to increase the miscibility of these substances in the culture broth without inhibiting production of paraherquamide A. Feeding experiments were performed on *P. fellutanum* (ATCC20841) with all four potential precursors, followed by isolation and purification of paraherquamide A. Within the limits of detection by ^{13}C NMR spectroscopy and mass spectrometry no incorporation was observed for VM55599 ((±)-**13**) or its oxidized counterpart (±)-**14**. In addition, no incorporation was observed for the diketopiperazine (±)-**16**. However, for the C-14 epimer of VM55599 ((±)-**15**), significant incorporation was observed by ^{13}C NMR spectroscopy at C-12 and C-18 of paraherquamide A. From analysis of the electrospray mass spectrum, incorporation was determined to be 0.72% for the intact doubly labeled material.[11] ^{13}C-Monolabeled paraherquamide A, from catabolism of (±)-**15**, was not detected in the mass spectrum. The implications of these observations are considerable.

Since the diketopiperazine (±)-**16** was not incorporated, this raises interesting questions concerning the timing of the reduction of the prolyl-derived carbonyl group. The incorporation of compound (±)-**15** in significant isotopic yield, indicates that the formation of the bicyclo[2.2.2]diazaoctane occurs at the stage with the nonoxidized tryptophyl moiety (that is, the indolyl group). This mandates that oxidations of the indole ring to form both the catechol-derived dioxepin and spirooxindole occur *after* the formation of this intermediate. It thus follows that the dioxepin-derived isoprenylation and the *S*-adenosylmethionine-mediated *N*-methylation reactions occur late in the pathway. These results also cast considerable doubt on the intermediacy of VM55599[6] and its oxidized precursor **14** in the paraherquamide biosynthesis and provide additional circumstantial evidence that VM55599 is a minor shunt metabolite. Finally, the present work documents the intermediacy of an advanced metabolite **15**, which contains the core structural elements of the paraherquamide framework, prior to a series of oxygenation reactions. Efforts to elucidate the exact sequence of biosynthetic reactions immediately preceding and following the formation of **15** are currently under way in these laboratories.

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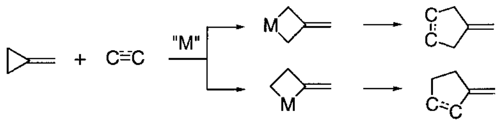
Novel [3+2] Cycloaddition of Alkylidenecyclopropanes with Aldehydes Catalyzed by Palladium

Itaru Nakamura, Byoung Ho Oh, Shinichi Saito, and Yoshinori Yamamoto*

A metal-catalyzed cycloaddition between methylenecyclopropane and a carbon–carbon multiple bond can proceed through two different reaction pathways to give regioisomeric [3+2] carbocycles (Scheme 1).[1–3] The research groups of



Scheme 1. Metal-catalyzed cycloaddition of methylenecyclopropane and a carbon–carbon multiple bond.

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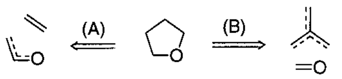
Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

Noyori, Binger, and Trost studied primarily the intermolecular [3+2] cycloaddition,[2] and more recently the research groups of Nakamura, Motherwell, and Lautens investigated the intramolecular version of the carbocycle formation.[3] However, to the best of our knowledge, there has been no report of the [3+2] cycloaddition between methylenecyclopropane and the carbon–oxygen double bond of aldehydes.[4]

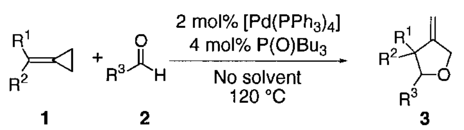
The synthesis of cyclic ethers by means of transition metal catalyzed [3+2] cycloadditions falls into two categories (Scheme 2). Type A: vinylic oxiranes are used as a “two-carbon and one-oxygen component” in the palladium-catalyzed cycloaddition with olefins to give 2-vinyltetrahydrofuran derivatives.[5] The catalytic cycloaddition of metal carbenoids with olefins also falls into this class.[6] Type B: the reaction of trimethylenemethane (TMM) precursors, which are thought to be “three-carbon components”, with carbonyl compounds in the presence of palladium catalysts gives 3-methylenetetrahydrofurans.[7]

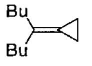
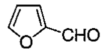
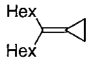
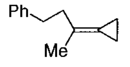
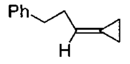
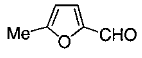
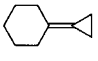
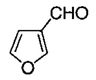
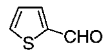
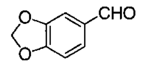
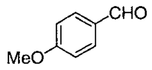


Scheme 2. Construction of tetrahydrofuran rings by transition metal catalyzed [3+2] cycloaddition.

We now report that the reaction of methylenecyclopropanes **1** with aldehydes **2** in the presence of 2 mol% of [Pd(PPh$_3$)$_4$] and 4 mol% of tributylphosphane oxide at 120 °C gives the corresponding [3+2] cycloadducts, the five-membered cyclic ethers **3**, in good to acceptable yields (Table 1).

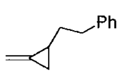
Table 1. Palladium-catalyzed cycloaddition of alkylidenecyclopropanes **1** with aldehydes **2**.[a]



Entry	1	2	Time [h]	3	Yield [%][b]
1	 **1a**	 **2a**	5	**3a**	75
2	 **1b**	**2a**	11	**3b**	71
3	 **1c**	**2a**	16	**3c**	86 (53:47)[c]
4	 **1d**	**2a**	20	**3d**	42 (54:46)[c]
5	**1a**	 **2b**	6	**3e**	65
6[d]	 **1e**	**2b**	20	**3f**	77
7	**1a**	 **2c**	12	**3g**	51
8	**1a**	 **2d**	19	**3h**	64
9	**1a**	 **2e**	19	**3i**	43
10[d]	**1a**	 **2f**	32	**3j**	38

[a] The reaction of **1** (0.5 mmol) with **2** (1.5 mmol) was carried out in the presence of 2 mol% of [Pd(PPh$_3$)$_4$] and 4 mol% of tributylphosphane oxide without solvent at 120 °C. [b] Isolated yield based on **1**. [c] The diasteromeric ratio of **3**. [d] Compound **1** (1 mmol) was treated with **2** (0.5 mmol), and the yield is based on **2**.

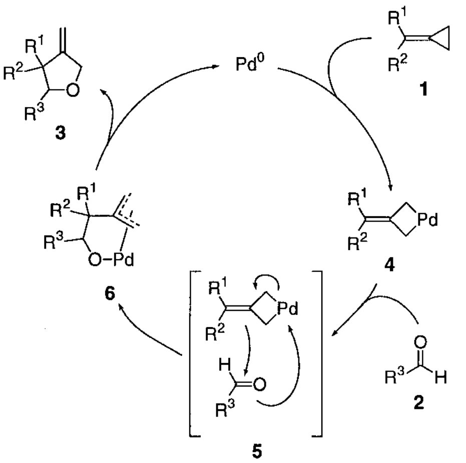
The reaction of 1-butylpentylidenecyclopropane **1a** (0.5 mmol) with furfural **2a** (1.5 mmol) in the presence of catalytic amounts of [Pd(PPh$_3$)$_4$] (2 mol%) and tributylphosphane oxide (4 mol%) but in the absence of solvent at 120 °C for 5 h gave the corresponding cycloadduct **3a** in 75% yield (Table 1, entry 1). The reaction of **1a** with **2a** did not proceed at all without the palladium catalyst. The use of [Pd(dba)$_2$]/PPh$_3$ (dba = *trans,trans*-dibenzylideneacetone) as a catalyst was less effective for producing **3a**, while [Pd$_2$(dba)$_3$] · CHCl$_3$, Pd(OAc)$_2$, allylpalladium chloride dimer, and [Pt(PPh$_3$)$_4$] were totally ineffective as catalysts. The reaction of **1a** with **2a** using traditional phosphane ligands, such as PPh$_3$, PBu$_3$, and P(OPh)$_3$, was slower than the reaction with P(O)Bu$_3$ and gave **3a** in lower yield. The use of THF as the solvent in the reaction of **1a** and **2a** gave **3a** in lower yield (36%). The reaction of 1-hexylheptylidenecyclopropane (**1b**), 1-methyl-3-phenylpropylidenecyclopropane (**1c**), and 3-phenylpropylidenecyclopropane (**1d**) with **2a** afforded **3b**, **3c**, and **3d** in yields of 71, 86, and 43%, respectively (Table 1, entries 2–4). The reaction of **1a** with 5-methylfurfural (**2b**) proceeded smoothly and the corresponding cycloadduct **3e** was produced in 65% yield (Table 1, entry 5). The spiro compound **3f** was obtained in 77% yield from the reaction of **2b** and two equivalents of cyclohexylidenecyclopropane (**1e**; Table 1, entry 6). The reactions of **1a** with 3-furaldehyde (**2c**) and with 2-thiophenecarbaldehyde (**2d**) produced **3g** and **3h** in yields of 51 and 64%, respectively (Table 1, entries 7 and 8). Benzaldehyde derivatives **2e** and **2f** bearing electron-donating groups gave the corresponding 2-aryl-4-methylenetetrahydrofuran derivatives **3i** and **3j** in modest yields (Table 1, entries 9 and 10) when treated with **1a**. The reaction of **2a** with methylenecyclopropane **1f**, which has a substituent on the ring, did not afford any cycloadducts at all.



1f

A plausible mechanism is illustrated in Scheme 3. Oxidative addition of palladium(0) to a distal bond of the alkylidenecyclopropane **1** leads to the palladacyclobutane complex **4**.[8] The pallada-enetype reaction of **4** with the aldehyde **2** may proceed as shown in **5**, to give the π-allylpalladium complex **6**.[9] Reductive elimination of palladium(0) then gives the [3+2] cycloadduct **3**.

The thermal [3+2] cycloaddition reactions of methylenecyclopropanone ketals with aldehydes[10] and imines[11] were reported recently. However, these reactions require the use of highly activated methyelenecyclopropanone derivatives.



Scheme 3. A plausible mechanism for the palladium-catalyzed [3+2] cycloaddition of alkylidenecyclopropanes **1** with aldehydes **2**.

In conclusion, we are now in a position to synthesize various types of *exo*-methylene–tetrahydrofuran derivatives through the palladium-catalyzed [3+2] cycloaddition between methylenecyclopropanes and aldehydes. The present atom-economical reaction may be potentially useful for constructing biologically important tetrahydrofuran skeletons.

Experimental Section

3a: Compounds **2a** (1.5 mmol) and **1a** (0.5 mmol) were added to a mixture of [Pd(PPh$_3$)$_4$] (11.5 mg, 0.01 mmol) and tributylphosphane oxide (4.4 mg, 0.02 mmol) under argon in a pressure vial. The reaction mixture was heated at 120 °C for 5 h, and then filtered through a silica-gel column using ethyl acetate as an eluent. The product was isolated by passing it through a silica-gel column, and purified by medium-pressure liquid column chromatography (silica gel) to afford the cycloadduct **3a**. IR (neat): $\tilde{\nu} = 2957-2870$, 1663, 1468, 1379, 1148, 1053, 1011, 980, 885, 733 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz): $\delta = 0.79$ (t, $J = 7.5$ Hz, 3H), 0.89–1.33 (m, 12H), 1.45 (td, $J = 13.8$, 4.0 Hz, 1H), 1.58 (t, $J = 8.5$ Hz, 2H), 4.45 (td, $J = 13.0$, 2.5 Hz, 1H), 4.60 (td, $J = 13.5$, 2.5 Hz, 1H), 4.78–4.79 (m, 2H), 5.02 (t, $J = 2.0$ Hz, 1H), 6.22 (d, $J = 3.5$ Hz, 1H), 6.32 (dd, $J = 3.2$, 2.0 Hz, 1H), 7.35 (dd, $J = 2.0$, 1.0 Hz, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): $\delta = 13.86$, 14.00, 23.28, 23.33, 25.78, 26.06, 32.52, 34.40, 51.79, 71.06, 82.82, 103.97, 107.61, 110.00, 141.56, 152.95, 153.45; HR-MS (EI): calcd for $C_{17}H_{26}O_2$: $[M]^+$ 262.1932, found 262.1932.

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[9] It is thought that **4** is a σ-allylpalladium species and may react as a pallada-ene.

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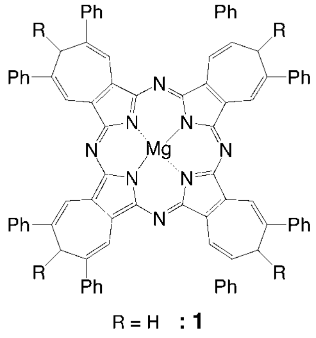
A Seven-Membered Carbon-Ring-Fused Phthalocyanine Analogue in which the π System Changes during Dehydrogenation/Hydrogenation Cycles**

Nagao Kobayashi,* Taro Nonomura, and Katsunori Nakai

Phthalocyanines (Pcs) have been the subject of intensive study in a variety of academic and commercial fields. For example, they have industrial applications as dyes and pigments, photoconducting reagents in photocopiers, catalysts for removing sulfur from crude oil, deodorants, in the photodynamic therapy of cancer, and as germicides.[1] However, Pc analogues which contain seven-membered carbon rings instead of benzene rings have so far not been reported.[2] Herein we report the first example of this kind of Pc analogue, namely, compound **1**. This compound contains four fused cycloheptatriene (CHT) rings on the periphery of the parent tetraazaporphyrin skeleton. Cycloheptatriene is well known for being able to convert between nonaromatic CHT and the aromatic tropylium cation through a redox reaction during the elimination/recombination of a hydride ion (H$^-$).[3] Accordingly, we considered that it might be possible to adjust the size of the π-conjugation system in **1** by dehydrogenation/hydrogenation of the CHT



R = H : **1**
R = Ph : **2**

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