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General and Selective Head-to-Head Dimerization of Terminal Alkynes Proceeding via Hydropalladation Pathway

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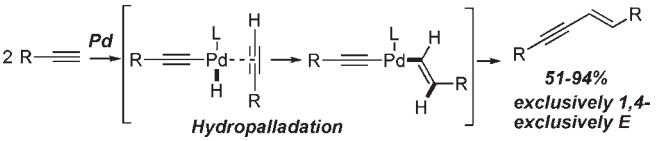
ABSTRACT



A general highly regio- and stereoselective palladium-catalyzed head-to-head dimerization reaction of terminal acetylenes is presented. This methodology allows for the efficient synthesis of a variety of 1,4-enynes as single *E* stereoisomers. Computational studies reveal that this dimerization reaction proceeds via the hydropalladation pathway.

Dimerization of terminal alkynes is a very practical and atom-economical approach toward conjugated enynes, important building blocks widely used in synthetic organic chemistry, medicinal chemistry, and materials science.[1] A number of transition metal complexes efficiently catalyze alkyne dimerization.[4−12] However, in most cases a mixture of different regio- and stereoisomeric enynes **2**−**4** is obtained (eq 1). The highly selective head-to-tail Pd-catalyzed dimerization of terminal alkynes toward 1,3-enynes **4** has been developed by Trost.[4a,b] However, Pd-catalyzed head-to-head dimerization of terminal alkynes usually leads to mixtures of stereoisomeric 1,4-enynes **2** and **3**[4e−h] or is limited to particular substrates.[4d,e] For example, our research group has developed the palladium-catalyzed head-to-head dimerization of terminal aryl acetylenes toward *E*-enynes **2**.[4d] However, despite the achieved high regio- and stereoselectivity, this method involving agostic interaction is limited to terminal aryl acetylenes possessing a requisite

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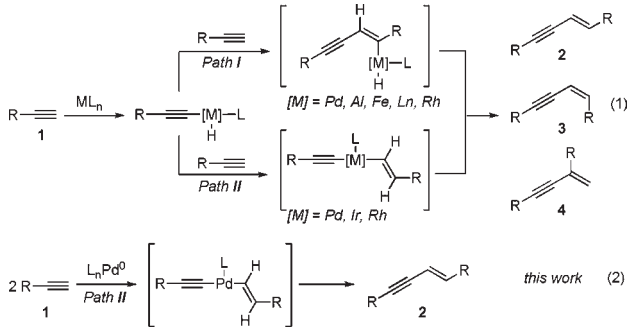
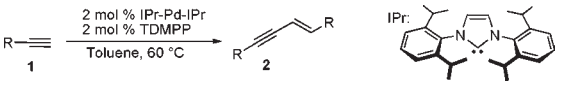
ortho-H atom. Moreover, despite the number of procedures reported,[4] there is no consensus on the mechanism of the palladium-catalyzed dimerization reaction of terminal acetylenes. Usually, the carbometalation pathway (eq 1, path **I**) is proposed.[4a,b,d,g,13] Alternatively, a hydrometalation pathway (eq 1, path **II**) has also been suggested.[4a,13−16] Herein, we report a highly regio- and stereoselective palladium-catalyzed head-to-head dimerization of a wide range of terminal acetylenes toward *E*-enynes **2**. DFT calculations unambiguously support the hydropalladation pathway for this transformation (eq 2).



In the course of our investigations,[17] we found that the bis-*N*-heterocyclic carbene palladium complex (IPr-Pd-IPr), in the presence of electron-rich and bulky phosphine ligand TDMPP (TDMPP = $P[(2,6\text{-}OMe)_2C_6H_3]_3$),[18] efficiently catalyzed the head-to-head dimerization reaction of phenylacetylene **1a** to give the corresponding *E*-enyne **2a** with high yield and perfect regio- and stereoselectivity (Table 1, entry 1).[19] Importantly, in contrast to our previous work,[4d] it was found that this transformation is

Table 1. Palladium-Catalyzed Head-to-Head Dimerization of Terminal Acetylenes[a]



entry	alkyne			yield of **2** (%)[b]
1			**1a**	92 (70) 86[c]
2		R = OMe	**1b**	77
3		R = Me	**1c**	81 (50)
4		R = F	**1d**	88 (0)
5		R = Me	**1e**	71 (0)
6			**1f**	66 (80)
7		R = OMe	**1g**	81 (57)
8		R = Me	**1h**	92 (86)
9		R = CN	**1i**	82 (91)
10		R = COOMe	**1j**	67
11		R = Cl	**1k**	51
12			**1l**	65
13			**1m**	93
14			**1n**	56
15			**1o**	78
16	$n\text{-}C_{10}H_{21}$		**1p**	91 (3)
17	*t*-Bu		**1q**	65
18			**1r**	71
19			**1s**	93
20			**1t**	81
21			**1u**	62
22			**1v**	94

[a] Reaction conditions: **1** (0.5 mmol), IPr−Pd−IPr (2 mol %), TDMPP (2 mol %), toluene (1 M), 60 °C. [b] Isolated yields; previously reported yields[4d] are in parentheses. [c] Reaction conditions: **1a** (5 mmol), IPr−Pd−IPr (0.5 mol %), TDMPP (1 mol %), toluene (1 M), 60 °C.

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(16) For a hydrometalation pathway on other metal-catalyzed dimerizations of terminal alkynes, see refs 7 , 9, 11c, and 11e.

(17) See Supporting Information for details.

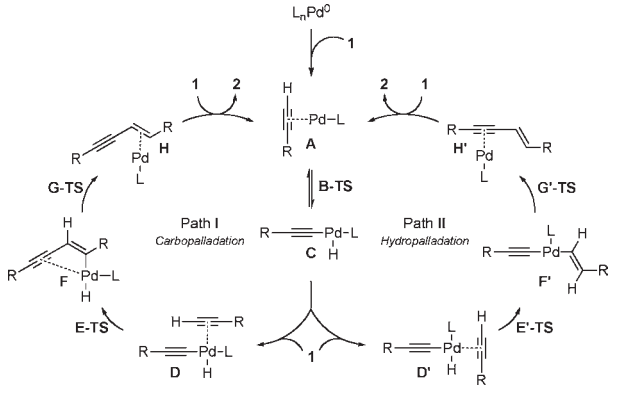
(18) The role of TDMPP is not completely understood. Most likely the TDMPP ligand helps regenerate the active catalyst by removing the product from the catalyst-bound product complex **H′** (Scheme 1). Hence, the dimerization of phenylacetylene in the presence of the IPr−Pd−IPr complex without any additives is perfectly regio- and stereoselective. However, addition of TDMPP to the reaction mixture led to the improvement of the reaction yield. See Table S1 of the Supporting Information for details.

(19) For reasonably selective head-to-head dimerization of alkynes in the presence of a palladium−imidazolium salt−Cs_2CO_3 system, see ref 4e.

equally efficient with terminal aryl acetylenes possessing one or even two substituents at the *ortho* position of the aromatic ring (entries 2−5). These results clearly indicate that this reaction does not involve agostic interactions.[4d] Thus, we investigated the generality of this process. To our delight, it was found that 1-naphtylacetylene **1f** and a variety of *para*-substituted aryl acetylenes, including electron-donating (methoxy **1g** and methyl **1h**) or electron-withdrawing (cyano **1i**, ester **1j**, and chloro **1k**) groups, were competent substrates for this dimerization reaction (entries 6−11). Likewise, a variety of terminal alkynes possessing heterocyclic groups, such as thiophene **1l** or pyridine **1m**, **1n** and quinoline **1o**, gave the corresponding *E*-enynes **2l**−**o** with good to excellent yields (entries 12−15). In addition, the reaction of alkyl acetylenes **1p** and **1q** proceeded highly selectively as well (entries 16, 17). Importantly, this reaction was perfectly compatible with various functional groups at the terminal alkynes, including propargyl ether **1r** and acetal **1s**, dimethylaminopropyne **1t**, and the protected and unprotected alcohol moiety **1u** and **1v** (Table 1, entries 18−22). The reaction was easily scalable, producing a comparable yield of **2a** even with a 0.5 mol % catalyst load (entry 1).

Naturally, we were interested in elucidating the mechanism of this dimerization reaction. As generally believed, the reaction begins with the oxidative addition of the acetylene **1** into the palladium complex (eq 1, M = Pd).[4a,b,d,g] However, two distinct pathways are possible for the migratory insertion of the second molecule of alkyne (eq 1, Scheme 1). The alkyne can undergo migratory insertion into either a Pd−C bond (path **I**: carbopalladation)[4a,b,d,g] or a Pd−H bond (path **II**: hydropalladation).[4a,14] Finally, reductive elimination with the formation of C−H or C−C bonds, respectively, gives *E*-enyne **2** and regenerates the Pd(0) catalyst.

Scheme 1. Proposed Mechanism for the Pd-Catalyzed Head-to-Head Dimerization of Terminal Acetylenes



In order to distinguish between these two pathways of the reaction, the DFT computational studies were performed at the B3LYP/SDD&6-311G(d) level.[17] As a relevant model for experimental study (Table 1), computational rationalization of the head-to-head dimerization of phenylacetylene catalyzed by an NHC−palladium complex is discussed (Scheme 1, L = NHC, R = Ph). The catalytic cycle including both pathways was investigated, and it is discussed below in terms of ΔG and ΔE energy surfaces (Figure 1).[20] Starting with π-complex **A**, the first step of the catalytic reaction involves C−H bond oxidative addition to the metal via the transition state **B-TS**, which leads to the formation of complex **C** (Scheme 1). According to the calculated energy surface, this process is endothermic, $\Delta G_{\mathbf{A}\rightarrow\mathbf{C}}$ = 14.8 (16.8) kcal/mol, with overcoming an energy barrier of $\Delta G^{\ddagger}_{\mathbf{A}\rightarrow\mathbf{B}\text{-}\mathbf{TS}}$ = 17.6 (20.4) kcal/mol (Figure 1a). Coordination of a second alkyne molecule to the Pd center of complex **C** may result in two different π-complexes retaining square planar geometry **D** and **D′** in which an η^2-coordinated alkyne is differently oriented toward the σ-alkynyl palladium moiety. Thus, the carbopalladation pathway leading to the product **2** starts with the complex **D**, while the hydropalladation pathway proceeds through the formation of **D′**. A small energy difference between the complexes **D** and **D′** (< 3 kcal/mol) indicates that both structures should be accessible in the studied system.

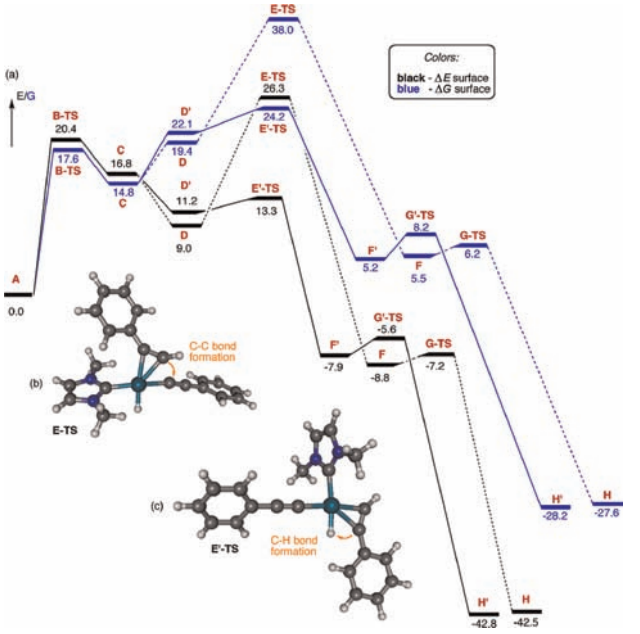


Figure 1. (a) Calculated ΔE and ΔG energy surfaces (in kcal/mol) of Pd-catalyzed head-to-head dimerization of terminal acetylenes (L = NHC, R = Ph; see Scheme 1 for structures **A**−**H**); starting from the intermediate **C** hydropalladation is shown with a solid line, and carbopalladation, with dashed line. (b) Optimized molecular structure of **E-TS**. (c) Optimized molecular structure of **E′-TS**.

In the carbopalladation pathway, coordinated alkyne insertion into the Pd−C bond is exothermic, $\Delta G_{\mathbf{D}\rightarrow\mathbf{F}}$ = −13.9 (−17.8) kcal/mol, though it requires 18.6 (17.3) kcal/mol of activation energy. The optimized molecular structure of the transition state **E-TS** clearly shows the necessary

(20) The discussion in the text is based on chemically reliable ΔG values (and ΔE values are given for comparison in parentheses).

geometry arrangement to undergo alkyne insertion in the desired fashion (Figure 1b). In the next step, C−H reductive elimination occurs with a small activation barrier (**G-TS**, bound as an alkenyl π-complex). In sharp contrast to the carbopalladation route, the hydropalladation pathway was calculated to be much more facile. Thus, alkyne insertion into the Pd−H bond was found to be more exothermic, $\Delta G_{\mathbf{D'}\rightarrow\mathbf{F'}} = -16.9\ (-19.1)$ kcal/mol. Remarkably, the activation barrier for this process is equal to only $\Delta G^{\ddagger}_{\mathbf{D'}\rightarrow\mathbf{E'}\text{-TS}} = 2.1\ (2.1)$ kcal/mol. Furthermore, the optimized molecular structure of **E′-TS** highlights the difference in the nature of the transition states (cf. Figure 1b, c). Formation of the product **2** through the hydropalladation pathway is completed via the Y-shaped transition state **G′-TS**, typical for the en-yne reductive elimination,[21] which requires overcoming a relatively small activation barrier of 3.0 (2.3) kcal/mol. The calculated **D′→E′-TS** hydropalladation barrier is more then 8 times lower compared to the **D→E-TS** carbopalladation barrier. Clearly, it is a tremendous difference in reactivity between these two pathways. Thus, if the Pd−H bond is available for alkyne insertion, it should react first. Alkyne insertion into the Pd−C bond becomes possible only if the Pd−H moiety is not available for reaction. Therefore, path **II** predominantly contributes to the product formation in the considered mechanism. The formation of both complexes **H** and **H′** is highly exothermic, thus providing the necessary driving force for the catalytic transformation. The difference between the alkenyl (**H**) and alkynyl (**H′**) binding mode of product **2** to the metal had a minor influence on the stability of these complexes: −27.6 and −28.2 kcal/mol, respectively. Finally, coordination of a new molecule of alkyne to **H** or **H′** releases the 1,4-enynes **2** and initiates the next catalytic cycle by regeneration of the catalytically active complex **A**.

Thus, the relative reactivity within pathways **I** and **II** is in excellent agreement on both ΔE and ΔG surfaces, with the marked upward shift of the latter being due to the expected entropy contribution on the alkyne coordination step (**C→D** and **C→D′**). With the overall energy surface taken into consideration, the carbopalladation pathway with alkyne insertion via the transition state **E-TS** was found to be the highest point on the calculated energy surface, 38.0 (26.3) kcal/mol. As far as hydropalladation is concerned, alkyne insertion proceeds more easily through **E′-TS** with a calculated energy of 24.2 (13.3) kcal/mol. A pronounced difference in the energies of **E′-TS** and **E-TS** provides doubtless support in favor of the hydropalladation mechanism.

In order to verify the generality of these findings, computation of carbopalladation and hydropalladation alkyne insertion steps for 1-hexyne was also performed,[17] which revealed exactly the same trend as in the case of phenylacetylene (*vide supra*). Therefore, a clear kinetic preference for an alkyne insertion into the Pd−H bond over the Pd−C bond was found for both aryl and alkyl acetylenes.

In conclusion, we have developed a general and highly regio- and stereoselective method for the palladium-catalyzed head-to-head dimerization reaction of terminal alkynes toward 1,4-enynes. This methodology is general for a variety of terminal acetylenes possessing various functional groups such as aryl, heteroaryl, alkyl, hydroxyl, propargyl ether, and amino groups. DFT calculations revealed that the reaction proceeds via a hydropalladation pathway.

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Supporting Information Available. Detailed experimental procedures, characterization data for all new compounds, details of computational procedure, optimized structures, and calculated energy and geometry parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.