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Cationic Palladium(II) Complex-Catalyzed Hetero Diels-Alder Reaction of Dienes with Aldehydes

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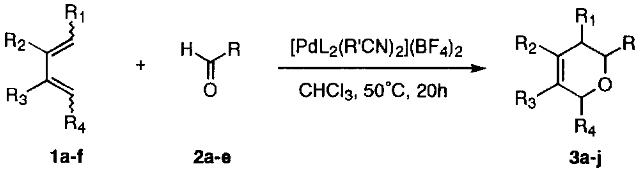
Abstract: Cationic palladium(II) complexes, $[PdL_2(RCN)_2](BF_4)_2$, have been found to catalyze the hetero Diels-Alder reaction of nonactivated simple dienes with aldehydes, affording the corresponding 5,6-dihydro-2*H*-pyrans in good yields under mild conditions.

The hetero Diels-Alder reaction using carbonyl compounds as dienophiles has been a very useful method to construct the dihydropyran skeleton and is used widely as a key step in the synthesis of natural products.[1, 2] However, there are only a few reports on the reaction of nonactivated simple dienes with aldehydes under forced conditions, *i.e.*, elevated temperature or strongly acidic conditions.[3] It is necessary to use activated dienes containing strong electron-donating groups such as 1-methoxy-3-trimethylsiloxybutadiene (Danishefsky's diene)[4] and/or activated carbonyl compounds containing electron-withdrawing groups such as glyoxylate esters[5 - 7] to conduct the reaction smoothly under mild conditions.

Here we wish to report that the hetero Diels-Alder reaction of nonactivated simple dienes (**1**) with aldehydes (**2**) is catalyzed by cationic palladium(II) complexes affording the corresponding 5,6-dihydro-2*H*-pyrans (**3**) in good yields (Scheme 1). It is the first example of the use of a palladium complex as a catalyst for Diels-Alder type cyclization which is usually catalyzed by Lewis acids such as BF_3, $AlCl_3$ and $TiCl_4$.

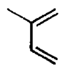
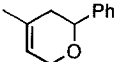
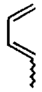
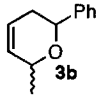
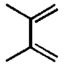
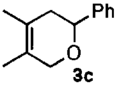
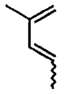
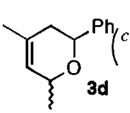
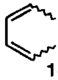
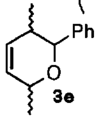
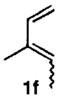
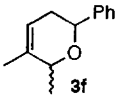
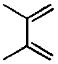
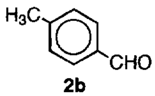
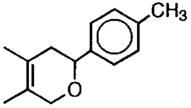
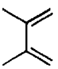
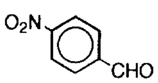
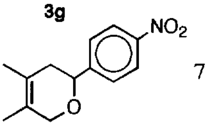
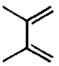
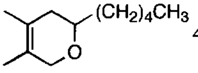
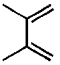
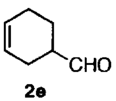
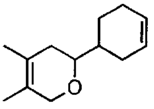
Scheme 1



The general procedure for the cationic palladium-catalyzed cyclization is as follows. A mixture of 2.5 mmol of **1**, 2.0 mmol of **2** and 0.04 mmol of $[Pd(dppp)(PhCN)_2](BF_4)_2$ or $[Pd(dppf)(PhCN)_2](BF_4)_2$ (dppp = 1,3-bis(diphenylphosphino)propane, dppf = 1,1'-bis(diphenylphosphino)ferrocene)[8] in 2 ml of dry $CHCl_3$ was stirred at 50 °C for 20 h under N_2 atmosphere in a sealed Schlenk tube. The reaction was quenched by adding ether to the mixture. Then the mixture was filtered through a short silica gel column and eluted with ether.

The results are summarized in Table 1. The reaction of 2-methyl (**1a**; entry 1), 2,3-dimethyl (**1c**; entry 3) and 1,3-dimethyl (**1d**; entries 4, 5) substituted 1,3-butadienes with benzaldehyde (**2a**) proceeded smoothly under mild conditions in the presence of 2 mol% of the cationic palladium(II) complexes. The cationic palladium complexes coordinated with other phosphine ligands such as PPh_3, dppe, and dppb (dppe = 1,2-bis(diphenylphosphino)ethane, dppb = 1,4-bis(diphenylphosphino)butane) also showed some catalytic activity. However, the bidentate ligands, dppp and dppf, were the most effective. Neutral palladium complexes such as $Pd(PPh_3)_2Cl_2$ or $Pd(CH_3CN)_2Cl_2$ did not show any catalytic activity at all. Polar coordinative solvents such as acetonitrile or THF inhibited the reaction and no cyclization product was obtained. The reactions of 1-methyl (**1b**; entry 2), 1,4-dimethyl (**1e**; entry 6) and 1,2-dimethyl (**1f**; entry 7) substituted 1,3-butadienes with **2a** were sluggish, affording the cyclization products in low yields.

Table 1. Cationic Palladium(II) Complex-catalyzed Hetero Diels-Alder Reaction of Dienes with Aldehydes[a]

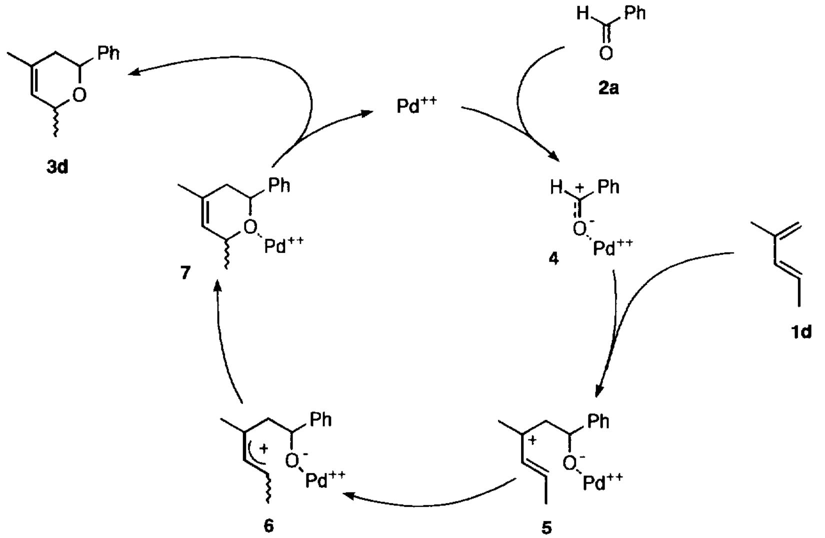
Entry	**1**	**2**	**3**[b]	Yield /%
1	 **1a**	PhCHO **2a**	 **3a**	$67^{c,\,e}$
2	 **1b**	PhCHO **2a**	 **3b**	$10^{c,\,e}$
3	 **1c**	PhCHO **2a**	 **3c**	$82^{c,\,f}$
4	(*trans*)  **1d**	PhCHO **2a**	 **3d**	$73^{c,\,e}$ (*cis* : *trans* = 74:26)
5	(*cis* : *trans* = 30:70)			$72^{c,\,e}$ (*cis* : *trans* = 74:26)
6	 **1e**	PhCHO **2a**	 **3e**	$6^{c,\,e}$
7	 **1f**	PhCHO **2a**	 **3f**	$8^{c,\,e}$
8	 **1c**	 **2b**	 **3g**	$50^{d,\,f}$
9	 **1c**	 **2c**	 **3h**	$75^{d,\,f}$
10	 **1c**	$CH_3(CH_2)_4CHO$ **2d**	 **3i**	$48^{c,\,f}$
11	 **1c**	 **2e**	 **3j**	$55^{d,\,f}$

a) The reaction was carried out as described in the text. b) The structure of the products was identified by IR, NMR, mass spectrometry. c) GLC yields estimated by internal standard method. d) Isolated yields by silica gel column chromatography eluted with hexane-AcOEt. e) $[Pd(dppp)(PhCN)_2](BF_4)_2$ was used as the catalyst. f) $[Pd(dppf)(PhCN)_2](BF_4)_2$ was used as the catalyst.

These experimental results indicate that the diene must possess a methyl substituent at the C-2 position and no substituent at the C-1 position for the smooth reaction (**1d** can be regarded as 2,4-dimethyl substituted 1,3-butadiene). It is noted that this reaction does not afford any ene product which often accompanies the hetero Diels-Alder product.[6, 7] The regioselectivity of this cyclization is very high, only one regio isomer as shown in Table 1 being obtained in all cases. The cyclization, however, did not proceed stereospecifically. Both *cis*- and *trans*-**3d** were obtained in the same ratio (*cis* : *trans* = 74 : 26) whenever the *trans* diene **1d** or *cis-trans* mixed diene **1d** (30 : 70) was used (entries 4, 5). The reaction of **1c** with functionalized benzaldehydes, **2b**, **2c**, afforded the corresponding cyclization products, **3g**, **3h**, in moderate to good yields (entries 8, 9). The reaction of **1c** with an aliphatic aldehyde, hexanal (**2d**), also proceeded smoothly to afford **3i** in 48% yield (entry 10). The carbon-carbon double bond in the ring did not influence the reaction as is shown in entry 11 where 1,2,3,6-tetrahydrobenzaldehyde (**2e**) was employed as the dienophile.

Two distinct mechanisms can be proposed for the present cyclization of dienes with aldehydes: a concerted pericyclic reaction and a stepwise addition *via* the zwitter ionic intermediate as is proposed in the cyclization of the Danishefsky diene with benzaldehyde mediated by $BF_3 \cdot OEt_2$.[9] If the reaction proceeds concertedly, it should be expected that the product is obtained stereospecifically and that the reactivity of the 1,3-butadiene substituted with a methyl group on the C-1 position (as **1b**) is slightly higher than that substituted with a methyl group on the C-2 position (as **1a**) by considering their energies and coefficients of HOMO.[10, 11] However, the obtained results are contradictory to these expectations (*vide supra*). Therefore, the reaction is assumed to proceed *via* the stepwise addition. The proposed reaction pathway for **1d** with **2a** is shown in Scheme 2.

Scheme 2



The cationic palladium complex coordinates to the carbonyl oxygen of **2a** to tinge the carbonyl carbon with a positive charge which allows the nucleophilic attack of **1d**. A zwitter ionic species **5** may be formed in this step. The presence of the methyl group on the positive carbon of **5** may help to stabilize the intermediate **5**. This can explain the difference in reactivity between **1a** and **1b**. The stereochemistry around the double bond may be lost during the ring closing step **5** → **6** → **7**.

Further studies including those on the enantioselective cyclization are in progress.

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References and notes

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8. These cationic palladium(II) complexes were prepared as described in the literature: Davies, J. A.; Hartley, F. R.; Murray, S. G. *J. Chem. Soc., Dalton Trans.* **1980**, 2246-2249. Typically, Pd(dppp)Cl_2 (590 mg, 1 mmol) was dissolved in a mixture of CH_2Cl_2 (35 ml) and benzonitrile (5 ml) under N_2 atmosphere and $AgBF_4$ (487 mg, 2.5 mmol) dissolved in nitromethane (10 ml) was added to the mixture with stirring. White precipitate of AgCl appeared immediately. After stirring for 3 h the solution was filtered by membrane filter (0.45 μm) and reduced to small volume *in vacuo*. A yellow solid was precipitated by dropwise addition of diethyl ether (50-100 ml). The product was filtered off, washed with diethyl ether (10 ml), and dried *in vacuo* at room temperature to yield up to 90 % of **[Pd(dppp)(PhCN)$_2$](BF$_4$)$_2$**. ^{1}H-NMR data (250 MHz, acetone-d_6): δ 2.44 (m, 2H), 3.23 (m, 4H), 7.53-7.75 (m, 22H), 7.78-7.95 (m, 8H). **[Pd(dppf)(PhCN)$_2$](BF$_4$)$_2$**, purple solid, ^{1}H-NMR data (250 MHz, $CDCl_3$): δ 4.68 (s, 8H), 7.35 (t, 4H), 7.48-7.58 (m, 18H), 7.93 (m, 8H).
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