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Reactivity Switch Enabled by Counterion: Highly Chemoselective Dimerization and Hydration of Terminal Alkynes

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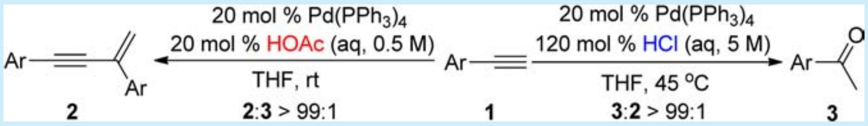
Supporting Information



ABSTRACT: A counterion-controlled reactivity tuning in Pd-catalyzed highly chemoselective and regioselective dimerization and hydration of terminal alkynes is reported. The use of acetate as counterion favors the formation of an alkenyl alkynyl palladium intermediate which forms hitherto less reported 1,3-diaryl-substituted conjugated enynes after reductive elimination. Using chloride, which is a better leaving group, leads to anion exchange on the alkenylpalladium intermediate with hydroxide which after reductive elimination and tautomerization delivered the hydration products.

Alkynes, one of the most important classes of organic compounds, have been extensively used as important building blocks and versatile synthons in organic synthesis.[1] The reactions of alkynes are of considerable interest and provide various synthetic methods for many important products such as enynes, ketones, diynes, alkynols, metal acetylides, and arene derivatives, etc.[2] Among these important applications, dimerization[3−6] and hydration[7−11] are practical and atom-economical methods for the synthesis of conjugated enynes and ketones, which are basic reactions in alkyne chemistry. Much progress has been achieved in dimerization of terminal alkynes.[3] Trost disclosed the first Pd(II)-catalyzed head-to-tail dimerization of terminal acetylenes in 1987.[5a,b] Since then, many efficient applications of this neutral dimerization method in cascade transformations have been developed.[2d,5f] Very recently, Guo and Han et al. reported the Pd(0)-catalyzed dimerization of terminal alkynes in the presence of a catalytic amount of Brønsted acid, which presented a powerful tool to access 1,3-disubstituted enynes.[6d] On the other hand, hydration of alkynes to form carbonyl compounds is one of the most useful and important functional group transformations.[7] Over the past several decades, numerous catalysts have been proven to be effective for this reaction.[8−11] The mechanism has been well studied and is generally classified into a Lewis acid or Brønsted acid catalyzed mechanism.[8,9] To our knowledge, alkyne hydration involving a new catalytic metal hydride mechanism has not been documented. Herein, we report our recent observation on highly chemoselective dimerization and hydration of terminal alkynes tuned by the counterions on the palladium catalyst, which provides a new protocol for the synthesis of 1,3-diarylenynes or aryl methyl ketones, respectively.

This study commenced with the dimerization of 4-methoxyphenylacetylene **1a** under conditions A (3 mol % of $Pd(PPh_3)_4$, 20 mol % of HOAc (aq, 0.5 M), THF, and rt), affording 77% isolated yield of 2,4-bis(4-methoxyphenyl)but-1-en-3-yne **2a** as the single product (entry 1, Table 1) (vide infra) (for detailed information of the optimization, see the Supporting Information). Neither 1,4-diarylenyne isomer nor hydration byproduct was observed from ^1H NMR analysis of the crude reaction mixture.

To obtain more insight into the mechanism of this dimerization reaction, 4-methoxyphenylboronic acid **4** was added under conditions A to trap some key intermediates. After the reaction was completed, 69% of **2a** together with 2% of 1,1-bis(4-methoxyphenyl)ethene **5** were formed (Scheme S1, Supporting Information).

On the basis of this result and consistent with previous mechanistic proposals,[5a,6d,12−14] a plausible mechanism for this dimerization reaction is proposed (Scheme 1). $Pd(PPh_3)_2$ formed through the disassociation of two PPh_3 ligands from $Pd(PPh_3)_4$ reacted with HOAc via oxidative addition to form palladium hydride intermediate **A**.[6d,12] The following hydropalladation of alkyne yielded alkenylpalladium intermediate **B**.[5a,6d,13] This could be strongly supported by the formation of the coupling product **5** which could be well rationalized as a result of transmetalation of **4** with intermediate **B** and subsequent reductive elimination.[13] Intermediate **B** further reacted with another molecule of alkyne to form intermediate **TS**. With the association of the acetate group, deprotonation of the terminal alkyne took place to generate intermediate **C**.[6d,14]

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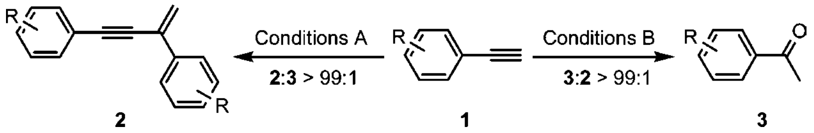
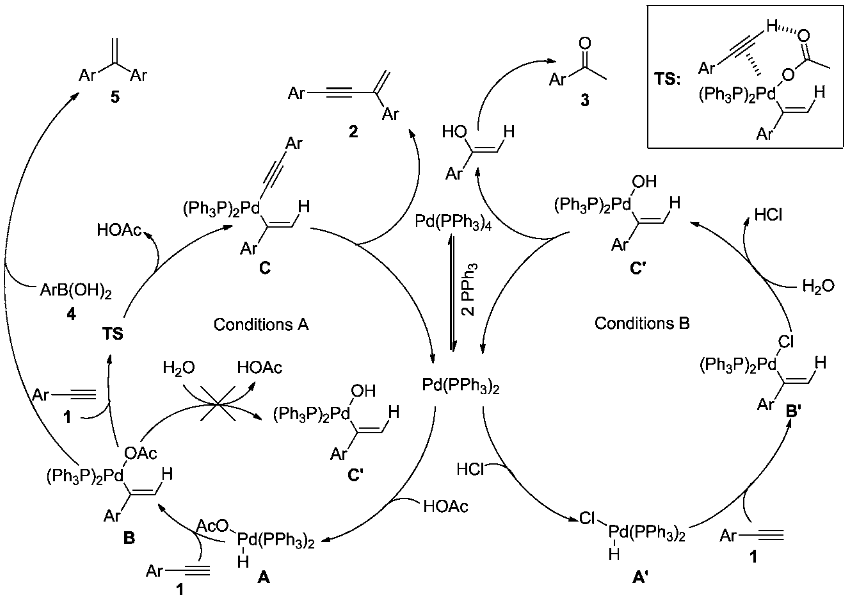
Table 1. Pd-Catalyzed Dimerization and Hydration of Terminal Alkynes



			conditions A[a,b]			conditions B[c,d]		
entry	1	R	time (h)	2	yield (%)	time (h)	3	yield (%)
1	**1a**	4-MeO	24	**2a**	77	24	**3a**	85
2	**1b**	3-MeO	24	**2b**	69	194	**3b**	45
3	**1c**	2-MeO	23	**2c**	89	168	**3c**	15 (65)[e]
4	**1d**	2,6-diMeO	26	**2d**	62	168	**3d**	10 (33)[e]
5	**1e**	2-MeO-5-Me	17	**2e**	77	168	**3e**	29 (19)[e]
6	**1f**	4-EtO	25	**2f**	72	32	**3f**	86
7	**1g**	4-Bu^{n}O	24	**2g**	87	55	**3g**	82
8	**1h**	4-BnO	23	**2h**	63	48	**3h**	80
9	**1i**	4-AcO	24	**2i**	63	26	**3i**	42
10	**1j**	4-NH$_2$	8	**2j**	f,g	0.5	**3j**	70
11	**1k**	2-PhCONH	6	**2k**	60[f]	60	**3k**	90[h]
12	**1l**	4-Me	12	**2l**	81	120	**3l**	56
13	**1m**	3-Me	10	**2m**	76	168	**3m**	30
14	**1n**	2-Me	11	**2n**	88	168	**3n**	29
15	**1o**	4-Et	11	**2o**	72	144	**3o**	63
16	**1p**	4-Bu^t	12	**2p**	63	192	**3p**	61
17	**1q**	4-Pentyl^n	12	**2q**	71	172	**3q**	70
18	**1r**	H	11	**2r**	70	178	**3r**	35
19	**1s**	4-F	29	**2s**	57	163	**3s**	38
20	**1t**	4-CN	10	**2t**	complicated	144	**3t**	NR (85)[e]
21	**1u**	4-Ac	12	**2u**	complicated	192	**3u**	NR (69)[e]

[a] The reaction was carried out using **1** (0.2 mmol), 3 mol % of $Pd(PPh_3)_4$, 20 mol % of HOAc (aq, 0.5 M), and THF (3 mL) at rt under argon atmosphere. [b] **2**:**3** > 99:1 and 1,3-diarylenynes/1,4-diarylenynes >99:1, based on ^{1}H NMR analysis of the crude reaction mixture. [c] The reaction was carried out using **1** (0.2–0.4 mmol), 20 mol % of $Pd(PPh_3)_4$, 120 mol % of HCl (aq, 5 M), and THF (3 mL) at 45 °C under argon atmosphere. [d] **3**/**2** > 99:1 and no arylacetaldehydes were formed, based on ^{1}H NMR analysis of the crude reaction mixture. [e] Recovery yield of **1**. [f] 10 mol % of $Pd(PPh_3)_4$ was applied. [g] **2j** decomposed quickly. [h] 250 mol % of HCl (aq, 5 M) was applied.

Scheme 1. Proposed Mechanism



Final reductive elimination produced 1,3-diarylenyne **2** and regenerated the catalytically active $Pd(PPh_3)_2$. Then it was speculated that if the counterion AcO^- on **B** was replaced by other anions with higher leaving ability, the resulting intermediate **B**′ might be susceptible to nucleophilic attack by water molecule to afford intermediate **C**′ which would undergo reductive elimination and rapid tautomerization to produce ketone **3** (Scheme 1).

To test this hypothesis, HCl was used instead of HOAc, since Cl^-, as a low coordinating anion,[11] is much easier to leave under the attack of H_2O. To our delight, after optimization, the hydration of **1a** under conditions B (20 mol % of $Pd(PPh_3)_4$, 120 mol % of HCl (aq, 5 M), THF, and 45 °C) afforded 85% isolated yield of 1-(4-methoxyphenyl)ethanone **3a** as the sole product (entry 1, Table 1) (vide infra) (for detailed information of the optimization, see the Supporting Information). Neither aldehyde isomer nor dimerization byproduct was observed from ^1H NMR analysis of the crude reaction mixture.

To gain more information of the mechanism of this hydration reaction, **4** was applied under conditions B to trap possible key intermediates. After full conversion, 2% of **5** was isolated together with 75% of **3a** (Scheme S2, Supporting Information). The formation of **5** indicated that intermediate **B′** might be involved in the reaction pathway.

To probe the possibility that the hydration reaction could be catalyzed by the in situ formed palladium(II) intermediate HPdCl which potentially acted as a normal Lewis acid, the comparatively more Lewis acidic catalyst $PdCl_2$ was tested under the optimized reaction conditions. Either with or without HCl, the reactions catalyzed by $PdCl_2$ led to complicated mixtures, with only a trace amount of the hydration product formed (Scheme S3, Supporting Information). These results disfavor a Lewis acid catalyzed mechanism and indicate that the palladium hydride mechanism is more plausible.

With the standard conditions in hands, we next investigated the scope of the dimerization and hydration with a variety of terminal alkynes (Table 1).

In the study of dimerization under conditions A, we first explored the electronic effect of substituents on the phenyl ring. Alkynes bearing an electron-donating group, such as alkoxy, acetoxy, benzamido, and alkyl (entries 1−9 and 11−17, Table 1), were easily converted to the desired 1,3-diarylenynes exclusively in good yields. Reactions of phenylacetylene **1r** (entry 18, Table 1) and alkyne possessing a weak electron-withdrawing group, like 4-fluorine atom, **1s** (entry 19, Table 1), also gave satisfactory results. The desired products **2r** and **2s** were formed in 70% and 57% isolated yields, respectively. However, reactions of alkynes with strong electron-withdrawing groups, such as 4-cyano and 4-acetyl (entries 20 and 21, Table 1), only resulted in complicated reaction mixtures. These results indicated that the electron effect played a key role in this reaction. We then studied the effect of the relative position of the substituents on the phenyl ring. Reactions of alkynes with either a methoxy or methyl group introduced to the 4-, 3-, or 2-position of phenyl ring (entries 1−3 and 12−14, Table 1) proceeded smoothly to give the corresponding products in similar yields, which suggested that the relative position of substituents on the phenyl ring had little influence on this reaction. Further studies with **1d** (entry 4, Table 1) led to the formation of **2d** in an isolated yield of 62%, which demonstrated that highly sterically hindered substrate was also tolerated in this reaction.

Next, hydration under conditions B was examined. Similar to conditions A, a strong electronic effect on the phenyl ring was observed. When alkynes are substituted with electron-donating groups, such as 4-alkoxy, 4-acetoxy, 4-amino, 2-benzamido, and 4-alkyl (entries 1, 6−12, and 15−17, Table 1), the corresponding ketones were formed in good yields. Reactions of alkynes with hydrogen or fluorine atom attached on the phenyl ring (entries 18 and 19, Table 1) gave the hydration products in low yields. Reactions of alkynes with a strong electron-withdrawing group, such as 4-cyano and 4-acetyl (entries 20 and 21, Table 1), did not proceed at all. Then we checked the position effect of substituents on the phenyl ring of alkynes. Different from dimerization reaction, the relative position of substituents showed great influence on this hydration reaction. The hydration of alkynes bearing a methoxy or methyl group at the 4-, 3-, or 2-position of phenyl ring afforded ketones in 85%, 45%, and 15% isolated yields (entries 1−3, Table 1), respectively. Similar results were also observed in the reactions of 4-, 3-, or 2-methyl-substituted arylacetylenes (entries 12−14, Table 1). Next, the steric effect was investigated. The reaction of **1d** (entry 4, Table 1) proceeded slowly to generate **3d** in a very low yield of 10%, which demonstrated that steric hindrance retarded this transformation. Finally, the reactivity of internal alkynes, like 1,2-diphenylethyne and prop-1-yn-1-ylbenzene, was studied. The desired hydration was not observed (Scheme S4, Supporting Information).

Notably, in all these reactions, excellent chemoselectivity and regioselectivity were observed from ^1H NMR analysis of the crude reaction mixture. Although the yields were low in some cases, no other byproducts were formed.

The reactivity of alkyl-substituted alkynes, like hex-1-yne **6**, was also explored toward both transformations. The dimerization of **6** gave only 31% isolated yield of 7-methyleneundec-5-yne **7**. The hydration of **6** did not take place at all (Scheme S5, Supporting Information).

In conclusion, we have developed a counterion-controlled reactivity shift between dimerization and hydration of terminal alkynes. This work features the employment of Pd(0) catalyst combined with Brønsted acid, with a neat tuning of reactivity between dimerization and hydration, as compared to the commonly used Pd(II) catalytic system. The employment of chloride as counterion promotes hydration of alkynes to ketones via an unprecedented mechanism involving a metal hydride intermediate. The reactivity tuning enabled by the counterion is expected to enrich the understanding of palladium chemistry and help guide studies in other systems. Further detailed mechanistic and synthesis studies are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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