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Sequential Actions of Cobalt Nanoparticles and Palladium(II) Catalysts: Three-Step One-Pot Synthesis of Fenestranes from an Enyne and an Alkyne Diester

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One of the challenging goals of the synthetic chemistry is the development of new reactions and strategies that allow for the facile conversion of simple compounds into complex materials, medicines, or molecules of theoretical interest. In this regard, the use of homogeneous transition metal catalysts has been very successful.[1] However, the in situ alignment of several distinct catalytic processes, which is quite common in enzyme catalyzed reaction sequence,[2] is still in its infancy in homogeneous transition-metal catalysts.[3] We herein report on the three-step one-pot synthesis of fenestranes from an enyne and alkyne diesters using cobalt nanoparticles and palladium(II) as catalysts. This is a rare example of the use of transition-metal nanoparticles as catalysts with the conventional homogeneous catalyst, Pd(II) in the synthesis of complex organic compounds in a one-pot reaction. In a recent paper[4] we have described the catalytic synthesis of fenestranes from dienediyne in the presence of dicobalt octacarbonyl under carbon monoxide. However, diendiynes have to be synthesized by multistep reactions.

We chose fenestranes as target compounds since most of the known synthetic methods for fenestranes involve multiple steps and have been associated with separation problems.[5] Scheme 1 shows a synthetic pathway to fenestranes. The first step is a catalytic Pauson−Khand reaction, the second Pd(II)-catalyzed allylic alkylation, and the third another catalytic Pauson−Khand reaction.

The first and second steps were easily accomplished by using cobalt on charcoal[6] and Pd(II) catalysts,[7] respectively. However, cobalt on charcoal was not effective in the third step. It appeared that the cobalt on charcoal system was damaged after the second step. Thus, alternative catalysts were sought for the third step. Recently, we recognized that cobalt nanoparticles act as catalysts in the Pauson−Khand reaction,[8] and cobalt nanoparticles[9] could be the best choice among the catalysts. As expected, cobalt nanoparticles were tolerant of all the reaction conditions and quite effective for both the first and third reactions. Thus, fenestranes were prepared from readily available chemicals in a three-step one-pot reaction.

Treatment of **a** with **1** in the presence of cobalt nanoparticles and allyl-Pd(II) complex led to the isolation of **8** in 74% yield (Scheme 2).[10]

Two different catalysts, cobalt nanoparticles and allyl palladium chloride, were capable of promoting three sequential but independent catalytic cycles in the desired chronological order, thereby allowing a new molecular queuing process to take place. The structure of **8** was established by X-ray diffraction investigation (Figure 1).[11] The nucleophilic addition to 1,3-disubstituted π-allylmetal complex afforded exclusively an α,β-unsaturated enone.[12] According to Keese's report,[5b] simple enone intermediates were not suitable for a second cyclization. Thus, they prepared specially designed enones and used them in the synthesis of fenestranes. However, we were pleased to observe that the enone generated in the second step was easily cyclized in the third step.

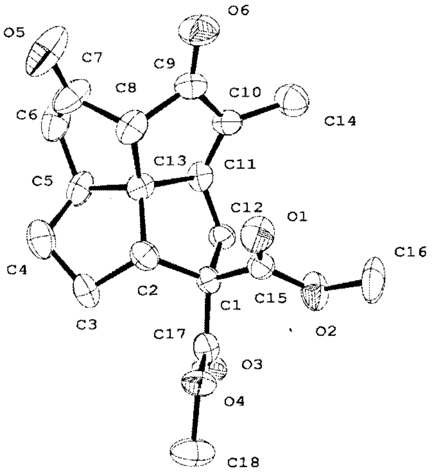
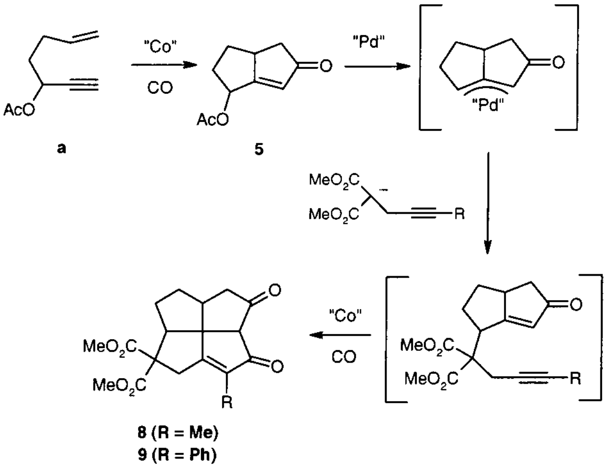
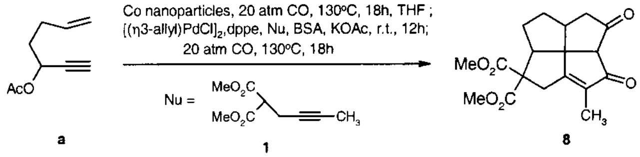


Figure 1. ORTEP plot of **8** showing 30% probability ellipsoids (hydrogen atoms were omitted for clarity).

Scheme 1



Scheme 2



We have tested a variety of enyne substrates **a**−**c** and alkyne diesters **1**−**4** (Chart 1 and Table 1). The reaction of **a** with **2** under

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Chart 1

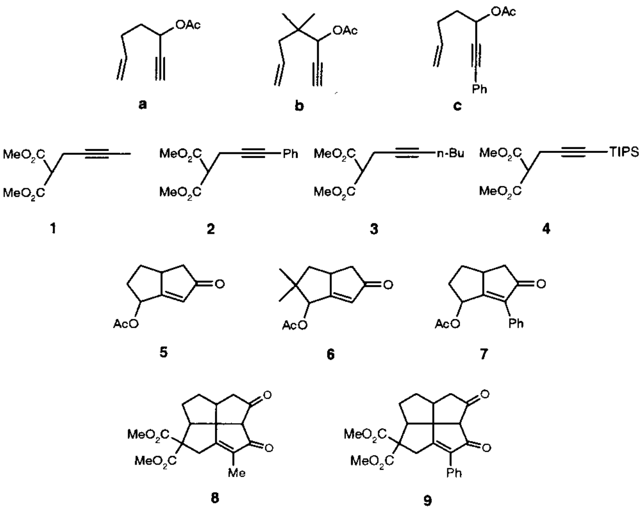

Table 1

entry	enyne	nucleophile	product	yield^a (%)
1	**a**	**1**	**8**	74
2	**a**	**2**	**9**	84
3	**a**	**3**	**5**	64
4	**a**	**4**	**5**	50
5	**b**	**1**	**6**	70
6	**c**	**1**	**7**	54

^{a} Isolated yield.

the same conditions gave **9** in 84% yield.[13] However, reaction of **a** with **3** or **4** under the same conditions did not produce the corresponding fenestranes. Instead, the Pauson−Khand reaction product **5** was obtained in 50−64% yield. Other enynes **b** and **c** having dimethyl substitutions at the 4-position or Ph-substituted alkyne did not afford the corresponding products. Instead, the Pauson−Khand reaction products **6** and **7** were produced in 54−70% yield. When **6** and **7** were treated with the palladium catalyst, no reaction was observed, presumably due to a severe steric hindrance. Thus, it appears that the steric effect of the substituent(s) on the enyne substrate and alkyne diester is an important factor for the Pd-catalyzed allylic alkylation to proceed.

In conclusion, we have shown the usefulness of the combination of cobalt nanoparticles and Pd(II) catalysts in a three-step one-pot reaction for the construction of tetracyclic compounds, fenestranes. Appropriate choice of enyne and alkyne diester allowed the realization of a carbonylative cycloaddition/allylic alkylation/carbonylative cycloaddition sequence as a one-pot reaction. We expect that the novel chemistry shown by the combination of cobalt nanoparticles and Pd(II) catalysts can be extended to other systems. Work in this direction is in progress.

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Supporting Information Available: Characterization data of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Synthesis of **8**: To 100 mL of a high-pressure reactor were added enyne **a** (0.15 g, 0.99 mmol), cobalt nanoparticles (92.5 mg, 45 wt %), and 5 mL of THF. The reactor was charged with 20 atm of CO at room temperature. It was then heated at 130 °C for 18 h. After the reactor was cooled to room temperature, it was flushed with nitrogen. To the reactor were added $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (3.6 mg, 0.0098 mmol) and dppe (7.9 mg, 0.020 mmol) in 5 mL of THF, alkyne diester **1** (0.217 g, 1.18 mmol), BSA (0.30 mL, 1.20 mmol), and a catalytic amount of KOAc in order. The reactor was stirred at room temperature for 12 h, recharged with 20 atm of CO at room temperature, and heated at 130 °C for 18 h. After the reactor was cooled to room temperature and the excess carbon monoxide was released, the reaction mixture was concentrated and chromatographed on a silica gel column eluting with hexane and diethyl ether (v/v, 5:1). White solids (0.243 g, 0.731 mmol) were obtained as a product. ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.78 (s, 3 H), 3.65 (s, 3 H), 3.33 (t, 8.4 Hz, 1 H), 3.31 (d, 15.0 Hz, 1 H), 3.14 (s, 1 H), 3.10 (d, 15.0 Hz, 1 H), 2.40 (m, 2 H), 2.20 (d, 16.0 Hz, 1 H), 2.03 (m, 2 H), 1.69 (s, 3 H), 1.33 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ 208.1, 200.8, 175.9, 170.5, 169.3, 132.4, 67.7, 64.9, 64.1, 53.1, 52.8, 50.2, 45.7, 42.6, 34.5, 33.6, 29.5, 8.63 ppm. IR ν(CO) 1745, 1728, 1701 cm^{-1}. HRMS (M$^+$) calcd 332.1254, obsd 332.1263.

(11) Single crystals of **8** suitable for X-ray diffraction study were grown by slow evaporation of the solvent of **8** in a mixture solvent of diethyl ether, dichloromethane, and hexane (v/v/v, 1:1:2) in a freezer. Crystallographic data (excluding structure factors) for **8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 171963. Copies of the data can be obtained free of charge in application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax (+44)1223-336-033; e-mail deposit@ccdc.cam.ac.uk).

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