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Thermal and Palladium-Catalyzed [3 + 2] Synthesis of Cyclopentadienone Acetals from Cyclopropenone Acetals and Acetylenes

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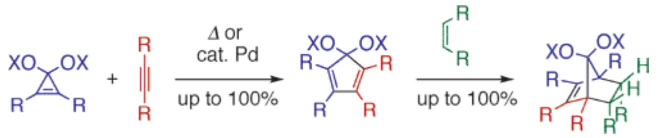
ABSTRACT



Substituted cyclopentadienone acetals (CPDAs) were synthesized by a thermal or palladium-catalyzed [3 + 2] cycloaddition reaction of a substituted cyclopropenone acetal to an electron-deficient acetylene. The synthesis afforded di-, tri-, and tetrasubstituted CPDAs of considerable structural varieties that undergo Diels–Alder reaction to produce bicyclo[2.2.1]heptenes.

The chemistry of cyclopentadienone and its acetal (CPDA) has seen its revival in recent years through development of useful applications in the synthesis of functional polycyclic compounds.[1,2] The range of these applications, however, remains rather limited due to the small variety of available derivatives.[3,4] We report here the synthesis of substituted CPDAs (**E** in Scheme 1) by thermal or palladium-catalyzed [3 + 2] cycloaddition of a substituted cyclopropenone acetal (CPA, **A**)[5−7] to an electron-deficient acetylene (**D**). The synthesis afforded di-, tri-, and tetrasubstituted CPDAs of considerable structural variety previously not available. The utilities of the new CPDAs are illustrated with their Diels−Alder reaction and a formal [2 + 2 + 2] construction of a substituted benzene.

Thermolysis of the CPA (**A**) results in reversible cleavage of the C−C σ-bonds[5] to generate an equilibrating mixture of dipoles **B** and **C** (Scheme 1, route a)[8] that might undergo [3 + 2] cycloaddition to an acetylene to give a CPDA, but the reaction of an unsubstituted CPA **1** with a disubstituted acetylene does not give the desired cycloadduct.[5] To the contrary, we found that thermal or Pd-catalyzed [3 + 2] cycloaddition of substituted derivatives (**2**−**9**) gives a variety of the cycloadducts (**E**; Figure 1, yields of thermal reaction in italic and Pd-catalyzed reaction in bold).[9]

The thermal reaction is described first. It is moderate-yielding but quite general, taking place with excellent

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[†] PRESTO, Japan Science and Technology Agency.

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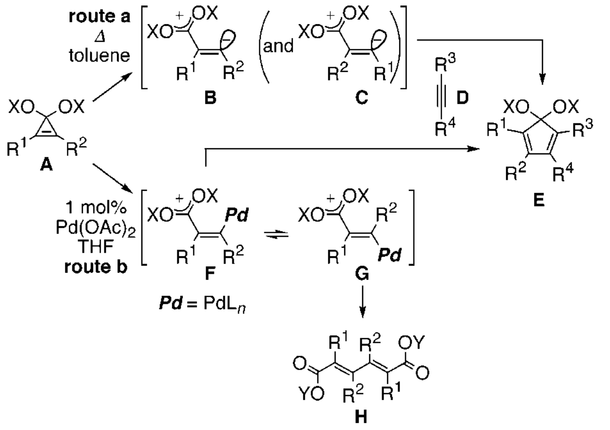
Scheme 1. [3 + 2] Synthesis of Cyclopentadienone Acetal[a]



[a] **A**: $R^1 = R^2 = H$ (**1**); R^1 = Et, R^2 = H (**2**); R^1 = Ph, R^2 = H (**3**); R^1 = 1-naphthyl, R^2 = H (**4**); R^1 = Ph, $R^2 = CO_2$*i*-Pr (**5**); $R^1 = 4\text{-}MeOC_6H_4$, R^2 = H (**6**); $R^1 = 4\text{-}ClC_6H_4$, R^2 = H (**7**); R^1 = 1-hydroxycyclohexyl, R^2 = H (**8**); $R^1 = SiMe_3$, R^2 = H (**9**). **D**: $R^3 = SO_2CF_3$, R^4 = Ph (**10**); $R^3 = R^4 = CO_2Me$ (**11**); $R^3 = CO_2Me$, R^4 = H (**12**); R^3 = Ph, $R^4 = CO_2Me$ (**13**). X,X = $-CH_2C(CH_3)_2CH_2-$, Y = $CH_2C(CH_3)_2CH_2OH$.

regioselectivity. For instance, ethyl-CPA **2** reacts with ethynyl sulfone **10** via **B** to afford the [3 + 2] cycloadduct **14a** in 67% yield, and Ph-CPA **3** reacts with dimethyl acetylenedicarboxylate (**11**) also via **B** in 40% yield. Interestingly, the product selectivity entirely reverses in the reaction of 1-naphthyl-CPA **4**, where the reaction took place via the regioisomer **C**. The disubstituted CPA **5** preferentially generates **B**, wherein the vinyl anion is stabilized by the ester group,[8] and regioselectively gives the tetrasubstituted CPDA **14d** in 40% yield. The observed regioselectivity conforms to our previous mechanistic proposal that there is a mobile equilibrium between **B** and **C** via CPA.[8] The yields of the thermal reactions are generally moderate. Nonetheless, the results indicated that the substituted CPDAs are easy to handle and therefore synthetically useful.

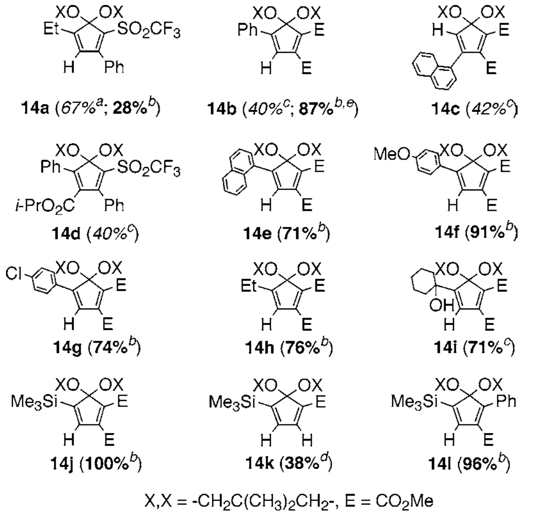


Figure 1. CPDAs obtained by thermal and Pd-catalyzed [3 + 2] cycloaddition. Yields of the thermal reaction are shown in italic and those of the $Pd(OAc)_2$-catalyzed reaction (catalyst load: 1 mol %) in bold. See Supporting Information for details. Stoichiometry of the reactants: [a]1.2 equiv of CPA; [b]2.0 equiv of CPA; [c]1.0 equiv of CPA; [d]2.0 equiv of **12**. [e]Compound **15** (**H**: R^1 = Ph, R^2 = H) was isolated as a side product in 22% yield.

Encouraged by this finding, we investigated transition metal catalysis seeking milder reaction conditions (Scheme 1, route b). We examined a number of transition metal complexes for the reaction of **11** with 1 equiv of **3** in toluene. We found that $Pd(OAc)_2$ (generally 1 mol %) is the best catalyst, allowing the reaction to proceed at room temperature. For instance, the reaction gave **14b** in 44, 29, and 4% in the presence of $Pd(OAc)_2$, $Pd_2(dba)_3$, and $Pd(PPh_3)_4$, respectively (all with 5 mol % catalyst loading).[10,11]

We obtained here some interesting pieces of information relevant to the reaction mechanism: Freshly recrystallized $Pd(OAc)_2$ is the reagent of choice, and its activity diminishes in the presence of a phosphine, suggesting that the phosphine ligand and a reactant competitively bind to the Pd vacant site. The use of THF instead of a nonpolar solvent such as toluene improves the product yield from 36 to 62%.[12] The material balance of the acetylene **11** was generally over 90%, and dimerization of CPA into (*E*,*E*)-diene **H** was the major side reaction (several % to ca. 20% based on CPA). The use of 2 equiv of CPA therefore gives a much improved product yield (e.g., from 62 to 87%).

The formation of the dimer exclusively in the (*E*,*E*)-geometry (e.g., **15**; **H**: R^1 = Ph, R^2 = H) provides a mechanistic hint. Transition metal-mediated ring opening of a cyclopropene generates a metal complex of a vinyl carbene,[5,11,13,14] but, in the case of the electron-rich CPA, the ring opening generates a vinylmetal (**F** and **G** in Scheme 1) that is, in fact, a resonance isomer of the corresponding carbene complex.[15] As previously shown for Ag(I)- or Cu(I)-mediated ring opening of substituted CPAs,[15] the vinylmetal may be produced first in the form of **F** but then slowly isomerize to **G** (likely in slow equilibrium with each other depending on the substituent). We therefore suggest (Scheme 1) that the (*Z*)-vinylpalladium(II) **F** undergoes irreversible [3 + 2] cycloaddition to the acetylene to give the CPDA **E**, while the (*E*)-vinylpalladium **G** competitively dimerizes by

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(9) Being similar to the thermal reaction of an unsubstituted CPA (ref 5), the thermal equimolar reaction of a substituted CPA **9** with methyl propionate afforded the product of C−H carbene insertion to the acetylenic C−H bond (30%) in addition to a small amount of the [3 + 2] cycloadduct (6%). The Pd-catalyzed reaction, on the other hand, afforded exclusively the [3 + 2] cycloadduct (vide infra).

(10) Reaction in the presence of metal complexes such as $Mn(CO)_6$, $Fe_3(CO)_{12}$, $Co_2(CO)_8$, $Ni(cod)_2$, $ZrCp_2Cl_2$, $Mo(CO)_6$, $Ru_3(CO)_{12}$, $W(CO)_6$, and $IrCl(CO)(PPh_3)_2$ gave none or very little of the desired product.

(11) Binger, P.; Biedenbach, B. *Chem. Ber.* **1991**, *124*, 2165−2170.

(12) Note that the yield of the Pd-catalyzed reaction is better than that of the thermal reaction (62 vs 40%; comparison made by using equimolar amounts of **3** and **11**).

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reacting with another molecule of CPA to give the (*E*,*E*)-dimer.[16]

The Pd-catalyzed [3 + 2] cycloaddition afforded a variety of CPDAs as shown in Figure 1 (yields in bold).[17] The catalyzed reaction is generally higher-yielding than the thermal reaction, while they are sometimes complementary; for instance, the sulfone product **14a** and the tetrasubstituted CPDA **14d** can be synthesized only by or in much better yield by the thermal route. In contrast to the thermal reaction, the 1-naphthyl-CPA reacted with the same regioselectivity as that of other compounds (**14e** vs others such as **14a**,**b**,**f**). The reaction conditions are mild enough to tolerate the presence of free hydroxy, halogen, and silyl groups and likely a variety of other functional groups. Electron-deficient acetylenes of reasonably wide structural varieties serve as acceptors of the cycloaddition. The reaction of methyl propiolate gave a 1,4-disubstituted CPDA (**14k**) as a thermally stable compound.[9] Interestingly, the regioselectivity of the reaction of methyl phenylpropiolate reversed to give CPDA **14l** in 96%.[18]

Among various possible applications of the densely functionalized cyclopentadienes thus synthesized, one is a Diels−Alder reaction with an olefin. The new CPDA derivatives are thermally stable enough not to undergo Diels−Alder dimerization,[2,4] but they undergo clean Diels−Alder reaction with activated and unactivated olefins to give bicyclo[2.2.1]heptenes (Figure 2). Thus, the CPDA **14b** reacts with maleic anhydride and acrylonitrile to give the hindered cycloadducts **16** and **17** in quantitative yield. It also reacts with atmospheric pressure ethylene, norbornadiene, and ethyl vinyl ether to give **18**−**20**, respectively, in excellent yield. Notably, furan also takes part in the Diels−Alder reaction as a dienophile.[19]

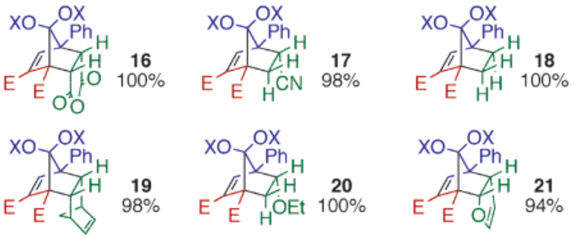
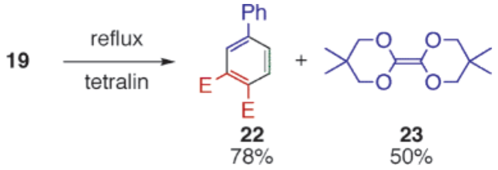


Figure 2. Bicyclo[2.2.1]heptenes obtained by Diels−Alder reaction of CPDA **14b** with olefins. Origins of the moieties are shown in colors: CPA in blue, acetylene in red, and dienophile in green. **16** resulted from maleic anhydride, **17** from acrylonitrile, **18** from ethylene, **19** from norbornadiene, **20** from ethyl vinyl ether, and **21** from furan.

An interesting application of the [3 + 2] cycloadduct is its conversion to a substituted benzene through thermolytic removal of a dialkoxycarbene moiety from the bicyclo[2.2.1] skeleton (the carbene moiety was identified as tetraalkoxyethylene **23**) (Scheme 2). Thermolysis of the norbornadiene adduct **19** in refluxing tetralin gave the substituted biphenyl **22** in 78% yield. As shown by color coding, this benzene synthesis formally comprises a [2 + 2 + 2] assembly of the aromatic ring from three components.

Scheme 2. Conversion of Diels−Alder Adduct **19** to a Substituted Benzene **22**



In summary, we found that substituted CPAs undergo [3 + 2] cycloaddition to electron-deficient acetylenes to give a variety of new substituted CPDAs. As viewed from the perspective of the metal-catalyzed ring-cleavage/cycloaddition reactions of cyclopropenes, the present reaction provides a unique example of a [3 + 2] reaction rather than a [1 + 2] cycloaddition reaction leading to three-membered rings that has been the only reaction type thus far observed.[6,13,14]

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(16) Dimerization reaction of CPA needs an oxidant, which remains unidentified. Given the facts that the dimer forms much in excess of the amount of the Pd(II) catalyst and that CPDA **14j** was obtained, under a nitrogen atmosphere, in 100% yield based on the acetylene, it is likely that the excess CPA acted as the oxidant.

(17) Under $Pd(OAc)_2$-catalyzed conditions, unsubstituted CPA **1** did not give the corresponding CPDA and instead underwent [2 + 2] dimerization [ref 5].

(18) This regioselectivity is inconsistent with the simple mechanism that **F** initially undergoes conjugate addition to the electron-deficient acetylene.

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