an overall activation barrier for the full isomerization process estimated at $\Delta G^{\ddagger}$ = 27.2 kcal/mol, which is consistent with the elevated temperatures needed to promote complete isomerization. Of important note, keto−enol tautomerization involving [Pd−H] intermediates has previously been suggested to involve DMF as a proton shuttle.[25] Toluene, the solvent used in our optimized catalytic conditions, does not offer such proton-shuttling capability. Similarly, a non-catalyzed tautomerization via a dimeric pathway was previously calculated to be kinetically unrealistic.[22c] Even though we are well within the expected accuracy compared to experimental data, $\mathbf{TS}_{C4-5}$ might be slightly overestimated due to possible limitations of implicit solvent models for charged separated species.[26] The π-bound carbonyl intermediate resulting from proton abstraction (**C.5**) is formally a negatively charged Pd(0) complex hydrogen-bonded to the phosphonium salt. This species subsequently evolves into a tight-contact ion pair (**C.6**) before the release of $\mathbf{Int}_{1-5}$ and regeneration of precatalyst [$(t\mathrm{Bu_3P})_2$Pd(H)(Cl)]. Sequence D, in which $\mathbf{Int}_{1-5}$ is converted into $\mathbf{Int}_{2-5}$ by deconjugation of the styrenyl unit, is composed of a more conventional sequence of migratory insertion and β-H elimination, the latter presenting the highest barrier at −0.7 kcal ($\Delta G^{\ddagger}$ = 21.5 kcal/mol from $\mathbf{Int}_{1-5}$). From $\mathbf{Int}_{2-5}$, conjugation of the C═C bond with the carbonyl to afford the final α,β-unsaturated aldehyde $\mathbf{P}_{3-5}$ proceeds again via a migratory insertion/β-H elimination process (sequence E, Figure 8). The corresponding transition states are located at similar energy levels and are likely to occur rapidly at room temperature with activation energy comprised between 17.9 and 18.2 kcal/mol. Furthermore, the relatively low barriers computed in sequences D and E suggest that thermal equilibration between aldehydes $\mathbf{Int}_{1-5}$, $\mathbf{Int}_{2-5}$, and $\mathbf{P}_{3-5}$ is rapid under the optimized reaction conditions. This observation is consistent with the fact that the regioisomeric ratio between these three species is dictated by thermodynamics (note that the predicted ΔG of 1.0 kcal/mol is in relatively good agreement with the regioisomeric ratio measured experimentally for **5a**).[27]

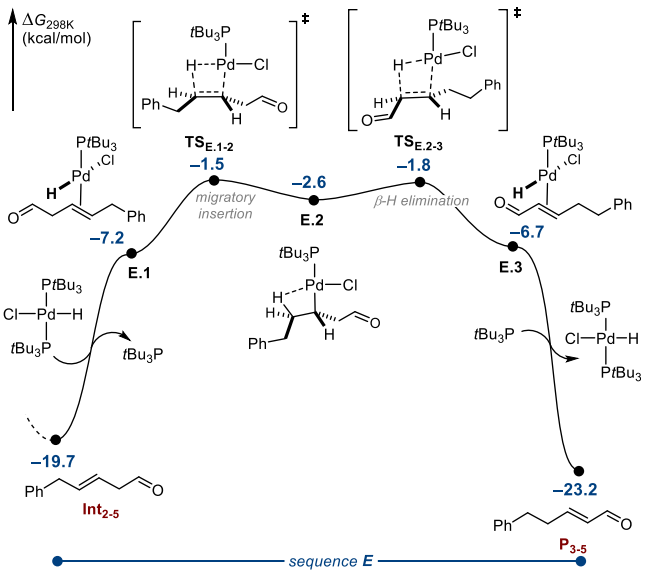

Figure 8. Computed free-energy profile for sequence E of the Pd-catalyzed isomerization of alkynyl alcohol **1a**/$\mathbf{SM}_{1-1}$. Level of theory: DLPNO-CCSD(T)/def2-TZVPP//ωB97X-D3(BJ)/def2-mTZVPP with CPCM(toluene).[23]

Because $\mathbf{P}_{3-5}$ is calculated to be the thermodynamic product, the apparent lack of reactivity of **5a** when subjected to catalysis may not result from irreversibility but rather from a thermodynamic equilibrium that lies in favor of the α,β-unsaturated product.

CONCLUSIONS

In summary, using a readily available palladium hydride complex, we developed a catalytic isomerization of alkynyl alcohols. The operationally simple protocol is effective for aryl-, heteroaryl-, and alkyl-containing substrates and provides access preferentially to the thermodynamically more stable α,β-

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unsaturated aldehydes in practical yields. We found that the functional group tolerance is broad and that the isomerization of both π-components of the initial C≡C bond can be sustained over several methylene units. Computational analyses were in agreement with our preliminary experimental mechanistic investigations. While most elementary steps consist of successive migratory insertion/β-hydride elimination sequences, we identified an unusual phosphine-assisted deprotonation as being energetically more favorable than a conventional β-hydride elimination in the rate-determining aldehyde-forming tautomerization steps. We anticipate that the results disclosed in our study may broaden the field of remote functionalizations by adding alkynes as a potential entry point in the arsenal of synthetic chemists.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c05136.

Experimental procedures, characterization of all new compounds, spectroscopic data, and computational procedures (PDF)

Additional data (ZIP)

Molecular coordinates of computed structures (XYZ)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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