*Note*

# A Regioselective Method for the Synthesis of Benzene Derivatives: Palladium-catalyzed Cyclotrimerization of Ethyl Propiolate

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**An $NEt_3$-induced palladium complex $PdL_2Cl_2$ catalyzed cyclotrimerization reaction of ethyl propiolate (EP) is reported for the first time. The reaction proceeded readily in a regioselective manner under mild conditions to give cyclotrimerization product 1,2,4-triethyl benzenetricarboxylate as well as its 1,3,5-isomer in good yields. Influences of the ligands, $NEt_3$, solvents, oxidants as well as temperature are studied, and a possible mechanism is also proposed.**

**Keywords** ethyl propiolate, palladium complex, cyclotrimerization, regioselectivity

## Introduction

One of the most fascinating chapters in organometallic chemistry concerns the transition metal-catalyzed cyclotrimerization of acetylene,[1] which is a useful method for the construction of substituted benzenes. Benzene derivatives are important structural components of many biological, pharmaceutical and polymer molecules. Among the catalysts, palladium chloride[2] and its complex $PdL_2Cl_2$ (the ligand L can be benzonitrile, methylnitrile, triphenylphosphine, *etc.*),[3] have the simplest forms and are the most convenient ones to use. Virtually many reactions proceeded smoothly in the presence of palladium complex under ambient conditions.[4]

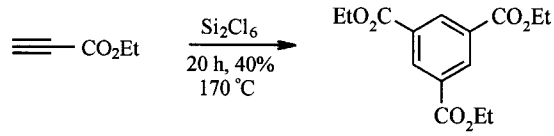
Ethyl propiolate (EP), which is a terminal alkyne and has an electron-withdrawing substituent, can cyclotrimerize to 1,2,4-triethyl benzenetricarboxylate and its 1,3,5-isomer in good yield in the presence of palladium complex. The yields and regioselectivity generally depend on the ligands coordinated with palladium. The new results and its possible mechanism will be proposed.

## Results and discussion

In our study of palladium-catalyzed cyclotrimerization of alkynes,[5] we occasionally found that EP could cyclotrimerize in the presence of $PdCl_2$-$CuCl_2$ in alcohol/benzene at room temperature. Although the yield was poor, it did encourage us to study, because the alkyne with an electron-withdrawing substituent hardly cyclotrimerize in the presence of palladium catalyst.

Many transition-metal catalysts can catalyze cyclotrimerization of EP. For example, $ClCo(PPh_3)_3$ catalyzed EP cyclotrimerization under mild conditions, 1,2,4-triethyl benzenetricarboxylate was obtained as the major product, and the minor product 1,3,5-isomer was also obtained.[6] The similar complex mixtures were obtained when EP reacted in the presence of $Ni(CO)_2(PPh_3)_2$.[7] Many reactions gave the products in poor yields, and needed rigorous conditions. For $Si_2Cl_6$-induced EP cyclotrimerization, 1,3,5-triethyl benzenetricarboxylate was obtained as the only product in 40% yield at 170 ℃ (Scheme 1).[8]

**Scheme 1**




Herein, we report a regioselective palladium catalyzed EP cyclotrimerization under mild conditions. Good yields (96%) and regioselectivities (up to 89:9) are achieved, and the major product is 1,2,4-triethyl benzenetricarboxylate instead of the 1,3,5-isomer. In this reaction, the influences of the ligands, solvents, oxidants as well as temperature were studied.

*Influence of catalyst system*

EP could cyclotrimeriz in the presence of $PdL_2Cl_2$.

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Preliminary results showed that the ligands of the palladium complex pla yimportant roles in this reaction. When EP reacted in the presence of $Pd(PhCN)_2Cl_2$-$CuCl_2$-$NEt_3$ in alcohol/benzene at 88 ℃ for 4 h (Entry 3, Table 1), high yield (96%) and regioselectivity (89:9) were achieved. The ligands coordinated with palladium have important influences on this reaction. In the presence of $PdCl_2$, no good result was obtained (32%, 70:20, Entry 5, Table 1). When ligand coordinated with palladium is $PPh_3$, the catalyst efficiency dropped slightly compared with $Pd(PhCN)_2Cl_2$ (86%, 86:10, Entry 6, Table 1). So did $Pd(MeCN)_2Cl_2$ (91%, 86:12, Entry 7, Table 1). From above, we can know that the catalytic efficiency of palladium catalysts is $Pd(PhCN)_2Cl_2$ > $Pd(MeCN)_2Cl_2$ > $Pd(PPh_3)_2Cl_2$ > $PdCl_2$. The experiments showed that other transition-metal like alloy of Ni-Al could not catalyze the cyclotrimerization of EP (Entry 8, Table 1).

The catalytic efficiency mainly depends on the tightness of the ligands coordinated with palladium. For example, the ligand PhCN binds palladium chloride ($PdCl_2$) loosely and takes little part in the subsequent reactions, so this complex could be thought of as "solubilized $PdCl_2$", which in fact was the "real" effective catalyst to cyclotrimerize EP. To some extent, the ligand MeCN binds $PdCl_2$ more tightly than PhCN, so the product with a slightly lower yield and regioselectivity were obtained. Meanwhile, the ligand $PPh_3$ binds palladium even more tightly, leading yield and regioselectivity to much lower.

*Influence of* $NEt_3$

EP cyclotrimerized readily in the presence of $NEt_3$, but in the absence of $NEt_3$ gave poorer yields and lower regioselectivity (Entry 4, Table 1). The effect of $NEt_3$ is obvious. In the absence of $NEt_3$, the yield decreased obviously, and the regioselectivity reduced as well (66%, 72:24, Entry 4, Table 1). How does it promote this reaction? And how can we explain it? Ghosh and his co-wokers[9] proposed a similarly possible mechanism, but it is just a rough mechamism for the product 1,3,5-benzenetricarboxylate. Based on this, we propose a possible mechanism for the main product 1,2,4-isomer (Scheme 2).

*Influence of oxidant and temperature*

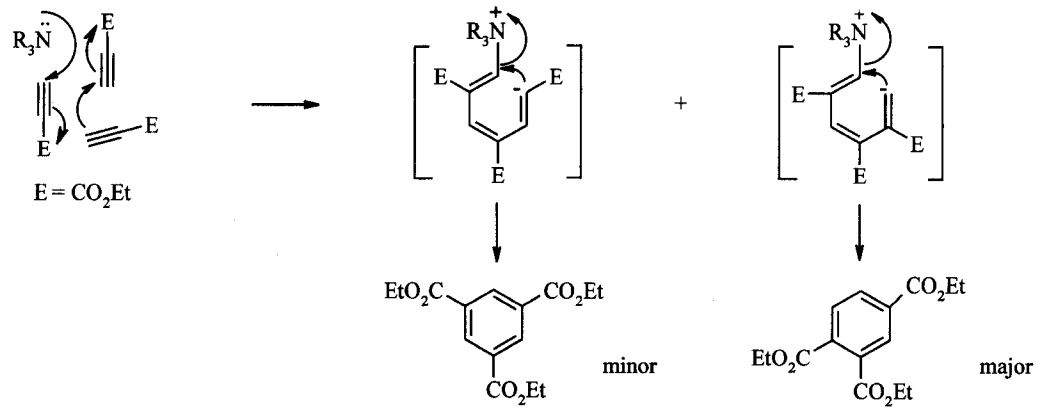
Besides $NEt_3$ and the ligands, other factors such as the

**Table 1** Palladium complex catalyzed cyclotrimerization of EP[a]

| Entry | Catalyst | Temperature (℃) | Convertion (%)[b] | Yield (%)[c] | Regioselectivity (2/3)[d] |
|---|---|---|---|---|---|
| 1 | $Pd(PhCN)_2Cl_2$ | r.t. | 66 | 33 | 65:31 |
| 2 | $Pd(PhCN)_2Cl_2$ | 88 | 100 | 96 | 89:9 |
| 3 | $Pd(PhCN)_2Cl_2$ | 96 | 98 | 86 | 89:12 |
| 4[e] | $Pd(PhCN)_2Cl_2$ | 88 | 86 | 66 | 72:24 |
| 5 | $PdCl_2$ | 88 | 82 | 32 | 70:20 |
| 6 | $Pd(PPh_3)_2Cl_2$ | 88 | 100 | 86 | 86:10 |
| 7 | $Pd(MeCN)_2Cl_2$ | 88 | 100 | 91 | 86:12 |
| 8 | Ni-Al | 88 | — | — | — |
| 9[f] | $Pd(PhCN)_2Cl_2$ | 88 | 96 | 74 | 89:9 |
| 10[g] | $Pd(PhCN)_2Cl_2$ | 88 | 100 | 94 | 86:8 |
| 11[h] | $Pd(PhCN)_2Cl_2$ | 88 | 100 | 92 | 89:9 |
| 12[i] | $Pd(PhCN)_2Cl_2$ | 88 | 100 | 92 | 89:9 |

[a] Reaction conditions: $PdL_2Cl_2$ (0.056 mmol), $CuCl_2$ (2 mmol), $NEt_3$ (1 mmol) and MeOH (10 mL) at 88 ℃ for 4 h. [b] Detected by GC analyses. [c] Isolated yields. [d] Ratio of 2/3. [e] In the absence of $NEt_3$. [f] In the absence of $CuCl_2$. [g] $Ce(SO_4)_2$ (2 mmol) instead of $CuCl_2$. [h] Benzene/*n*-BuOH as the solvent. [i] EtOH as the solvent.

**Scheme 2**



oxidant ($CuCl_2$), to some extents, can affect this cyclotrimerization reaction. EP could cyclotrimerize even in the absence of $CuCl_2$, but the rate decreased (Entry 9, Table 1). The reaction also can be carried out smoothly with the oxidant Ce $(SO_4)_2$, although the yield and regioselectivity declined a little (94%, 86:8, Entry 10, Table 1).

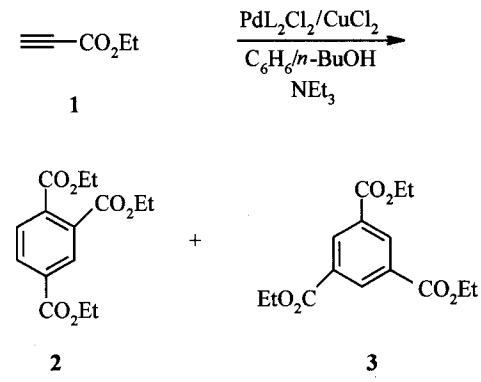
The reaction temperature is very important, and the appropriate temperature is 88 ℃. Higher temperature (Entry 3, Table 1) or lower temperature (Entry 1, Table 1) led to poorer yield as well as lower regioselectivity.

The effect of the reaction time is not obvious. Experimental data showed that 4 h is the optimum choice, and longer time would lead to more side reactions.

*Influence of solvents*

The solvents could affect the cyclotrimerization reactions slightly. At first, the reactions were carried out in benzene/*n*-BuOH (the ratio: 10:0.6) as our previously successful work, however, just on the way round, we did not receive the anticipated results. It was found that the reaction could proceed smoothly in MeOH or EtOH and give unexpected elegant yield (Entries 1 and 12, Table 1). For the reactions in benzene/*n*-BuOH (10:0.6), some side reactions occurred (Entry 11, Table 1), which led to lower yields. In a word, the solvents can affect the yields slightly, while they have no effects on the regioselectivity. Other protonic solvents like *s*-BuOH, *n*-BuOH are also effective for the reaction. In conclusion, experimental results showed that the optimum reaction conditions are: $PdL_2Cl_2$ (0.056 mmol), $CuCl_2$ (2 mmol), $NEt_3$ (1 mmol), at 88 ℃ in MeOH (10 mL) for 4 h (Scheme 3).

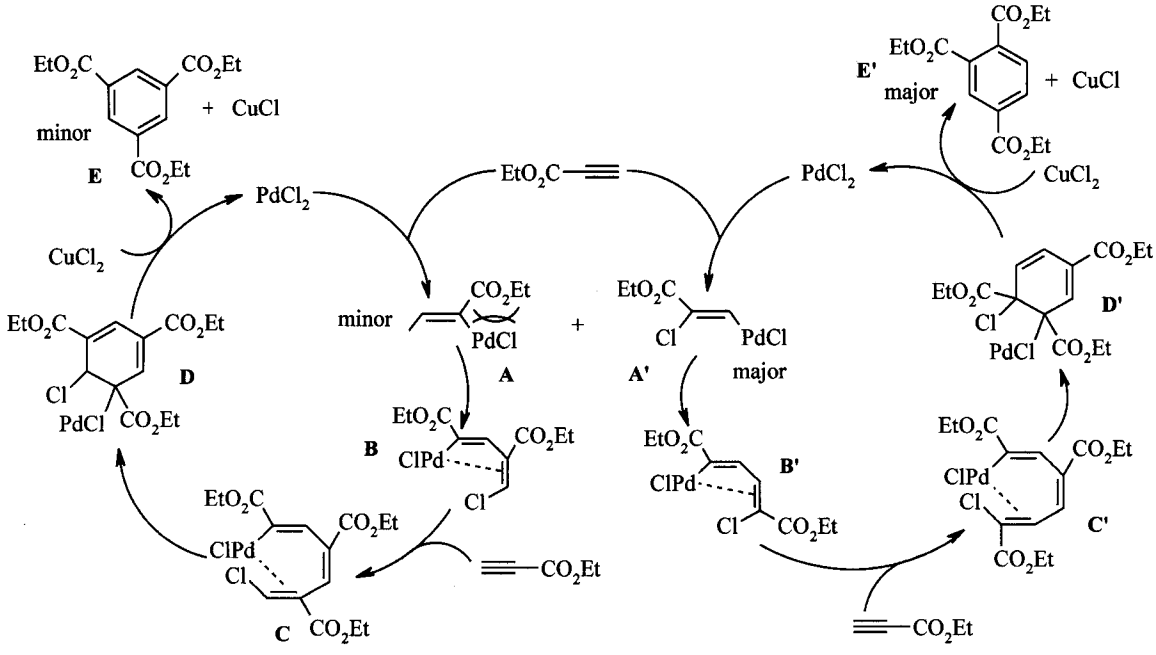
**Scheme 3**




*Proposed reaction mechanism*

In $PdL_2Cl_2$ catalyzed reactions, the catalytic effective part is the "solubilized $PdCl_2$". The mechanism of EP cyclotrimerization catalyzed by $PdCl_2$ together with $CuCl_2$ and $NEt_3$, is proved to involve a series of stepwise *cis* insertions of coordinated alkyne EP as shown in Scheme 4. (I) Firstly, EP insertion into a Cl—Pd bond gives **A**; and (II) EP insertion into a vinyl-Pd bond gives a $\sigma$-butadienyl-Pd complexes **B**, **B'**; (III) then the third insertion occurs to give a $\sigma$-hexatrienyl-Pd complexes **C**, **C'**, which can then undergo an internal *cis* insertion; (IV) the internal insertion gives the substituted palladiacyclopentadienes **D**, **D'** (Scheme 4). With the assistance of $CuCl_2$ and $Et_3N$, the reaction gives benzene derivatives **E**, **E'**, and regenerates the active $PdCl_2$. Maitlis and his co-worker has laid the emphasis on the mechanism induced by $CuCl_2$.[8a,10,11] More spatial resistance of intermediate

**Scheme 4**



**A** inclined to the obtained major product **E'** (Scheme 4).

In conclusion, we reported a novel regioselective and highly chemoselective procedure for cyclotrimerization of ethyl propiolate. The effects of catalyst ligands, oxidants, $NEt_3$ and solvents in the Pd(II)-catalyzed cyclotrimerization of ethyl propiolate were also discussed. Proper mechanism is given in this $NEt_3$-induced cyclotrimerization of EP catalyzed by palladium complexes and $CuCl_2$.

## Experimental

A $^1H$ NMR spectra were recorded at 400 MHz using $CDCl_3$ as the solvent. TLC was performed using commercially prepared 100—400 mesh silica gel plates ($HF_{254}$) and visualization was effected at 254 nm. $CuCl_2$ was dried at 130 ℃ under HCl gas. All other reagents were used directly as obtained commercially. All melting points are uncorrected.

*General procedure for the cyclotrimerization of ethyl propiolate*

To a mixture of $PdL_2Cl_2$(0.056 mmol), $CuCl_2$(2 mmol) and $NEt_3$(1 mmol) in MeOH (10 mL), ethyl propiolate (2 mmol) was added. The reaction was stirred at desirable temperature for 4 h. After complete conversion of acetylene as monitored by GC analyses, the mixture was filtered, and the MeOH was removed by rotary evaporation to give crude products, which were purified by preparative TLC on silica gel (light petroleum-ethyl ether). The conversions were measured by GC analyses using an internal standard.

1,2,4-Triethyl benzenetricarboxylate (**2**) and 1,3,5-isomer (**3**):[8a] White needle crystals, m.p. (uncorrect), 102—107 ℃; $^1H$ NMR ($CDCl_3$) $\delta$: 8.83 (s, 1H), 7.36 (s, 1H), 7.24 (s, 1H), 4.27 (dd, $J$ = 7.2, 3.6 Hz, 6H), 1.36 (t, $J$ = 4.0 Hz, 9H); IR (KBr) $\nu$: 2985, 2935, 1728, 1448, 1371, 1244, 1111, 1070, 931, 862 $cm^{-1}$; MS (70 eV) $m/z$ (%): 1,3,5-isomer (**3**): 294 ($M^+$), 266, 251, 249, 223, 221, 195, 193, 165, 148, 120, 102, 91, 73, 65, 45, 29; 1,2,4-isomer (**2**): 294 ($M^+$), 250, 249, 222, 221, 194, 193, 176, 165, 148, 137, 120, 103, 91, 75, 65, 45, 29.

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