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A simple $PdCl_2/O_2$/DMF catalytic system for highly regioselective cyclotrimerization of olefins with electron-withdrawing groups

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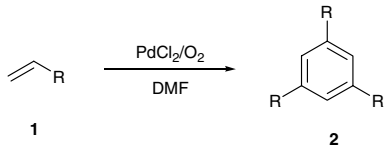
Abstract—A highly regioselective cyclotrimerization of olefins with electron-withdrawing groups in a $PdCl_2/O_2$/DMF catalytic system is disclosed, and a possible mechanism has also been proposed, which reveals the $PdCl_2$-catalyzed cyclotrimerization of olefins with electron-withdrawing groups goes through a quite different pathway from that of alkynes.

The synthesis of polysubstituted aromatic compounds has long been of great interest in industrial and academic research. Traditionally these compounds have been synthesized via aromatic electrophilic substitution reactions or a variety of metal-mediated multistep coupling reactions generally involving alkynes.[1,2] Although transition-metal-catalyzed cyclotrimerization of alkynes has made great advances, the regioselectivity of the process is still troublesome.[3] Besides, all these methodologies suffer the challenges of available and cheap starting materials, environmentally benign and atom economical process.

Homogeneous catalytic systems involving Pd^{II} complexes have been used as one of the most efficient oxidase catalysts with the use of molecular oxygen as a terminal oxidant.[4] Molecular oxygen is an ideal oxidant owing to its availability and subsequent production of totally environment-safe byproducts such as water or hydrogen peroxide.

In our previous studies, a cyclotrimerization product of methyl acrylate has been detected in a $PdCl_2/O_2/scCO_2$/MeOH catalytic system.[5] Recently, a triannelation of acrylates to 1,3,5-benzenetricarboxylates catalyzed by a $Pd(OAc)_2$/HPMoV/$CeCl_3/O_2$ system was reported by Ishii.[6] Herein we disclose for the first time a highly regioselective cyclotrimerization of olefins with electron-withdrawing groups in a $PdCl_2/O_2$/DMF catalytic system (Eq. 1), and also propose a possible mechanism.



1 2 (1)

Our initial efforts to probe the cyclotrimerization of olefins with electron-withdrawing groups focused on the reactivity of methyl acrylate. Table 1 shows the results of optimization for the reaction under ranges of reaction conditions, including dosage of catalyst, pressure of molecular oxygen, temperature and reaction time. A typical reaction was carried out with methyl acrylate **1a** (4 mmol) in 1 mL DMF, which was chosen as the reaction solvent due to its excellent solubility of $PdCl_2$, compared with *n*-hexane, CH_2Cl_2, toluene and THF.

It is noteworthy that the cyclotrimerization of **1a** was catalytically achieved to give **2a** in a regioselective manner. The dosage of catalyst had an obvious effect on the cyclotrimerization of **1a**. When the amount of $PdCl_2$ was increased to 5 mol %, **2a** was obtained in 55.8% isolated yield (Table 1, entries 1 and 2). Further loading of $PdCl_2$ to 7.5%, the yield decreased to 39.8% with a more serious concomitant formation of palladium black (Table 1, entry 3). The formation of **2a** exhibits a sharp dependence on the pressure of molecular oxygen and reaches a maximum value of 65.4% at 0.6 MPa (Table 1, entry 6). But further increase of the pressure of molecular oxygen

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Table 1. Cyclotrimerization of **1a** to **2a** by the catalysis of the $PdCl_2/O_2$/DMF system under ranges of reaction conditions[a]

Entry	Dosage of catalyst (mmol)	Temperature (°C)	Pressure of oxygen (MPa)	Time (h)	Isolated yield (%)
1	0.1	50	0.5	24	42.0
2	0.2	50	0.5	24	55.8
3	0.3	50	0.5	24	39.8
4[b]	0.2	50	Ambient air	24	9.1
5	0.2	50	0.1	24	36.8
6	0.2	50	0.6	24	65.4
7	0.2	50	0.7	24	42.3
8	0.2	50	0.9	24	28.7
9	0.2	50	0.6	12	32.0
10	0.2	20	0.6	24	Trace
11	0.2	70	0.6	24	35.7
12[c]	0.2	50	0.6	24	Trace
13[d]	0.2	50	0.6	24	60.2

[a] Reaction conditions: methyl acrylate (4 mmol), DMF (1 mL).
[b] Oxygen was introduced by use of a balloon.
[c] $Pd(OAc)_2$ was used as catalyst.
[d] $PdCl_2(CH_3CN)_2$ was used as catalyst.

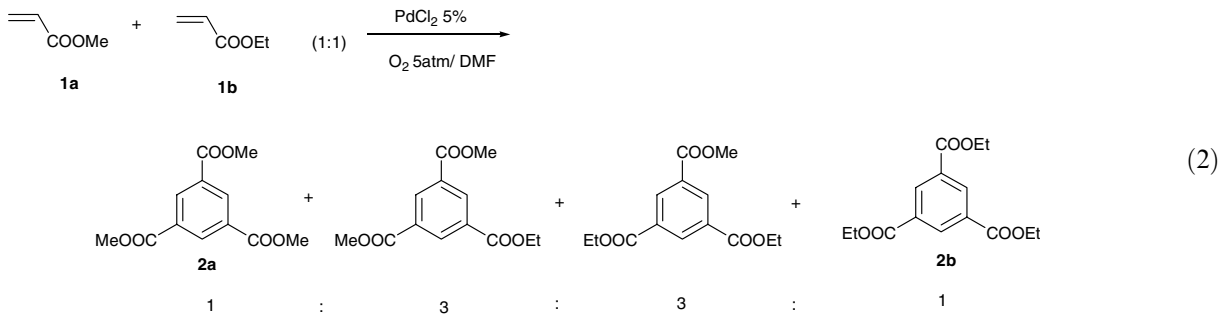
leads to a dramatic decrease of the yield of **2a** (Table 1, entries 7 and 8). Prolongation of reaction time from 12 h to 24 h results in a marked increase of the yield of **2a** (Table 1, entries 9 and 6). At lower temperatures of 20 °C, (Table 1, entry 10), trace of the product was detected. $Pd(OAc)_2$ seemed to be an inefficient catalyst for the reaction, while $PdCl_2(CH_3CN)_2$, the solvate of $PdCl_2$, could catalyze the reaction smoothly (Table 1, entries 12 and 13).

Cyclotrimerization of different olefins was investigated under optimized reaction conditions and the results are shown in Table 2.[7] It can be learned that the cyclotrimerization of both alkyl and aryl olefins with electron-withdrawing groups can occur smoothly in the $PdCl_2/O_2$/DMF catalytic system. With an increasing number of carbon atoms in the R group of alkyl acrylates, its reactivity decreased distinctly. Therefore both a higher temperature and a longer time could promote the cyclotrimerization (Table 2, entry 3). In the case of methyl vinyl ketone, this simple catalyst system also show a rather good activity (Table 2, entry 4). As to different aryl olefins, we can see from Table 2 (entries 5–7), aspiring results can also be obtained. These corresponding products are very important initiators for the synthesis of well-defined star polymers, which has became an important field in macromolecular chemistry due to their unique spatial shapes and rheological properties.[8] To the best of our knowledge, this is the first synthesis of these very useful compounds from simple olefins.

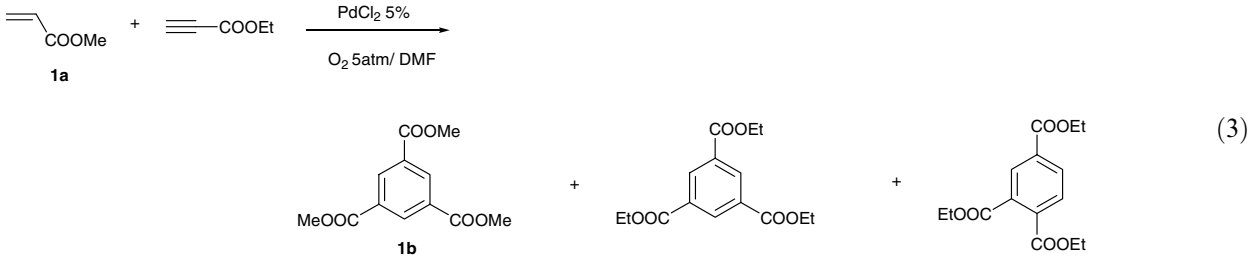
When 2 mmol **1a** and 2 mmol **1b** were mixed with 5 mol % $PdCl_2$ under 0.5 MPa O_2 in 1 mL DMF, a mixture of cyclotrimerization products can be found with an approximate ratio of 1:3:3:1 in yields (Eq. 2), which implied that the cyclotrimerization pathway of olefins with electron-withdrawing groups may experience a three-step process.

When the mixture of 2 mmol **1a** and 2 mmol ethyl propiolate was catalyzed by 5 mol % $PdCl_2$ under 0.5 MPa O_2 in 1 mL DMF, no cross products of carbomethoxy and ethoxy-carbonyl were detected (Eq. 3). In addition, the cyclotrimerization of **1a** gave **2a** alone, while the cyclotrimerization of ethyl propiolate gave a mixture of 1,3,5- and 1,2,4-benzenetricarboxylates in the yields of 47% and 46%, respectively, (based on ethyl propiolate by GC–MS).

On the basis of the above results, several noteworthy points can be summarized. (1) The $PdCl_2$-catalyzed cyclotrimerization of olefins with electron-withdrawing groups goes through a quite different way from that of alkynes. (2) The cyclotrimerization of olefins with electron-withdrawing groups is sensitive to the concentration of molecular oxygen in solvate, which means it



(2)



(3)

needs an appropriate oxygen pressure. (3) Characteristic of the α-carbonyl group of the substrates, including its electron-withdrawing property, might be vital to the reaction. (4) The choice of solvents is important due to its solubility of $PdCl_2$ and the electric property.

$$H–Pd–Cl + O_2 \rightarrow H–O–O–Pd–Cl \quad (4)$$

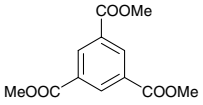
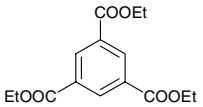
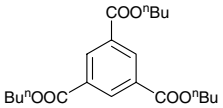
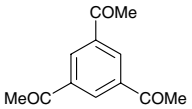
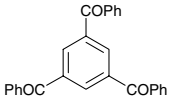
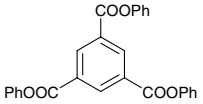
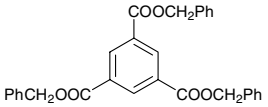
$$H–O–O–Pd–Cl + HCl \rightarrow PdCl_2 + H_2O_2 \quad (5)$$

A plausible reaction pathway for the cyclotrimerization of **1** to **2** is outlined in Scheme 1.[9] Coordination of olefin **1** to $PdCl_2$ prefers to undergo chloropalladation and then β-H elimination to vinylpalladium intermediate **4**. The presence of molecular oxygen converted H–Pd–Cl to Cl–Pd–OOH, which releases H_2O_2 and keeps Pd(II) oxidative state (Eqs. 4 and 5).[10] Subsequent insertion of olefins **1** to Pd–C bond and then β-H elimination–oxidation afford the new chloropalladation intermediate **6**, which then cyclizes by closing the ring to generate intermediate **7**. The active $PdCl_2$ species is regenerated.

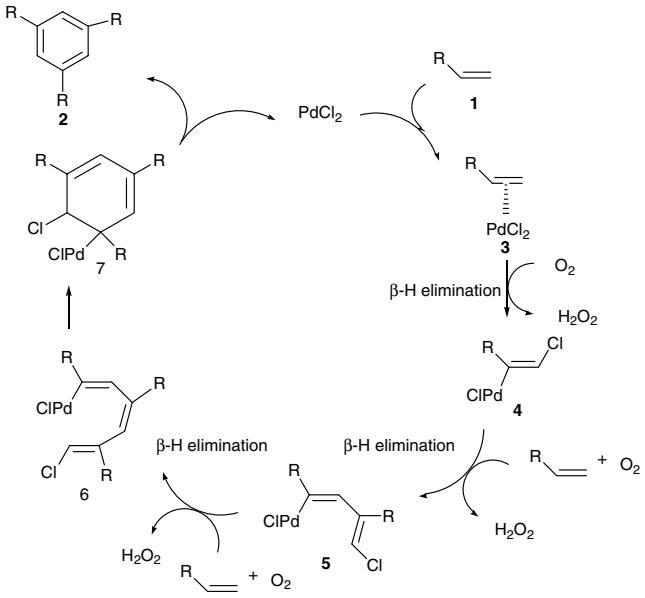
Why did the cyclotrimerization of olefins with electron-withdrawing groups yield the sole regioselective product in comparison with that of alkynes? We speculate that the insertion of olefins to Pd–C bond might strongly depend on electronic nature[11] and different molecular orbit states of sp-C atoms and sp^2-C atoms.[12]

In summary, we have developed a simple palladium catalyst system for the highly regioselective cyclotrimerization of olefins with electron-withdrawing groups to 1,3,5-trisubstituted benzene derivatives. The brand new

Table 2. Cyclotrimerization of different olefins[a]

Entry	R	Product	Isolated yield (%)
1	COOMe	 **2a**	65.4
2	COOEt	 **2b**	53.2
3[b]	COO^nBu	 **2c**	38.4
4	COMe	 **2d**	58.4
5[c]	COPh	 **2g**	25.3
6[c]	COOPh	 **2e**	59.2
7[c]	$COOCH_2Ph$	 **2f**	48.7

[a] Reaction conditions: acrylate (4 mmol), $PdCl_2$ (0.2 mmol), DMF (1 mL), Pressure of O_2 (0.6 MPa), 50 °C, 24 h.
[b] Reaction was run at the temperature of 70 °C for 36 h.
[c] Reaction was run at the temperature of 50 °C for 18 h.



Scheme 1.

proposed mechanism may highlight the study of cyclotrimerization of olefins.

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7. A Typical procedure for the cyclotrimerization. All reactions were carried out in a HF-25 autoclave. Catalyst $PdCl_2$ (0.2 mmol, 5 mol %) and substrate (4 mmol) were added into the autoclave in sequence. O_2 was pumped into the autoclave using a cooling pump to reach the desired pressure, then the autoclave was put into an oil bath under magnetic stirring for the desired reaction time. Product **2** was purified by a short column chromatography of SiO_2. Compound **2a**. IR(neat): $\nu = 3091$, $3007\ cm^{-1}$ (C_6H_3); 2956, $2847\ cm^{-1}$ (CH_3); $1731\ cm^{-1}$ (C=O); $1254\ cm^{-1}$ (C–O–C). MS (EI): $m/z = 252$ (M^+), 221, 193, 147, 75, 29. ^1H NMR (400 MHz, TMS, $CDCl_3$): $\delta = 3.953$ (s, 9H, CH_3), 8.835 (s, 3H, C_6H_3). Compound **2b**. IR(neat): $\nu = 3095\ cm^{-1}$ (C_6H_3); $2993\ cm^{-1}$ (CH_3); $1722\ cm^{-1}$ (C=O); 1240, $1024\ cm^{-1}$ (C–O–C). MS (EI): $m/z = 294$ (M^+), 266, 249, 221, 193, 73, 29. ^1H NMR (400 MHz, TMS, $CDCl_3$): $\delta = 1.412$ (t, $J = 7.2$ Hz, 9H, CH_3), 4.421 (q, $J = 7.2$ Hz, 6H, CH_2), 8.830 (s, 3H, C_6H_3). Compound **2c**. IR(neat): $\nu = 3093\ cm^{-1}$ (C_6H_3); $2853\ cm^{-1}$ (CH_3); $1728\ cm^{-1}$ (C=O); 1242, $1028\ cm^{-1}$ (C–O–C). MS (EI): $m/z = 378$ (M^+), 323, 305, 267, 249, 211, 193, 165, 120, 56, 41, 29. ^1H NMR (400 MHz, TMS, $CDCl_3$): $\delta = 0.971$ (t, $J = 7.2$ Hz, 9 H, CH_3), 1.423–1.516 (m, 6H, CH_2), 1.728–1.799 (m, 6H, CH_2), 4.360 (t, $J = 6.8$ Hz, 6H, CH_2), 8.817 (s, 3H, C_6H_3). Compound **2d**. IR(neat): $\nu = 3064\ cm^{-1}$ (C_6H_3); 2922, $2852\ cm^{-1}$ (CH_3); $1688\ cm^{-1}$ (C=O); 1225, $1096\ cm^{-1}$ (C–O–C). MS (EI): $m/z = 204$ (M^+), 189, 161, 119, 91, 75, 32,28. ^1H NMR (400 MHz, TMS, $CDCl_3$): $\delta = 2.694$ (s, 9H, CH_3), 8.684 (s, 3H, C_6H_3). Compound **2e**. IR(neat): $\nu = 3902$, 3446, 3061, 2926, 2885, 1722, 1662, 1247, 1009, 714, $794\ cm^{-1}$. MS (EI): $m/z = 390$ (M^+), 313, 285, 105, 77, 58, 44, 32. ^1H NMR (400 MHz, TMS, $CDCl_3$): $\delta = 8.379$ (s, 3H, C_6H_3), 7.838–7.817 (m, 6H, C_6H_5), 7.613–7.594 (m, 3H, C_6H_5), 7.518–7.480 (m, 6H, C_6H_5). Compound **2f**. IR(neat): $\nu = 3742$, 3449, 2921, 2855, 1796, $1233\ cm^{-1}$. MS (EI): $m/z = 438$ (M^+), 359, 345, 317, 224, 196, 168, 139, 103, 89, 75, 65, 51, 32. ^1H NMR (400 MHz, TMS, $CDCl_3$): $\delta = 9.228$ (s, 3H, C_6H_3), 7.453 (t, $J = 8$ Hz, 6H, C_6H_5), 7.320–7.246 (m, 9H, C_6H_5). Compound **2g**. IR(neat): $\nu = 3433$, 3088, 3034, 2956, 2854, 1721, $1224\ cm^{-1}$. MS (EI): $m/z = 480$ (M^+), 389, 373, 336, 283, 267, 229, 167, 149, 107, 91, 71, 65, 43, 32. ^1H NMR (400 MHz, TMS, $CDCl_3$): $\delta = 8.883$ (s, 3H, C_6H_3), 7.440–7.337 (m, 15 H, C_6H_5), 5.386 (s, 6H, CH_2).
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