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$PdCl_2(HNMe_2)_2$-Catalyzed Highly Selective Cross [2 + 2 + 2] Cyclization of Alkynoates and Alkenes under Molecular Oxygen

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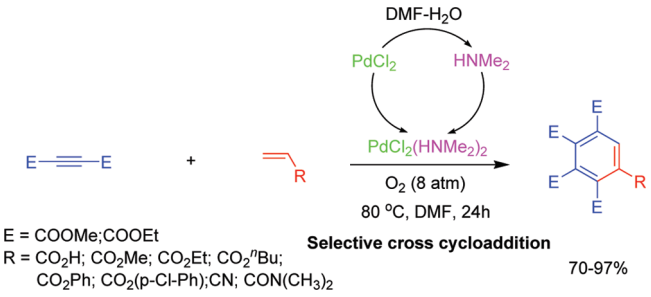

In the course of our study on palladium-catalyzed aerobic oxidation synthesis, we found that the $PdCl_2/O_2$/DMF system consistently experienced DMF hydrolysis to afford $PdCl_2(HNMe_2)_2$, which is the real active catalyst for the aerobic oxidation. Although in situ DMF hydrolysis has been widely used in generating supramolecular assembly architectures, as far as we know, it is the first successful example to utilize $PdCl_2(HNMe_2)_2$ in synthetic reactions. The highly selective cross [2 + 2+2] cyclization of alkynoates and different alkenes with electron-withdrawing groups could be smoothly catalyzed by $PdCl_2(HNMe_2)_2/O_2$/DMF to afford the corresponding functionalized pentasubstituted benzenes in good to excellent yields (70−97%). The extension of alkyne surrogates for cross [2 + 2 + 2] cyclization from special alkenes with leaving groups to simple alkenes under molecular oxygen led to a paradigm shift in arene synthesis.

Polysubstituted benzenes are highly useful compounds which are widely used in industry as well as in the laboratory.[1] Traditionally, the regioselective construction of polysubstituted benzenes has been mainly achieved by stepwise introduction of the substituents via electrophilic substitution reactions such as the Friedel−Crafts reaction (eq 1).[2] However, high regioselectivity and yield can only be achieved by the careful choice of the reagents and synthetic route which usually is necessary to convert and/or protect−deprotect the substituents properly.

In 1948, Reppe and Schweckendiek[3] discovered that transition metals can catalyze the cycloaddition of alkynes to form substituted benzenes. The efficiency, atom-economy, and ease of transition-metal-catalyzed [2 + 2 + 2] cycloaddition reactions are clearly evident, but the high regioselectivity was inherently limited to attempts at heterotrimerization using two or more different alkynes.

The most common strategy used to overcome this limitation has relied on tethering two or three of the alkyne components, and high regioselectivity may be controlled by the geometric and entropic restrictions imparted by the tether. This partially or completely intramolecular approach was continually studied during the last decades;[4] however, it always need much more complicated substrate precursors and always affords "big molecules" (eqs 2 and 3).

Attempts at "small molecules" by a more general approach to substituted aromatics requires a fundamentally different strategy, one that completely eliminates the tether (eq 4), and it has been the focus of more recent studies.[5] The lingering regioselective problem has been solved by strategies based on different ligands and transition-metal catalysts,[6] strategies based on a covalent linkage as temporary boron tethers,[7] and strategies based on substrates: alkynes with extreme electronic differentiation of the π components[8] or some special alkenes as alkyne equivalents through dehydration,[9] dehydroxylation,[10] and dehydrocarboxylation,[11] etc. Significant challenges still remain. Expanding the substrate scope to include more diverse alkynes and alkyne surrogates as well

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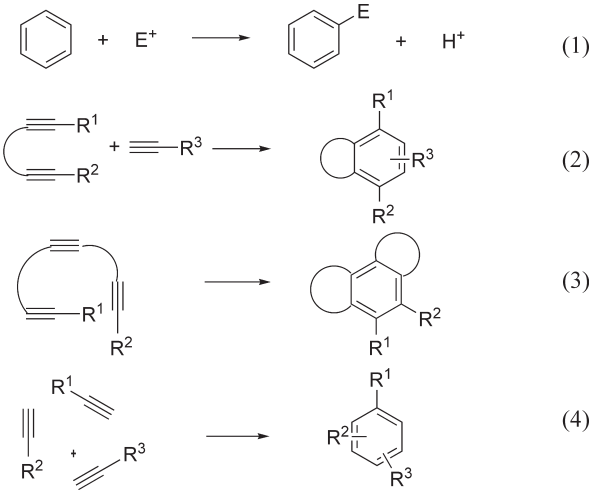
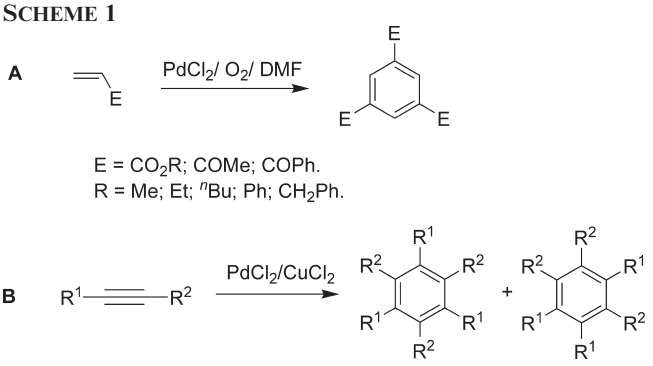
as solving the regioselectivity problem are still being investigated.



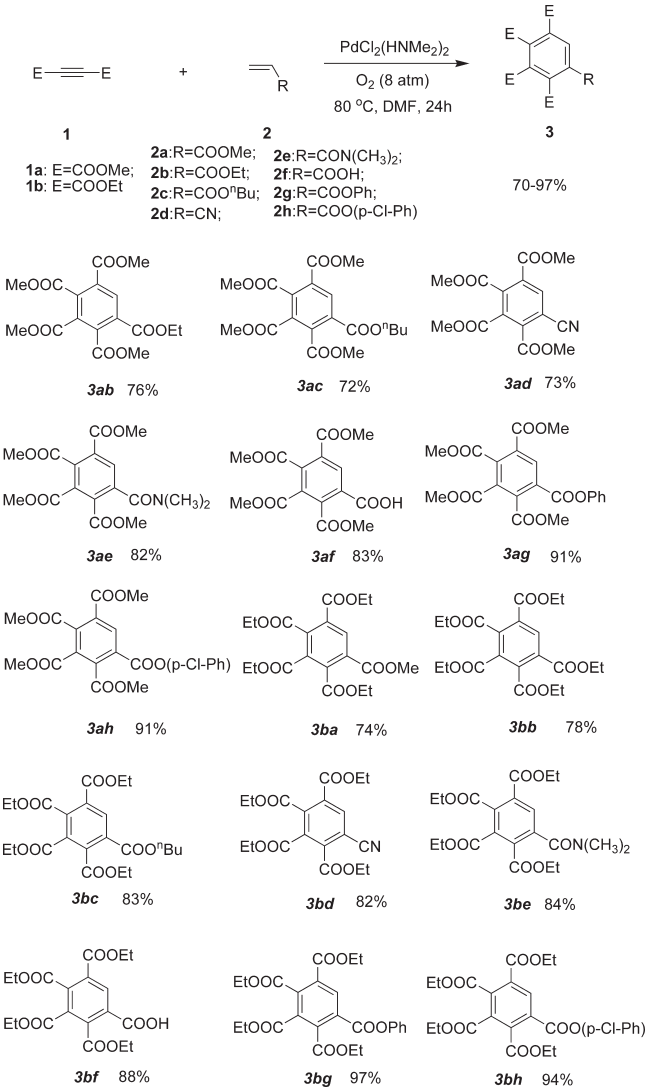
In the course of our study on palladium-catalyzed aerobic oxidation synthesis, we found that $PdCl_2/O_2$/DMF is an efficient catalyst system for [2 + 2 + 2] cyclotrimerization of alkenes with electron-withdrawing groups to selectively afford 1,3,5-trisubstituted benzene derivatives (Scheme 1A).[12] A few years ago, we also developed a regioselective and highly chemoselective method for preparing benzene derivatives via palladium chloride-catalyzed cyclotrimerization of alkynes in the presence of $CuCl_2$ (Scheme 1B).[13] Taking into account these precedents and detailed evaluation of the palladium-catalyzed aerobic oxidation, we envisaged that functionalized multisubstituted benzene derivatives could be directly prepared by controlled cross-cyclization of alkyne and alkene. Here, we report the extension of this palladium chemistry to the highly selective cross [2 + 2 + 2] cyclization of alkynoates and alkenes with electron-withdrawing groups under molecular oxygen (Scheme 2) and disclose for the first time that the in situ DMF hydrolysis-produced $PdCl_2(HNMe_2)_2$ is the key to actively catalyze the oxidative reaction and that the extension of alkyne surrogates from special alkenes with leaving groups to simple alkenes under molecular oxygen led to a paradigm shift in arene synthesis.

DMF, one of the important classes of dipolar and aprotic amides, is well known for its ability to coordinate transition-metal ions as unidentate O-donor ligands or lattice solvates[14] and is usually an inert solvent.[15] But during our experiment with DMF as solvent, the result is not good when the system is strictly dehydrated (Table 1, entry 17). We finally found that the $PdCl_2/O_2$/DMF system consistently experienced DMF hydrolysis during oxidation (eq 5) and resulted in the formation of $PdCl_2(HNMe_2)_2$, whose

SCHEME 1



SCHEME 2. Synthesis of Pentakis-Substituted Benzenes from Alkynoates and Alkenes[a]



[a]Reaction conditions: alkynoate **1** (1 mmol), alkene **2** (1 mmol), $PdCl_2$ (3 mol %), pressure of molecular oxygen (0.8 MPa), 80 °C for 24 h in 1 mL of DMF without drying. [b]Isolated yields based on **1**.

structure was characterized by X-ray crystal diffraction measurement.[16] Therefore, we believe that $PdCl_2(HNMe_2)_2$

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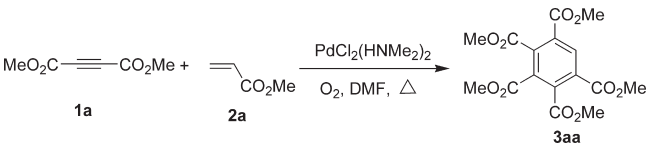
TABLE 1. Optimization of Reaction Conditions[a]



entry	cat.[b] (%)	**1a**/**2a**	O_2 (MPa)	temp (°C)	time (h)	GC yield[c] (%)
1	1	2:1	0.6	70	24	27
2	3	2:1	0.6	70	24	56
3	5	2:1	0.6	70	24	58
4	3	3:1	0.6	70	24	34
5	3	2:2	0.6	70	24	69
6	3	2:3	0.6	70	24	62
7	3	1:1	ambient air	70	24	11
8	3	1:1	0.3	70	24	23
9	3	1:1	0.8	70	24	75
10	3	1:1	1	70	24	73
11	3	1:1	0.8	50	24	35
12	3	1:1	0.8	80	24	79 (70)[d]
13	3	1:1	0.8	100	24	72
14	3	1:1	0.8	80	18	53
15	3	1:1	0.8	80	30	81
16[e]	3	1:1	0.8	80	24	47
17[f]	3	1:1	0.8	80	24	36

[a]Reaction conditions: dimethyl but-2-ynedioate **1a** (1 mmol), DMF without drying (1 mL). [b]Dosage of $PdCl_2$ based on **1a**. [c]GC yield based on **1a**. [d]Isolated yield in the parentheses. [e]0.1 mL of distilled water was added. [f]Dryness with anhydrous $MgSO_4$ and then vacuum distillation of DMF before using.

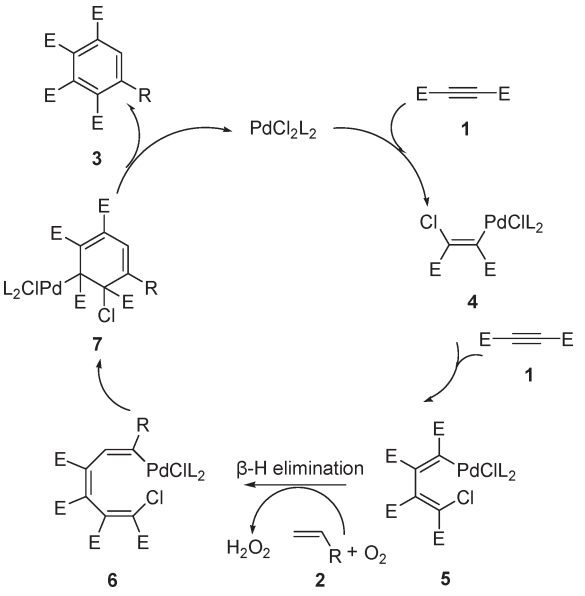
is the real catalytically active palladium complex in our system.

$$HCON(CH_3)_2 + H_2O \rightarrow HN(CH_3)_2 + HCOOH \quad (5)$$

In situ DMF hydrolysis has been widely used in generating supramolecular assembly architectures.[17] Interestingly, few references were found about in situ DMF hydrolysis being utilized in synthetic reactions. As far as we know, only in 1974, in a study of α-olefin oxidations with the Clement−Selwitz system, Fahey et al. reported that the in situ DMF hydrolysis produced $PdCl_2(HNMe_2)_2$ resulted in the complete poison of catalyst $PdCl_2$.[18]

Our initial efforts were focused on reaction optimization for the selective cross [2 + 2 + 2] cyclization of dimethyl but-2-ynedioate (**1a**) and methyl acrylate (**2a**) in DMF without drying, including the optimization of dosage of $PdCl_2$, molar ratio of alkynoates to alkene, pressure of molecular oxygen, temperature, and reaction time (Table 1). It indicated that the best dosage of $PdCl_2$ was 3 mol % (Table 1, entries 1−3), which is a relative small dosage for transition-metal-catalyzed [2 + 2 + 2] cyclization reactions, generally ranging between 5 and 10 mol %. This may be attributed to the high catalytic activity of the in situ produced catalyst $PdCl_2(HNMe_2)_2$. The molar ratio of **1a** to **2a** seems to have an obvious effect on the selective formation of **3aa**; when the ratio was more than 1:1, cyclotrimerization of **1a** partially occurred (Table 1, entries 4−6). The reaction exhibits a sharp dependence on the pressure of molecular oxygen and reaches a maximum value of 75% at 0.8 MPa (Table 1, entries 7−10). The optimized temperature and time for the reaction is 80 °C for 24 h (Table 1, entries 10−15). Entry 16 of Table 1 shows that extra water was not beneficial for the reaction. As we see in the reaction of direct utilization of molecular oxygen as the sole oxidant, water is necessary for the in situ DMF hydrolysis to afford the catalyst $PdCl_2(HNMe_2)_2$; however, it is also the byproduct of the oxidation, and too much water in the system inhibits the formation of **3aa**.

SCHEME 3. Plausible Reaction Mechanism



Under the optimized conditions, the reaction was applied to a range of different alkenes (Scheme 2). It can be learned that the $PdCl_2(HNMe_2)_2$-catalyzed cross [2 + 2 + 2] cyclization of alkynoates and alkenes with electron-withdrawing groups can be achieved in a highly selective 2:1 cross-coupling manner to give **3** under molecular oxygen. The scope of substrates successfully moves beyond acrylates only, and different alkenes with electron-withdrawing groups, including acrylonitrile and acrylic acid, etc., could smoothly and successfully react with alkynoates to afford the corresponding pentasubstituted benzenes in good to excellent yields (70−97%). Many useful substituting groups, such as acylamide, aryloxycarbonyl, and cyano, were successfully introduced into the product, and product **3ag** is structurally characterized by X-ray crystal diffraction measurement. It should be noticed that the cyano group can be reserved while in most cases it turns out to form pyridines,[19] and the introduction of an aryl group could find potential utilizations in all kinds of cross-coupling reactions initiated by palladium, including well-known Heck, Suzuki, etc.

A plausible mechanism of this cyclization was shown in Scheme 3. The reaction started with the cis chloropalladation of the C−C triple bond of alkyne **1** by $PdCl_2(HNMe_2)_2$ giving vinyl−Pd intermediate **4**,[20] and the succeeding

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insertion reaction into the Pd−vinyl bond afforded intermediate **5**. Coordination of **2** to **5** underwent insertion and then β-H elimination−oxidation in the presence of molecular oxygen, leading to the new chloropalladation intermediate **6**, where Pd−Cl made a further insertion into the carbon−carbon double bond generating intermediate **7**.[21] The presence of molecular oxygen converted H-PdL_2-Cl to Cl-PdL_2-OOH, which released H_2O_2 and kept the Pd(II) oxidative state. Finally, β-Cl elimination of **7** yielded the product **3**, and the catalyst $PdCl_2(HNMe_2)_2$ was regenerated.[22]

Why was $PdCl_2(HNMe_2)_2$ so highly efficient a catalyst for the selective cross coupling [2 + 2 + 2] cyclization of alkynoates and alkenes with electron-withdrawing groups under oxygen while it failed when 2,2-bipyridine or phenanthroline was used as ligand to stabilize the reduced palladium species during oxidation? According to the literature,[23] compounds of geometrical rigidity, introduced by a bidentate ligand forming a small metallacycle, like the complex (2,2-bipyridine)diethylpalladium, will suppress the β-hydride elimination, a reaction with an increase in coordination number and considerable geometry change. In addition, the (2,2-bipyridine)diethylpalladium has a decomposition point at 109 °C while we found that the decomposition point of the $PdCl_2(HNMe_2)_2$ is between 218 and 219 °C. Due to its thermal stability and less geometrical rigidity around the metal center of $PdCl_2(HNMe_2)_2$, we believe that in situ DMF hydrolysis to produce $PdCl_2(HNMe_2)_2$ was an excellent catalyst for this reaction.

In conclusion, we have established an in situ DMF hydrolysis producing $PdCl_2(HNMe_2)_2$ to catalyze highly selective cross [2 + 2 + 2] cycloaddition of alkynoates and alkenes with electron-withdrawing groups under molecular oxygen to synthesize pentakis-substituted benzenes in good to excellent yields (70−97%). This methodology not only makes an extension of alkyne surrogates from special alkenes with leaving groups to simple alkenes under molecular oxygen but also opens a brand new way for the utilization of DMF hydrolysis in synthetic reactions. The relatively cheap and accessible starting materials, green oxidant molecular oxygen, and environmentally benign byproduct made the present atom-economic cycloaddition more attractive.

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Experimental Section

Palladium-Catalyzed Highly Selective Cross [2 + 2 + 2] Cyclization of Dimethyl But-2-ynedioate 1a and Methyl Acrylate 2a: A Representative Procedure. All reactions were carried out in a HF-15 autoclave with magnetic stir bar. $PdCl_2$ (0.03 mmol, 3 mol %), DMF (1 mL, undrying), dimethyl but-2-ynedioate (**1a**, 1 mmol), and methyl acrylate (**2a**, 1 mmol) were added into a 15 mL autoclave in sequence. O_2 was pumped into the autoclave to the desired pressure. The autoclave was then put into an oil bath under magnetic stirring for the desired reaction time. After the reaction, the autoclave was allowed to cool to room temperature. Surplus O_2 was vented, and the residual was extracted with 50 mL ether and distilled water (5 × 2 mL). The combined extract was dried with anhydrous $MgSO_4$. The solvent was evaporated to dryness under reduced pressure, and the crude product was separated by column chromatography to give a pure sample **3aa**.

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Note Added after ASAP Publication. Scheme 2 contained an error in the version published ASAP January 27, 2010; the corrected version posted January 28, 2010.

Supporting Information Available: Full experimental details, copies of NMR spectral data, and the ORTEP and CIF files for the X-ray crystal structures of $PdCl_2(HNMe_2)_2$ and **3ag**. This material is available free of charge via the Internet at http://pubs.acs.org.