

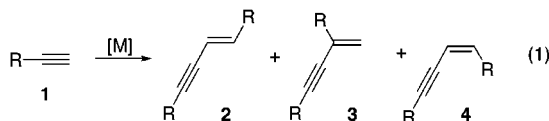
Can Agostic Interaction Affect Regiochemistry of Carbopalladation? Reverse Regioselectivity in the Palladium-Catalyzed Dimerization of Aryl Acetylenes

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Dimerization of terminal alkynes is a very practical and straightforward approach to conjugated enynes - important building blocks for synthetic organic chemistry and key units found in a variety of biologically active compounds.^{1,2} A number of transition metal complexes effectively catalyze alkyne dimerization;³ however, in most cases a mixture of regio- and stereoisomeric enynes **2–4** is obtained (eq 1). The factors that affect



regio- and stereoselectivity depend mainly on the electronic effects and steric hindrance at the alkyne substituent and the coordination sphere of the metal. Although a powerful method for selective construction of head-to-tail enynes **3** in the presence of the Pd(OAc)₂-TDMPP (TDMPP = P[(2,6-OMe)₂C₆H₃]₃) system has been developed by Trost,⁴ precedents on Pd-catalyzed head-to-head dimerization of terminal alkynes are limited to the terminal silyl acetylenes^{4,5} and nonselective dimerization of phenylacetylene.⁶ Herein we wish to report an unusual, highly regio- and stereoselective head-to-head dimerization of terminal aryl acetylenes **1** (R = Ar) in the presence of a palladium catalyst to give E-enynes **2**.

In the course of our investigation of sequential trimerization reaction⁷ we found that the Pd(PPh₃)₄ and Pd₂dba₃·CHCl₃/(*o*-Tol)₃P (dba = dibenzylideneacetone) systems efficiently catalyze head-to-tail dimerization of terminal acetylenes to produce enynes **3**. Surprisingly, we discovered that the Pd₂dba₃·CHCl₃/TDMPP combination not only produced the head-to-tail enyne **3a** (R = Ph), but also an unexpected regioisomeric head-to-head enyne **2a**. The best head-to-head selectivity was achieved with 1:5 Pd/P ratio.⁸ However, other alkynes tested reacted in a less selective fashion.

(1) See, for example: (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Nicolaou, K. C.; Dai, W. M.; Tsay, S. C.; Estevez, V. A.; Wrasidlo, W. *Science* **1992**, *256*, 1172.

(2) Hubner, H.; Haubmann, C.; Utz, W.; Gmeiner, P. *J. Med. Chem.* **2000**, *43*, 756.

(3) For most recent reviews on Ru-catalyzed dimerization, see: (a) Trost, B. M.; Toste, D.; Pinkerton, A. *Chem. Rev.* **2001**, *101*, 2067. (b) Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311. On other transition metals, see: (c) (M = Y) Duchateau, R.; van Wee, C. T.; Teuben, J. H. *Organometallics* **1996**, *15*, 2291. (d) (M = Co, Rh) Field, L. D.; Ward, A. J.; Turner, P. *Aust. J. Chem.* **1999**, *52*, 1085. (e) (M = Ir) Ohmura, T.; Yorozuya, S.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2000**, *19*, 365. (f) (M = Ti) Akita, M.; Yasuda, H.; Nakamura, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 480.

(4) Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Ruhter, G. *J. Am. Chem. Soc.* **1997**, *119*, 698.

(5) Ishikawa, M.; Ohshita, J.; Ito, Y.; Minato, A. *J. Organomet. Chem.* **1988**, *346*, C58.

(6) Herrmann, W.; Bohm, V.; Gstottmayr, C.; Grosche, M.; Reisinger, C.-P.; Weskamp, T. *J. Organomet. Chem.* **2001**, *617–618*, 616.

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Table 1. Palladium-Catalyzed Head-to-Head Dimerization of Terminal Aryl Acetylenes^a

	R		time, h	yield of 2 , % ^b
1	Ph	1a	2	70
2	4-MeC ₆ H ₄	1b	4	86
3	4-MeOC ₆ H ₄	1c	3	57
4	4-NCC ₆ H ₄	1d	1.5	91
5	4-F ₃ CC ₆ H ₄	1e	2	93
6	1-naphthyl	1f	16	80
7	2-naphthyl	1g	1.5	79
8	9-anthryl	1h	24 ^c	13 ^d
9	<i>n</i> -nonyl	1i	20	3 ^{e,f}

^a [(π -allyl)PdCl]₂ 5 mol %, TDMPP 10 mol %, Et₂NH 1 equiv, rt, THF (1 M). ^b Isolated yield unless specified otherwise. ^c Reaction was carried out at 60 °C. ^d 13% of head-to-tail product was also formed. ^e NMR yield. ^f 20% of head-to-tail product was also formed, 30% of starting material left.

Further optimization indicated that [(π -allyl)PdCl]₂ efficiently catalyzed formation of the head-to-head dimers.⁹ It was also found that only electron-rich, bulky, hemi-labile ligands such as TDMPP¹⁰ gave exclusively the head-to-head product **2a**, whereas use of other phosphines resulted in a dramatic drop of both product regioselectivity and yield.¹¹ Assuming excess TDMPP was necessary for maintaining high basicity of the reaction media, a number of amines as additives were tested. Indeed, the addition of 1 equiv of Et₂NH to the [(π -allyl)PdCl]₂/TDMPP mixture allowed for the reduction of the phosphine ligand amount down to 8–10 mol % (to maintain the Pd:P ratio of 1:1), and shortened the reaction time to 2 h. Finally, these optimized conditions were tested for the dimerization reaction of different terminal alkynes (Table 1).

It was found that most arylacetylenes tested smoothly underwent the dimerization reaction to produce the head-to-head dimers in good to very high yield (Table 1, entries 1–7). It is worth noting that in all the above cases no other regio- or stereoisomeric products were detected by GC/MS and NMR analyses of the crude reaction mixtures. 9-Anthryl alkyne **1h** reacted much more sluggishly and unselectively (entry 8). Finally, aliphatic alkyne **1i** did not produce the corresponding head-to-head dimer **2i** at all (entry 9).¹² Analysis of the results summarized in the Table 1 revealed that both good yields and high selectivity were observed only for the dimerization of aryl alkynes possessing ortho hydrogen atoms.¹³ To test this proposal, a series of differently ortho-substituted aryl alkynes **1j–n** have been synthesized and examined in the dimerization reaction (eq 2, Table 2). We found

(8) It was a rather surprising finding, since it was demonstrated on the Pd(II)–TDMPP series (Kurosawa, H.; Tsuboi, A.; Kawasaki, Y.; Wada, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3563) and supported by our experiments on Pd₂dba₃·CHCl₃/TDMPP system, that one Pd atom can accommodate no more than one TDMPP ligand at a time. See Supporting Information for details.

(9) [(π -allyl)PdCl]₂/TDMPP combination used in a ratio of 1:5 (Pd:P) gave head-to-head dimer **2a** exclusively in 93% NMR yield after stirring overnight at room temperature.

(10) It is well-documented that TDMPP can serve as bidentate ligand with hemilabile metal–O bond. See: Ma, J.-F.; Kojima, Y.; Yamamoto, Y. *J. Organomet. Chem.* **2000**, *616*, 149.

(11) Employment of monodentate PCy₃, which is almost as basic as TDMPP, resulted in no reaction. On the other hand, use of the more basic, hemilabile P[(2,4,6-OMe)₃C₆H₂]₃ gave the same result as the reaction with TDMPP. For the discussion on basicity of the phosphines, see: Wang, D.; Angelici, R. *Inorg. Chem.* **1996**, *35*, 1321.

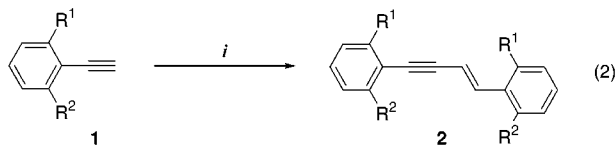
(12) Analogously, attempts to dimerize non-aryl alkynes with functionalized side chain under above-mentioned conditions resulted in total decomposition of the reaction mixtures.

(13) It occurred to us that possible interaction between the metal center and the ortho H of the aryl ring at some stage of the reaction may be responsible for the observed reversal of the regiochemistry of dimerization. For stabilization of transition metal complexes caused by agostic coordination of *o*-C–H bond to a metal center see, for example: Crabtree, R. H. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 789.

Table 2. Palladium-Catalyzed Dimerization of Differently Ortho-Substituted Phenylacetylenes

	R ¹	R ²		time, h	yield of 2, % ^a
1	H	H	1a	2	70 ^b
2	Me	H	1j	48	50 ^{c,d}
3	Me	Me	1k	36	NR ^e
4	F	H	1l	2	71
5	F	F	1m	24	NR ^e
6	OMe	OMe	1n	24	NR ^e

^a Isolated yield. ^b Result from the Table 1. ^c NMR yield. ^d 17% of head-to-tail product was also formed. ^e Formation of traces of isomeric dimerization products were observed by GC/MS analyses.



that the introduction of one methyl group (**1j**) substantially diminished the efficiency of the head-to-head dimerization reaction (entry 2), whereas substitution of both ortho hydrogen atoms with a methyl group completely inhibited this process (entry 3). In contrast to its methyl analogue, α -fluorophenylacetylene **1l** easily underwent the dimerization affording the enyne **2l** (entry 4) with an efficiency similar to that observed for phenyl-acetylene (entry 1). As expected, α,α' -difluoroarylalkyne **1m** did not undergo dimerization at all (entry 5).¹⁴ Dimethoxy derivative **1n** did not undergo dimerization reaction either (entry 6). It became obvious that indeed, at least one ortho hydrogen in the molecule of aryl acetylene is needed for a selective head-to-head dimerization reaction.

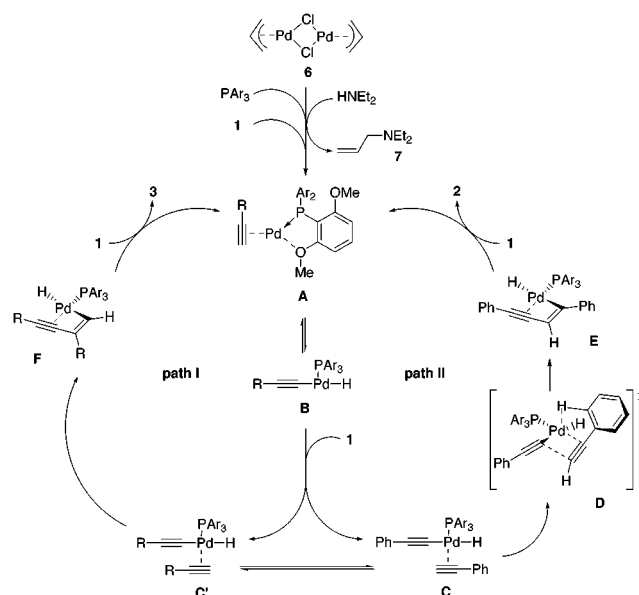
Taking into account the experimental evidence discussed above, we suggest the following rationale for the mechanism of this unusual transformation (Scheme 1). Initially, Pd(II) species **6** is transformed into the catalytically active complex **A**. This step is accomplished by reduction of **6** with diethylamine producing allylamine **7** as a byproduct.¹⁵ Palladium(0) species **A** is stabilized by TDMPP as an electron-rich chelating ligand and aryl acetylene as a π -acceptor.¹⁶ Subsequent reversible¹⁷ oxidative addition of the aryl acetylene provides a σ -complex **B**. Coordination of another molecule of **1** with **B** produces complexes **C** and **C'** in which η^2 -coordinated alkyne is differently oriented toward the σ -alkynyl palladium moiety. For the following carbopalladation step, potentially, there are two regiochemistry-determining pathways, **I** and **II**. Dimerization of alkynes **1h** and **1i** (Table 1, entries 8, 9) partly proceeds via path **I**, a Markovnikov-type addition, which is controlled by electronic factors and results in the formation of the vinylpalladium species **F** leading to the head-to-tail dimer **3**.^{4,7} On the other hand, aryl alkynes possessing ortho hydrogen atoms undergo carbopalladation via path **II**, producing the σ -complex **E** which affords the head-to-head product **2**. We propose that transition state **D** is responsible for path **II**. Although such a transition state should be electronically less favorable, the contribution of an agostic interaction of the metal center with the o -C–H bonds would decrease the energy barrier for the

(14) A control experiment with **1m** under the head-to-tail dimerization conditions described in the ref 4 proceeded smoothly affording a head-to-tail dimer **3m** in good yield.

(15) Formation of allyldiethylamine was detected by GC/MS and NMR analyses of reaction mixtures. For detailed mechanism of this known transformation, see: (a) Bricout, H.; Carpentier, J.-F.; Montreux, A. *Tetrahedron* **1998**, *54*, 1073. (b) Canovese, L.; Visentin, F.; Uguagliati, P.; Chessa, G.; Lucchini, V.; Bandoli, G. *Inorg. Chim. Acta* **1998**, *275*–276, 385.

(16) (a) For examples of analogous stabilization of Pd–TDMPP complex with alkenes, see 15b. (b) The formation of some 1:1:1 Pd–TDMPP-arylalkyne complex was observed by low-temperature NMR experiments. See Supporting Information for details.

(17) Reversibility of the transformation **A** to **B** was supported by observed rapid H/D scrambling between series of protio- and deuterio-phenylacetylenes and diethylamine. See Supporting Information for details.

Scheme 1

reaction making this pathway possible for aromatic substrates possessing ortho hydrogen atoms.¹⁸ Kinetic isotope effect studies that may provide additional support for the involvement of agostic interaction in the stabilization of the transition state were performed.¹⁹ The substantial value of the isotope effect obtained, $k_H/k_D = 3.0 \pm 0.1$, supports the above proposal.²⁰ The observed median k_H/k_D value indicates that the reaction may or may not proceed through the reversible insertion of the metal into the o -C–H bond of aryl alkyne.²¹ However, our test experiments with phenyl-*d*₅-acetylene and **1a** demonstrated that H/D exchange at the ortho position of aryl acetylenes does not occur during the reaction, which would be unavoidable in the case if the reversible insertion of metal into the o -C–H(D) bond takes place. Although at this stage it is not entirely clear why the 1:1 Pd–TDMPP complex should be particularly effective for the agostic interaction with the o -C–H bond, we believe that the proposed mechanistic rationale reasonably explains the unusual head-to-head regiochemistry observed in the dimerization of aryl alkynes.

In conclusion, a novel, highly regio- and stereoselective head-to-head dimerization of aryl alkynes catalyzed by Pd(0) complexes was found. It was proposed that an agostic interaction between the transition metal and ortho protons of the aromatic ring in the substrate is responsible for the observed unusual anti-Markovnikov regioselectivity of the reaction. To the best of our knowledge, there are no precedents on agostic interactions in the transition state that affect the regiochemistry of the carbopalladation process.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(18) Heteroatoms at the ortho position could have also stabilized a complex of type **D** via donation of a lone pair of electrons to the palladium center. However, as it is obvious from the Table 2 (entry 6), it is not the case.

(19) Deuterium kinetic isotope effect was calculated as a ratio of k_H/k_D , where k_H and k_D are observed rate constants measured for the reactions of phenylacetylene and phenyl-*d*₅-acetylene, respectively (See Supporting Information for details).

(20) For the precedents of a substantial deuterium kinetic isotope effect caused by agostic interaction ($k_H/k_D = 2.30$ –2.55) in the Zr-catalyzed α -olefin polymerization, see: Krauledat, H.; Brintzinger, H.-H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1412.

(21) Yagyu, T.; Aizawa, S.; Funahashi, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 619.