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Palladium-Catalyzed Synthesis of Heteroarene-Fused Cyclooctatetraenes via Dehydrogenative Cyclodimerization

Keita Fukuzumi,^[a] Yuji Nishii,*^[b] and Masahiro Miura*^[a]

Abstract: Arene-fused cyclooctatetraenes (COTs) possess unique structural and electronic properties originated from their saddle-shaped π -conjugated architectures. Considerable attention has been paid for the transition-metal-mediated synthesis of these cyclic compounds; however, limited achievements have been represented to date in the efficient construction of heteroarene-fused COTs. In this contribution, we report a novel Pd-catalyzed dehydrogenative cyclodimerization of biheteroarenes via four-fold C–H activation toward the synthesis of a series of heteroarene-fused COTs. A set of mechanistic examinations indicated the involvement of high-valent Pd species prior to the dimerization event in the catalytic cycle. The redox behavior of the obtained COTs is also described briefly.

Tetraphenylene and related arene-fused cyclooctatetraenes (COTs) have saddle-shaped three-dimensional architectures where the four arene rings are alternately oriented upward and downward.^[1] Although tetraphenylene itself is an achiral molecule due to its D_{2d} symmetry, an installation of appropriate substituents or a replacement of the benzene rings by heteroaromatics will break the symmetry, providing versatile chiral π -conjugated scaffolds. In another perspective, a structural change of the central COT moiety into a planar form can be triggered in response to redox stimuli because of the aromaticity in the corresponding oxidized 6π dication or reduced 10π dianion.^[2] Such a flexible redox behavior is one of the significant characteristics of COTs, particularly, those constructed by five-membered heteroaromatics where the tubto-plane interconversion of the saddle-shaped skeleton is sufficiently facilitated.^[3] Additionally, an antiaromatic character can be invoked if the COT core is planarized by an additional annulation while maintaining its neutral 8π system.^[4] Owing to the unique structural and electronic properties, there exist potential applications in various fields including asymmetric synthesis^[5] and supramolecular chemistry.^[1,6]

As a conventional synthetic method for these arene-fused COTs, the transition-metal-mediated homocoupling of a 2,2'-dihalo-1,1'- biphenyl-derived Grignard reagent, organolithium, or organozinc has been widely used (Scheme 1a).^[7] Such a reaction, however, often gives a complicated mixture of oligomers, and the desired product is obtained in low to moderate yields. Recently, the Pd-

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catalyzed cyclodimerization of biphenyl derivatives based on Suzuki-Miyaura coupling^[8] and Ullman-type coupling^[9] (Scheme 1b and 1c) has emerged as an effective tool for preparing tetraphenylenes. Shi et al.^[10] and Zhang et al.^[11] independently developed a novel reaction system involving the catalytic C–H functionalization^[12] of 2-iodo-1,1'-biphenyl derivatives (Scheme 1d). It is noteworthy that biphenylene can be catalytically converted into tetraphenylene, while the synthetic utility of this reaction is limited by the narrow structural diversity of biphenylene derivatives.^[13] Furthermore, an elegant study on the Rh-catalyzed enantioselective [2+2+2] cycloaddition of triynes was reported by Shibata and coworkers.^[14]





Scheme 1. Conventional synthetic methods for tetraphenylene derivatives.

Despite the significant research interest in this field, limited achievements^[15] have been represented to date in the efficient construction of heteroarene-fused COTs besides those relevant to Scheme 1a.^[16] In this context, we focused our attention on the dehydrogenative coupling strategy due to the simplicity of starting materials,^[17] and we herein describe a Pd-catalyzed construction of thiophene-fused COT frameworks through the dehydrogenative cyclodimerization of 3,3'-bithiophenes. The protocol is applicable to various heteroarene-fused COTs (vide infra).^[18] A set of mechanistic examinations suggested the involvement of palladacycle intermediates as well as high-valent Pd species in the catalytic cycle.

Firstly, we examined the oxidative cyclodimerization of 5,5'diphenyl-3,3'-bithiophene (**1a**) as a representative substrate using 10 mol% of a Pd(OAc)₂ catalyst in combination with a stoichiometric oxidant and an additive (Table 1). The corresponding coupling product **2a** was obtained in 63% yield in the presence of Ag₂CO₃ and PhCO₂H (entry 1). Sodium benzoate as the additive gave a comparable product yield to the parent benzoic acid (entry 2), indicating that these additives acted as carboxylate sources in the present catalytic system.

This is consistent with the fact that AgOPiv prompted the catalytic turnover without any additive, whereas no coupling product was formed by using Ag_2CO_3 alone (entries 3 and 4). Consequently, we examined several oxidants and the highest yield was achieved with the combination of AgOPiv and PhCO₂H (entries 5–7). Exclusion of any oxidant resulted in a minimal yield of the desired product (entry 8).

Table 1: Optimization study for Pd-catalyzed cyclodimerization of 1a. [a]

Ph	S Pd(OAc) oxidant (additive (2 (10 mol%) 1.0 equiv.) (50 mol%)	S Ph
	toluene,	120 °C, 16 h Ph S	S Ph
entry	oxidant	additive	yield ^[b]
1	Ag ₂ CO ₃	PhCO ₂ H	63%
2	Ag ₂ CO ₃	PhCO ₂ Na	60%
3	AgOPiv (2.0 equiv.)		53%
4	Ag ₂ CO ₃		n.d.
5	AgOAc (2.0 equiv.)	PhCO ₂ H	49%
6	AgOPiv (2.0 equiv.)	PhCO ₂ H	78%
7	Cu(OAc) ₂ •H ₂ O	PhCO ₂ H	15%
8		PhCO ₂ H	trace

[a] Reaction conditions: **1a** (0.1 mmol), Pd(OAc)₂ (0.01 mmol), oxidant, and additive (0.05 mmol) in toluene was heated at 120 °C for 16 h.
[b] Isolated yield.

Under the optimized conditions, we examined the substrate scope with respect to the substituent on the C5 and C5' positions (Table 2). Aryl-substituted bithiophenes 1b-d reacted smoothly to furnish the desired cyclodimers in good yields 5,5'-Dimethyl-3,3'-bithiophene (1e) gave a (entries 1–3). somewhat lower yield, and in this case a significant amount of oligomers was detected in MS analyses (entry 4). Ester and amide functionalities were tolerated in the catalytic system (entries 5 and 6). Exclusion of the C5 and C5' substituents resulted in the formation of a complicated mixture of oligomers, and no desired product was obtained (entry 7). Bibenzo[b]thiophene derivatives were not applicable (not shown). The cyclodimerization protocol could be extended to other heteroarenes including furan, thiazole, and oxazole to give the corresponding products 4, 6,^[3b] and 8, respectively (Scheme 2), further optimization studies to improve the catalytic while turnover for these heterocycles are needed.

The cyclic voltammogram of **2a** in MeCN/*o*-dichlorobenzene (1:10) exhibited reversible two oxidation waves at $E_{1/2} = +0.60$ V and +0.90 V (vs. Fc/Fc+),^[19] and the other COTs **4**, **6**, **8** showed quasi-reversible two-electron oxidation waves. These flexible redox behaviors can be attributed to their dynamic conformational change, where the tub-to-plane interconversion occurs upon the redox cycles. The HOMO energy levels

obtained from the first oxidation waves reasonably corresponded with the computational values. $\ensuremath{^{[20]}}$

Table 2: Pd-catalyzed cyclodimerization of 3,3'-bithiophenes.^[a]



[a] Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), AgOPiv (0.2 mmol), and $PhCO_2H$ (0.05 mmol) in toluene was heated at 120 °C for 16 h. [b] Isolated yield.



Scheme 2. Cyclodimerization using other heteroaromatics.



Notably, an unsymmetrical biheteroaryl **9** was converted into the corresponding COT **10** as a single regioisomer and no thiophene-furan linkage was formed (eq. 1). The structure was confirmed by X-ray diffraction measurement and a smaller dihedral angle between two furan rings (42.62°) compared to that between two thiophenes (50.45°) is consistent with the connectivity (Figure 1).^[21] In a similar manner, a thiophene-

thiazole cyclodimer **12** was obtained (eq. 2).^[21] Construction of these "composite" arene-fused COTs has been difficult with conventional methods, demonstrating the utility of the present dehydrogenative coupling protocol.



Figure 1. Molecular structure of **10** (left) and **12** (right) with 50% thermal probability. Hydrogen atoms and solvent molecules are omitted for clarity.

To shed light on the reaction mechanism, a number of controlled experiments were conducted. A linear thiophene tetramer **13**, which is a possible intermediate supposed that the cyclodimerization proceeds through the independent two-fold dehydrogenative coupling, was treated under the standard conditions (eq. 3). Interestingly, a negligible amount of the cyclized product **2a** was formed and an inseparable mixture of oligomers was obtained. This result clearly ruled out the intermediacy of **13** in the catalytic cycle and prompted us to perform further mechanistic examinations.



It should be cited that a series of transition-metal-catalyzed transformation reactions of biphenylene into tetraphenylene were found to involve the corresponding metallacycle complexes as the key intermediates. Eisch et al. described the dimerization of Ni(PEt₃)₂(2,2'-biphenyl) to form a dinuclear Ni(I)-Ni(I) complex, and its thermal decomposition resulted in the rapid formation of tetraphenylene along with metallic nickel.^[13b] Thereafter, a transient species bearing formal Ni(III)-Ni(I) valencies was reported by Johnson and coworkers.[13f] For the platinum catalysis, Jones et al. successfully characterized a ninemembered complex Pt(PEt₃)₂(2,2'-tetraphenyl) which was probably formed via reductive elimination from the parent Pt(IV) complex Pt(PEt₃)₂(2,2'-biphenyl)₂.^[13d,22] It was proposed that similar reaction mechanisms could be drawn for the related Pdcatalyzed tetraphenylene formation, while a limited experimental evidence was provided.

Accordingly, we prepared a palladium complex 14 by treating with 2,2'-dilithio-3,3'-bithiophene PdCl₂(dcpe) (dcpe bis(dicyclohexylphosphino)ethane),[23] and potential its intermediacy for the present catalytic system was examined (Scheme 3). The complex was remained intact after heating at 80 °C in toluene and no dimerization of the bithiophene fragment was detected. Addition of benzoic acid or Ag₂CO₃ did not resulted in the formation of any dimers. In sharp contrast, cyclodimer 2a was isolated in 7 % yield along with 13 when the complex was heated at 80 °C in the presence of AgOPiv. At 120 °C, formation of the liner dimer 13 was suppressed and 2a was obtained in 43% yield.^[24] These results indicate that high-valent palladium species^[25] are involved in the reaction mechanism and carboxylate sources are essential not only for the C–H activation but also in the dimerization stage. Furthermore, the isolation of **13** implies the intermediacy of a nine-membered palladacycle complex, which is similar to Pt(PEt₃)₂(2,2'-tetraphenyl).^[13d,22]



Scheme 3. Reaction of complex 14 in the presence of AgOPiv.



Scheme 4. A proposed reaction mechanism for the Pd-catalyzed cyclodimerization of bithiophenes.



Scheme 5. KIE measurement for the Pd-catalyzed cyclodimerization.

On the basis of these observations, a plausible reaction mechanism for the catalytic cyclodimerization is illustrated in Scheme 4. Bithiophene 1 is reacted with the catalytically active Pd(II) species and converted into the corresponding fivemembered complex **A** via two-fold C–H activation. This complex is then oxidized by the Ag(I) salt added into a high-valent Pd complex **B**. While the exact mechanism of this oxidation step remains unclear, the indispensability of a carboxylate anion suggests the involvement of a carboxylate-bridged Pd(III) dinuclear species^[26] prior to the formation of the Pd(IV) intermediate.^[27] To gain insight into the nuclearity of Pd, a kinetic study was carried out. A reaction order of 1.12 with respect to Pd(OAc)₂ was obtained and, additionally, a primary kinetic isotope effect (KIE: $k_{\rm H}/k_{\rm D} = 2.96$) was observed between two separate reactions using **1a** and **1a**–*d*₂ (Scheme 5). These

results suggest that the initial formation of **A** is a turnoverlimiting step. Reductive elimination affords a nine-membered complex **C** and then liberate the cyclodimer **2**. In certain instances, acyclic products will be given through protonation of the intermediate **C**. The catalytic cycle is completed by the reoxidation of thus formed Pd(0) species into Pd(II). The observed high regioselectivity for the formation of thiophenefuran cyclodimer **10** as well as thiophene-thiazole cyclodimer **12** might be attributed to the conformation of Pd(IV) intermediate that corresponds to **B**; preliminary DFT calculations for the complex similar to **B** exhibited the lowest energy content when the two furan subunits occupy the trans positions^[20] that might interrupt the thiophen-furan bond formation.

In summary, we have developed a Pd-catalyzed dehydrogenative cyclodimerization of biheteroaryls for the facile construction of heteroarene-fused COT derivatives. The obtained cyclic tetramers show flexible redox behaviors that can be attributed to their conformational changes. Controlled experiments using the palladacycle complex **14** clearly support the intermediacy of high-valent Pd species in the catalytic cycle.

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Keywords: palladium • dehydrogenative coupling • metallacycle • cyclooctatetraene • thiophene

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A Pd-catalyzed construction of thiophene-fused COT frameworks through dehydrogenative cyclodimerization of 3,3'-bithiophenes (X = S, Y = CH) has been developed. The protocol is applicable to various heteroaromatics, achieving the facile synthesis of "composite" arene-fused COTs. Mechanistic study indicates the involvement of palladacycle intermediates as well as high-valent Pd species in the catalytic cycle.

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