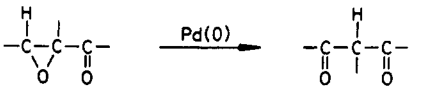
Palladium(0)-Catalyzed Reaction of α,β-Epoxy Ketones Leading to β-Diketones

Sir:

β-Diketones are an important class of compounds in view of the distinct structural properties and high synthetic utility, particularly as building blocks for the elaboration of polycarbocyclic frameworks and heterocyclic nuclei. The preparation has been effected usually by condensation reactions of carbonyl compounds under such strongly basic or acidic conditions that cause serious side reactions.[1] Disclosed herein is a straightforward entry achievable under entirely neutral and aprotic conditions.

The method consists simply of heating of α,β-epoxy ketones[2] at 80–140 °C in toluene containing catalytic amounts of tetrakis(triphenylphosphine)palladium(0) and 1,2-bis(diphenylphosphino)ethane (dpe) (eq 1). The typical experimental



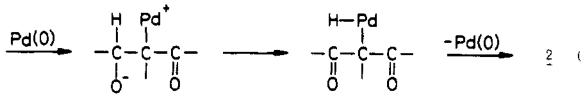
$$\underbrace{-\overset{H}{\overset{|}{C}}-\overset{|}{C}-}_{O}\underset{\underset{O}{\|}}{C}- \xrightarrow{Pd(0)} -\underset{\underset{O}{\|}}{C}-\overset{H}{\underset{|}{\overset{|}{C}}}-\underset{\underset{O}{\|}}{C}- \qquad (1)$$

1 **2**

procedure is exemplified by the synthesis of 2-methyl-3,5-hexanedione from 2-methyl-3,4-epoxy-5-hexanone. A mixture of the epoxy ketone (5.66 g, 44 mmol), $Pd(PPh_3)_4$ (767 mg, 0.66 mmol), and dpe (266 mg, 0.67 mmol) in degassed toluene (15 mL) was placed in a sealed glass tube and heated at 140 °C for 60 h under argon atmosphere. The reaction mixture was subjected to column chromatography on silica gel (50 g) using hexane (100 mL) and then ether (250 mL) as eluant. The combined ether fractions were concentrated and distilled in vacuo to give the desired β-diketone (4.53 g, 80% yield) as an oil, bp 82–84 °C (50 mmHg).

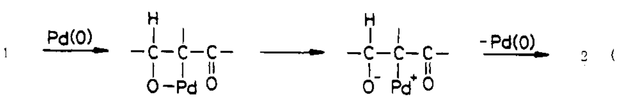
Some examples of the Pd-catalyzed transformation are given in Table I. In most cases, addition of the bidentate auxiliary ligand, dpe, was necessary to obtain reasonable reaction rate and to avoid metal precipitation so that the Pd(0) catalyst gives a high turnover.[4] Epoxy ketones possessing an α-alkyl group react only sluggishly (entry 11). Strained epoxides appear to undergo the isomerization facilely. Particularly noteworthy is the efficient synthesis of 1,3-cyclopentanedione (a prized compound[5]) from readily accessible 2,3-epoxycyclopentanone (entry 10).

Two mechanisms, outlined in eq 2 and 3, may be considered for the Pd(0)-catalyzed reaction of epoxy ketones. One is a mechanism involving back-side displacement of an epoxy ring by Pd(0) catalyst[6,7] (either in a classical nucleophilic manner or via an electron-transfer process) (eq 2). The zwitterionic



$$\xrightarrow{Pd(0)} -\overset{H}{\underset{\underset{O^-}{|}}{\overset{|}{C}}}-\overset{Pd^+}{\underset{|}{\overset{|}{C}}}-\underset{\underset{O}{\|}}{C}- \longrightarrow -\underset{\underset{O}{\|}}{C}-\overset{H-Pd}{\underset{|}{\overset{|}{C}}}-\underset{\underset{O}{\|}}{C}- \xrightarrow{-Pd(0)} \mathbf{2} \qquad (2)$$

3 4

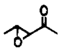
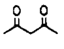
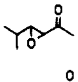
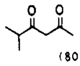
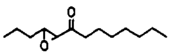
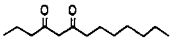
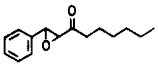
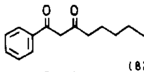
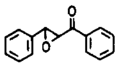
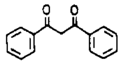
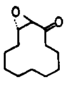
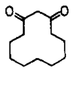
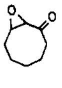
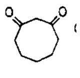
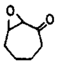
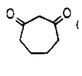
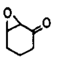
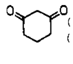
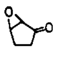
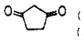
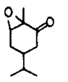
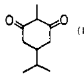


$$\mathbf{1} \xrightarrow{Pd(0)} -\overset{H}{\underset{\underset{O-}{|}}{\overset{|}{C}}}\!-\!\overset{|}{\underset{\underset{Pd}{|}}{C}}-\underset{\underset{O}{\|}}{C}- \longrightarrow -\overset{H}{\underset{\underset{O^-}{|}}{\overset{|}{C}}}-\overset{|}{\underset{\underset{Pd^+}{|}}{C}}-\underset{\underset{O}{\|}}{C}- \xrightarrow{-Pd(0)} \mathbf{2} \qquad (3)$$

5 6

intermediate **3** thus formed could isomerize to the Pd(II) hydride **4**,[6c] which in turn undergoes reductive elimination to afford β-diketone **2** and Pd(0) catalyst.[8,9] The other is the front-side, oxidative addition mechanism (eq 3). Reaction of a C–O bond and the zerovalent metal may generate a palladaoxetane structure **5**. Possible heterolytic rupture of the O–Pd bond, producing the zwitterion **6**, and subsequent 1,2-hydride migration accompanying regeneration of Pd(0) species would give β-diketone **2**.

Table I. Palladium(0)-Catalyzed Reaction of α,β-Epoxy Ketones[a]

		conditions				
entry	epoxy ketone	$Pd(PPh_3)_4$ mol %	dpe[b] mol %	temp °C	time h	product (% yield[c])
1		3.0 2.9	3.0 0	140 140	1.1 1.1	 (81[d])[e] (11[d])
2		1.5	1.5	140	60	 (80)[f,g]
3		5.2	5.2	140	90	 (90)[h]
4		5.0	5.0	140	1.7	 (82)[h]
5		5.0	5.0	120	30	 (84)[e]
6		9.6 12.0	9.6 0	140 140	97 100	 (54)[f,i] (7)
7		5.0	4.9	140	96	 (52)[f,i]
8		4.1	3.9	100	20	 (60)[f,j]
9		3.2 2.4	3.2 0	80 80	24[k] 24	 (62)[e] (30)
10		3.3 3.9	3.3 0	80 80	2.5 7[k]	 (94)[e] (89)
11		10.1	10.1	140	66	 (18)[h]

[a] Unless otherwise stated, reaction was carried out in toluene under argon atmosphere. [b] 1,2-Bis(diphenylphosphino)ethane. [c] Isolated yield (silica gel chromatography or distillation). [d] Determined by GLC analysis. [e] Spectral properties were compared with those of commercial sample. [f] Spectral data were identical with reported ones or those of authentic specimen. [g] Conrad, M.; Gast, R. *Ber.* **1898,** *31,* 1339. [h] A new compound which gave consistent NMR and IR characteristics and correct elemental analysis. [i] Reference 1e. [j] Eistert, B.; Haupter, F.; Schank, K. *Justus Liebigs Ann. Chem.* **1963,** *665,* 55. [k] Two-phase reaction in toluene-water (50:50 v/v).

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Supplementary Material Available: Spectral and analytical data for the new compounds (1 page). Ordering information is given on any current masthead page.

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(2) α,β-Epoxy ketones are accessible under neutral conditions by epoxidation of allylic alcohols followed by oxidation of the hydroxyl group: Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136. Pfitzner, K. E.; Moffatt, J. G. *Ibid.* **1965**, *87*, 5661. For the synthesis from α,β-unsaturated ketones by basic hydrogen peroxide oxidation, see Lewis, S. N. "Oxidation", Augustine, R. L., Ed.; Marcel Dekker: New York, 1969; Vol. 1, Chapter 5.

(3) Coulson, D. R. *Inorg. Syn.* **1972**, *13*, 121. The complex should be purified before use by recrystallization from a 3:1 THF–ether mixture at 0 °C.

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(4) The ligand effect was examined in detail in the reaction of 3,4-epoxy-2-pentanone. Other multidentate phosphine ligands, such as bis(diphenylphosphino)propane, (+)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (diop), or bis(2-diphenylphosphinoethyl)phenylphosphine (a tridentate ligand), worked much less effectively. In the presence of such ligands, metal precipitation was avoided, but consumption of the starting material was slow. Unidentate ligands, $P(C_6H_5)_3$, $P(C_6H_5)_2CH_3$, $P(CH_3)_2C_6H_5$, $P(n\text{-}C_4H_9)_3$, etc., did not give any satisfactory results either. See also entries 1, 6, 9, and 10 in Table I.

(5) Lick, C.; Schank, K. *Chem. Ber.* **1978,** *111,* 2461, and references cited therein.

(6) (a) Trost, B. M. *Tetrahedron,* **1977,** *33,* 2615. (b) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977,** *10,* 434. (c) Suzuki, M.; Oda, Y.; Noyori, R. *J. Am. Chem. Soc.* **1979,** *101,* 1623, and references cited therein.

(7) The α position of α,β-epoxy ketones is highly susceptible toward nucleophilic displacement. See Horstmann, H. In "Methoden der organischen Chemie (Houben-Weyl)", Bayer, O., Ed.; Georg Thieme Verlag: Stuttgart, 1977; Vol. VII/2c, Chapter 9, p 2380.

(8) Alternatively the hydrogen migration may occur via an 3-ketoenolate–palladium hydride complex formed by β-elimination in **3.**

(9) The accelerating effect by the added dpe ligand is notable, but the exact reason has not yet been elucidated. For related ligand effects on the reactivity of group 8 metal complexes, see: Yoshida, T.; Yamagata, T.; Tulip, T. H.; Ibers, J. A.; Otsuka, S. *J. Am. Chem. Soc.* **1978,** *100,* 2063. Dedieu, A.; Hoffmann, R. *Ibid.* **1978,** *100,* 2074.

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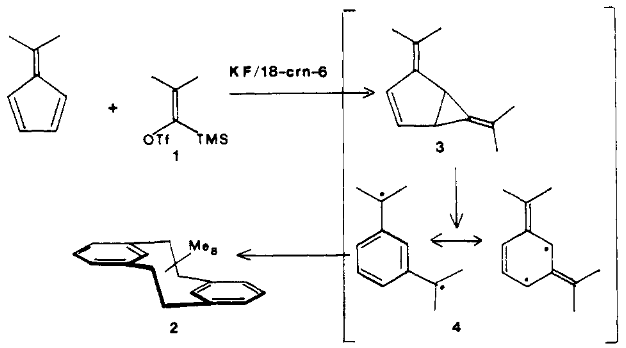
Generation of a *m*-Xylylene Derivative and Formation of a 2,2-Metacyclophane

Sir:

Cross-conjugated π biradicals like trimethylenemethane and 2,2′-bisallyl represent an interesting class of reaction intermediates. Usually derived from opening of small rings with appendaged methylene groups, these species have only $(n/2)-1$ π bonds where n is the number of π electrons. Thus they have been the object of studies to determine their geometry and electron spin state.[1] They are analogous to carbenes in the questions they present to experimentalists and theorists.

m-Xylylene (*m*-quinodimethane) is a member of this group of diradicals, and it too appears to be formed by ring opening of an appropriate precursor. Thus potassium fluoride induced decomposition of the silyl triflate (**1**)[2] in tetrahydrofuran or carbon tetrachloride containing 6,6-dimethylfulvene and 18-crown-6 gives the white crystalline octamethyl-2,2-metacyclophane (**2**) in 20% yield after recrystallization from ethanol. Physical properties of **2**: mp 221–224 °C; *m/e* 320, base peak 161;[3] ^{1}H NMR δ 0.89 (s, 12 H), 1.5 (s, 12 H), 4.9 (s, 2 H), 7.1 (m, 6 H). The characterization follows particularly from the two-proton singlet which results from the aromatic protons residing over the other aromatic ring in the anti conformation.[4] When the reaction is run in an NMR tube at room temperature, the proton resonances of **2** appear as rapidly as those of fluorotrimethylsilane are formed. Further, the yield according to NMR integrations is 40% based on triflate decomposed. No other products appear in the NMR although a solid deposits on the walls of the tube.



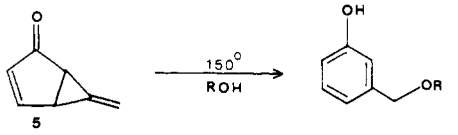
Since electrophilic carbenes like isobutylidene would be expected to add to the internal π bonds of the fulvene on the basis of electronic effects and since steric effects reinforce this expectation,[5] it is not unreasonable that 4,6-diisopropylidenebicyclo[3.1.0]hex-2-ene (**3**) is formed. Ring opening of **3** could lead to the *m*-xylylene (**4**) which dimerizes. Whether triplets are involved in this reaction is not yet clear, although CIDNP signals indicative of triplets are not observed despite the PPP-SCF-CI calculation that triplet *m*-xylylene is 0.34 eV lower in energy than the lowest singlet state of the parent biradical.[6] The assumption that **3** can ring open at room temperature follows from bond-energy considerations which indicate that the *m*-xylylene (**4**) is 20 kcal/mol more stable than its bicyclic precursor, **3**, assuming that each radical site is stabilized to the extent of benzyl radical resonance energy (11 kcal/mol). Thus the bridge bond energy in **3** is roughly −20 kcal/mol!

While it may be surprising that radical recombination is so favorable in this case, it it true that $k_{\text{comb}}/k_{\text{dis}}$ for cumyl radicals is 20.[7]

Attempts to trap a monomeric species with TCNQ and with di-*tert*-butyl nitroxide at room temperature have led to intractable reaction mixtures. Clearly low-temperature generation of the *m*-xylylene would provide useful information, but we have thus far been unsuccessful in doing so. It will also be instructive to determine if the two *exo*-isopropilidene groups become equivalent in the reaction.

Previous attempts to generate *m*-xylylene include irradiation of *m*-xylene[8] and reductive debromination of α,α'-dibromo-*m*-xylene.[9] In the former case an electronic spectrum was assigned to *m*-xylylene, but no products were obtained. In the latter case no evidence for the biradical was obtained.

Numerous syntheses of 2,2-metacyclophanes have been reported, but most involve bond formation between two previously linked aromatic rings.[10] Only the original synthesis via a Wurtz coupling of α,α'-dibromo-*m*-xylene may involve *m*-xylylene.[11] Thus the route to **2** reported here may be unique and worthy of further exploration. It is also relevant that Berson prepared and isolated 6-methylenebicyclo[3.1.0]hex-3-en-2-one (**5**).[12] This remarkably stable material undergoes ring opening only above 150 °C in alcohol solvents to give the addition product of *m*-quinomethane. The greater stability of **5** compared with **3** may be a result of the greater strength of the CO over the CC double bond. Upon photolysis in an ESR cavity **5** gives a spectrum which appears to be that of the triplet of *m*-quinomethane.



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(2) Stang, P. J. *Acc. Chem. Res.* **1978,** *11,* 107–114.

(3) *m/e* 320.2501; calcd for $C_{24}H_{32}$, 320.2504. For cracking of metacyclophanes, see Flammang, R.; Figeys, H. P.; Martin, R. H. *Tetrahedron* **1968,** *24,* 1171–1185.

(4) Vögtle, F.; Neumann, P. *Angew. Chem., Int. Ed. Engl.* **1972,** *11,* 73–83. The high-field aromatic protons of the parent are at δ 4.25, and methyl substitution on the central ring shifts the resonance to lower field.

(5) Stang, P. J.; Madsen, J. R.; Mangum, M. G.; Fox, D. P. *J. Org. Chem.* **1977,** *42,* 1802–1804.

(6) Baudet, J.; *J. Chim. Phys.-Chim. Biol.* **1971,** *68,* 191–7. The experiments reported here do not necessarily rule out a triplet ground state.

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