



Steric buttressing in the Pauson-Khand reactions of benzyl enynes



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ABSTRACT

The application of the intramolecular Pauson-Khand reaction of 1,*n*-enynes provides a convenient method for the construction of polycyclic frameworks but this process has largely been limited to the formation of 5,5- and 5,6-fused ring systems. In this report, we describe the application of the Pauson-Khand cyclization to 1,8-enynes embedded in an aromatic ring system wherein it is determined that the presence of steric buttresses in the form of *t*-butyl groups facilitates the cycloaddition. These reactions proceed in good yields with either thermal or oxidative activation and in the former case, the diastereoselectivities are high. An investigation of the tolerance of this cycloaddition to substitution around the 1,8-enyne demonstrates that only 2,2-disubstitution does not result in productive cyclization. Cycloadditions with hydroxyl groups at the propargylic position while leading to fused rings are compromised by side reactions leading to reduction and in some cases tautomerization. However, these byproducts are easily minimized through conversion of the hydroxyl group to the corresponding silyl ether.

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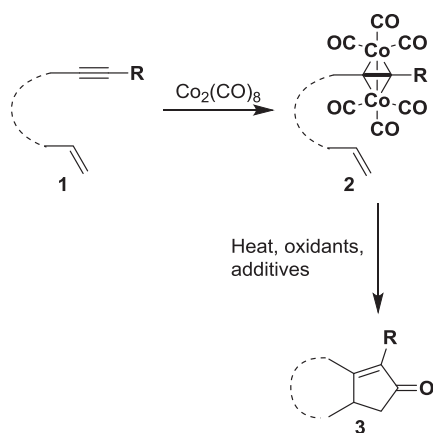
The Pauson-Khand (PK) reaction, the [2 + 2 + 1] co-cyclization of an alkene, an alkyne and carbon monoxide has evolved into a reliable method for the construction of cyclopentenones (**1**→**3**, Scheme 1).¹ In its original incarnation it involved the formation of the dicobalt hexacarbonyl complex **2** and thermolysis to afford the corresponding cyclopentenone (Scheme 1).² This reaction is known both intermolecularly and intramolecularly, and can be mediated or catalyzed by a variety of metal complexes in addition to the classical method with Co₂(CO)₈-derived complexes as initially reported by Pauson and Khand. Photochemical variants are known and it has even been extended to flow conditions.³ During the development of this transformation other substrates have been found to engage in this reaction including allenes,⁴ dienes⁵ and even some heterocumulenes.^{4,6} However, despite these notable advances, there still remain limitations with this cycloaddition that prevent the full realization of its synthetic potential.⁷ For example, whereas there are many examples of intramolecular cyclizations which result in the formation of 5,5- and 5,6-fused bicyclic systems, the construction of larger fused rings had not been described until quite recently. Over the past fifteen years or so, several groups,⁸ including ours have begun to identify strategies for overcoming these limitations, leading to reports of the construction of medium-sized rings annulated to the cyclopentenone.⁹ Our initial approach to

this problem was to use enynes which were constructed around an aromatic scaffold¹⁰ as a means to pre-organize the reacting functional groups, in essence to increase the concentration of the reactive conformation (or conceivably decrease the concentration of non-productive conformations).¹¹ An advantage of this approach was that it permitted the evaluation of additional structural elements on the aromatic ring to further reduce the conformational degrees of freedom – using so-called steric buttressing.^{11b–d} In our first generation studies of this approach, we employed aryl enynes e.g., **4** and found that in the presence of *ortho* substituents cyclization occurred to produce bridged ring systems e.g., **6** rather than the initially expected cycloadducts (Scheme 2).^{11b,11c,12} In this manuscript, we describe the extension of this chemistry to the more conformationally flexible benzylic enynes where an additional methylene group is incorporated between the aryl ring and the alkyne to assess the limitations of this strategy.^{11d}

Our studies commenced by the synthesis of the parent substrate starting from *o*-salicylaldehyde (**7**) which was allylated by treatment with allyl bromide and potassium carbonate (Scheme 3). The resulting aldehyde **8** was treated with acetylenic Grignard reagents (R = H, TMS, Ph) to provide the expected enynes **9–11** in generally good yields. Each enyne was converted to the corresponding Co₂(CO)₆-complex and then subjected to PK cyclization (Scheme 3) under either thermal conditions (PhMe, 70 °C, Condition A) or oxidative conditions (CH₂Cl₂, NMO, Condition B) (Table 1).¹³ While the cobalt complexes were formed uneventfully, only one of these substrates **11** (R = Ph) delivered a cyclopentenone in 31% yield

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Scheme 1.

under thermal conditions (70 °C, PhMe) and 8% yield under oxidative conditions (NMO, CH_2Cl_2 , 0 °C to rt). Interestingly, it was found that the corresponding TBS-ether **15** underwent thermal

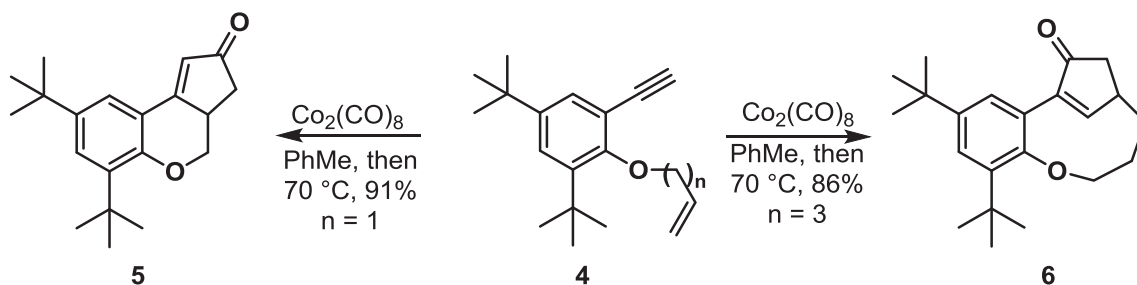
Table 1
Yields from the PK reactions of the *o*-salicylaldehyde derived enynes **9–11**.

Entry	Substrate	Conditions ^a	Product	%-Yield
1	9	A	12	0
2	9	B	12	0
3	10	A	13	0
4	10	B	13	0
5	11	A	14	31
6	11	B	14	8

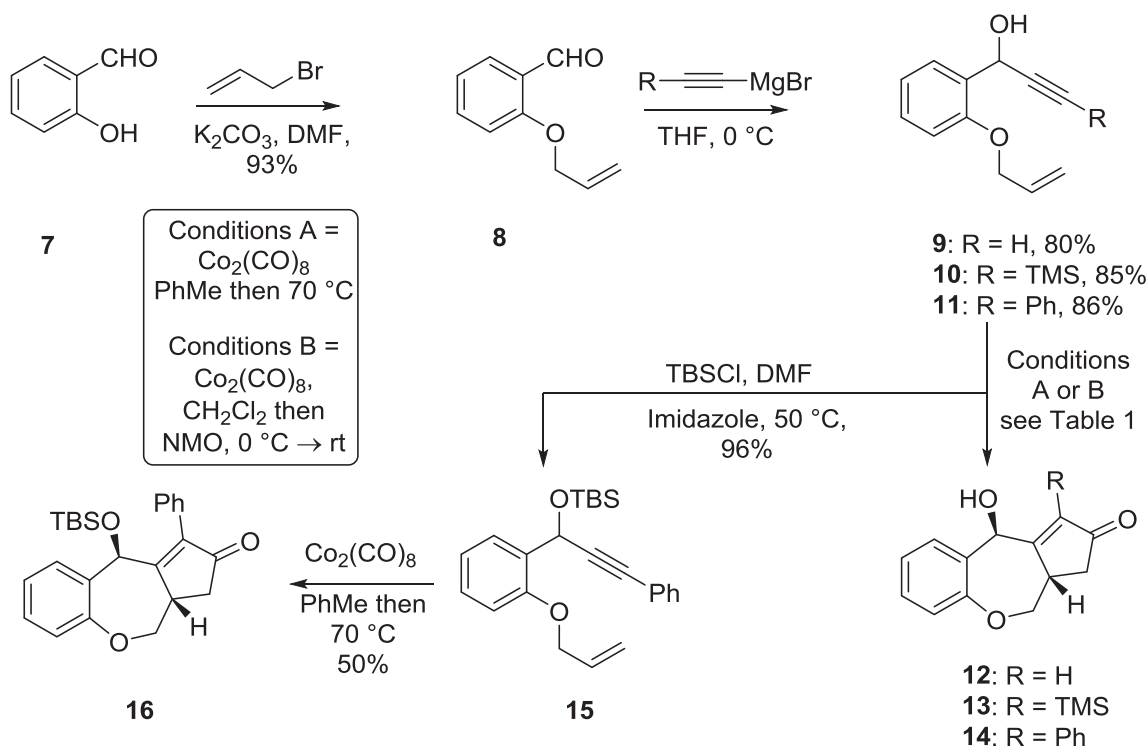
^a Condition A = $\text{Co}_2(\text{CO})_8$, PhMe, then 70 °C; Condition B = $\text{Co}_2(\text{CO})_8$, CH_2Cl_2 , then NMO.

cycloaddition in a somewhat improved 50% yield. It is of note that Perez-Castells reported unsuccessful attempts to cyclize related substrates.^{8b} Given that the cycloadditions of the parent substrate were on the whole poor, we turned our attention to substrates containing substituents *ortho* to the *O*-allyl moiety.

Starting with 4,6-di-*tert*-butylsalicylaldehyde (**17**), it was converted to the allyl ether **18** in the same manner as the parent system **7** and then reaction with the same three Grignard reagents provided the corresponding propargylic alcohols **19–21** in good yields



Scheme 2.



Scheme 3.

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