Catalytic activity of dodecacarbonyltetracobalt in aqueous media: a "greening" of the Pauson–Khand reaction

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The unprecedented reactivity of $Co_4(CO)_{12}$ with enynes under aqueous conditions, representing the development of a *mild and simple aqueous-phase cobalt-catalyzed* PK reaction protocol, is described herein.

Dodecacarbonyltetracobalt, $Co_4(CO)_{12}$ ¹ is not as widely used in organometallic reactions as dicobaltoctacarbonyl, $Co_2(CO)_8^2$ and $Co_3(CO)_9(\mu^3-CH)$.³ While $Co_2(CO)_8$ has been extensively applied in the Pauson–Khand reaction (PKR),^{4,5} it was not until recently that we discovered the activity of $Co_4(CO)_{12}$ under mild PKR conditions.⁶ This was an important finding because the deterrence of $Co_4(CO)_{12}$ formation had been the basis of all previous efforts toward an effective catalysis of the PKR using $Co_2(CO)_8$.⁶ In follow-up work, we also found that, depending on the nature of the enyne, $Co_4(CO)_{12}$ can effect a reductive PK reaction and reductive cyclization.⁷ These results led us further to probe the reactivity of $Co_4(CO)_{12}$ in aqueous media,⁸ since success toward this end would be significant, in particular, as the "greening" of the Pauson–Khand reaction becomes increasingly relevant.⁹

Significant development in realizing catalysis in the Pauson– Khand reaction and related PK-type reactions has been seen only in the past few years.¹⁰ Early attempts involved supercritical fluids, such as CO₂ and ethylene, in Co₂(CO)₈-catalyzed PKR, albeit these reactions required highly pressurized conditions.¹¹ Relative to our focus, in a water–sodium dodecyl sulfate (SDS) medium, colloidal cobalt nanoparticles were found to be a recoverable and reusable mediator for PK reactions, although a loading of 67 mol% (130 °C, 20 atm CO) was necessary.¹² Rhodium catalyzed PK-type reactions have been reported using formaldehyde as the CO source under aqueous conditions,¹³ and using aromatic and aliphatic aldehydes (1.5 equiv to 20 equiv) in organic solvents.¹⁴ We disclose herein the unprecedented reactivity of Co₄(CO)₁₂ with enynes under aqueous conditions, and the development of a *mild and simple aqueous phase cobalt-catalyzed* PK reaction protocol.¹⁵

Stoichiometric amounts of $Co_4(CO)_{12}$ were used in our initial studies under aqueous conditions (Table 1). We were delighted to

Table 1 PK reactions using stoichiometric $Co_4(CO)_{12}$ in water–CTAB media^{*a*,15}



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^{*a*} Water (0.05 M), 1 equiv Co₄(CO)₁₂, 0.6 equiv CTAB, 70 °C, nitrogen, with a small amount of Celite, *ca.* 18 h. CTAB = cetyltrimethyl ammonium bromide. ^{*b*} Using 2 equiv of Co₄(CO)₁₂ and 1 equiv of CTAB, 66% of the bicyclooctanone was isolated. ^{*c*} In the absence of CTAB, and in the presence of 1 equiv of Co₄(CO)₁₂, 21% bicyclooctanone and 5% unreacted **1** were isolated.

find that typical substrates that would undergo the PKR furnished bicycloctenones in good yields, in the presence of CTAB (entries 2-5).¹⁵ However, an enyne bearing a terminal alkyne moiety provided a bicyclooctanone, instead of the expected bicyclooctenone (entry 1). In fact, substrates of this type have been observed to easily undergo reductive PKR with Co₄(CO)₁₂ in isopropanol,⁷ or colloidal nanoparticles in aqueous media.¹²

Encouraged by these results, we proceeded to investigate the use of catalytic amounts of $Co_4(CO)_{12}$ in water, and in the presence of surfactants or detergents. Cyclization of enyne **5** in water alone using only 10% of $Co_4(CO)_{12}$, under a blanket of carbon monoxide, was found to be inefficient, providing only a modest yield of the cycloadduct **6** (35%) and unreacted **5**. Similar low efficiencies were observed in cyclizations conducted in the presence of 0.2 equiv of triphenylphosphane-3,3',3"-trisulfonic acid trisodium salt, tetrabutylammonium bromide, Fisher detergent, or Triton[®] X-100 reduced form. Fortunately, cyclization efficiency was greatly improved by using Triton[®] X-100 (0.5 equiv) with 20 mol% of catalyst giving rise to 80% of enone **6**. For comparison, cyclocarbonylation of **5** using 20 mol% of $Co_2(CO)_8$ in the presence of 0.5 equiv of Triton[®] X-100 provided only 69% yield of **6**.

To explore the scope of this aqueous catalytic protocol, the cyclization efficiency of various enynes was examined under the catalytic protocol (Table 2, condition I), and compared to the stoichiometric variants (conditions II and III).¹⁵ Results indicated that PK reactions conducted using the former protocol proceeded more efficiently than the latter two. Enynes that would undergo PK reactions conducted in organic solvents^{4,5} also cyclized smoothly under condition I. An envne with heavily-substituted unsaturated groups underwent cyclization providing an adduct with a tetrasubstituted angular center (entry 4). Further, substrates bearing groups prone to hydrolysis, such as the acetal (entry 6), amide (entry 7) and ester groups (entry 8) are stable under aqueous, catalytic conditions. It is noteworthy that no cycloadduct was obtained from the reactions of enynes 17 and 19 in a water-CTAB medium under condition II. We also observed in our earlier work that cyclizations in organic solvents under anhydrous conditions, of substrates bearing alkynes substituted with electron-withdrawing groups, occur in low to modest yields.¹⁶ The thermally-promoted PKR of 17 (toluene, 70 °C, 3 days) gave a 15% yield of 18, and the NMO-promoted variant (CH2Cl2, rt) provided a modest 59% yield.16 Hydrogenolysis of the heteroatom group in the propargylic position did not occur under these conditions although it has been observed as a side reaction in PK reactions in organic solvents (entries 9, 10).17 In fact, it was recently reported that substrates bearing propargylic heteroatoms undergo substantial hydrogenolysis (~50%) under Co₄(CO)₁₂-mediated PKR in DME with only 20 equiv of water.¹⁸ Cyclizations of 1,7-enynes 19 and 23 proceeded smoothly under the aqueous protocol (entries 8 and 11). Reaction of 23 furnished the PKR adduct in higher yield (entry 11) than with the NMO-promoted method (66%).16 A substrate devoid of substitution on the tether, and thus lacking Thorpe-Ingold assistance in the cyclization, cleanly underwent PKR under these conditions (entry 12). It should be noted that, under our catalytic or stoichiometric conditions, the reactions of terminal alkynes led to the formation of saturated ketones. PK and PK-type reactions in water or organic solvents which use aldehydes as a CO source have only been successful with internal alkynes as well.^{12–14}

Table 2 Cobalt-mediated PK reactions under aqueous conditions



^{*a*} I: water, 20 mol% $Co_4(CO)_{12}$, 0.5 equiv of Triton X-100, 70 °C, CO atm in a resealable tube. II: water, 1 equiv $Co_4(CO)_{12}$, 0.6 equiv CTAB, 70 °C, nitrogen atm. III: water, 1 equiv $Co_2(CO)_8$, 0.6 equiv CTAB, 70 °C, nitrogen atm. Reactions were complete in *ca*. 6 h.

Lastly, the issue of a CO-free catalytic PKR procedure was briefly addressed.^{12–14} We observed a slight decrease in the yield of cycloadducts from reactions conducted under an argon atmosphere. For example, PK cyclization of enynes **5** and **7** using 20 mol% of $Co_4(CO)_{12}$ furnished 70% and 59% yields of cyclopentenones **6** and **8**, respectively (*cf.* Table 2, entries 2 and 3, condition I). Nevertheless, these results show the potential of the aqueous protocol in the absence of CO, and warrant further studies.

In summary, we have illustrated the reactivity of $Co_4(CO)_{12}$ towards enynes in a water–CTAB medium, and more importantly, its catalytic activity in the PKR in a water–Triton[®] X-100 medium. These conditions have led to the first examples of a mild and simple cobalt-catalyzed aqueous protocol for the thermal PK reaction of enynes bearing internal alkynes. The water–Triton[®] X-100 medium using $Co_4(CO)_{12}$ has rendered the catalytic, aqueous thermal PKR one which proceeds with high efficiency, exceeding that of the aqueous reactions using stoichiometric amounts of $Co_4(CO)_{12}$ and $Co_2(CO)_8$. Enyne substrates that possess groups prone to undergo hydrolysis were shown to be stable under these conditions.¹⁹

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