Steric Promotion of the Intramolecular Pauson–Khand Reaction of Aryl Enynes

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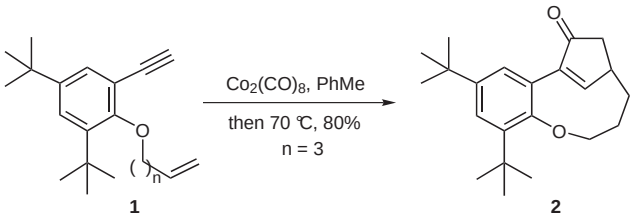
Abstract: The intramolecular Pauson–Khand reaction of 1,8-enynes derived from salicylaldehyde derivatives has been investigated. Substrates derived from salicylaldehyde itself reacted poorly in this reaction, but related substrates containing *ortho*-*tert*-butyl substituents participated quite effectively and in many cases the cyclizations proceeded with high levels of diastereoselectivity.

Key words: organometallic, substituent effects, cyclization, stereoselectivity, cobalt–alkyne complexes



Scheme 1

Our lab has been interested for several years in extending the scope of the intramolecular Pauson–Khand (PK) reaction to permit the construction of a cyclopentenone annulated to a medium-sized ring, with the expectation of using this strategy in natural product total synthesis endeavors.[1–3] Our earliest efforts along these lines involved the use of phenylacetylene analogues derived from iodophenols.[4–6] The basic idea was to use the aromatic framework as a means to reduce the conformational mobility of the enyne, and thus enhance the encounter rate of the alkene and the Co-complexed alkyne. While systems of this type provided 5,6-fused systems quite efficiently,[7] extension to higher homologues was not successful. However, it was found that the introduction of a steric buttressing element *ortho* to the olefin-containing side chain led to both enhanced reaction rates and access to medium-sized rings.[8] Perhaps the most interesting result obtained in the course of this investigation was that these systems cyclized to give bridged systems, a mode of cyclization hitherto unobserved (e.g. **1** → **2**, Scheme 1).[9] This outcome was rationalized in terms of both electronic and steric factors that are thought to control the PK reaction in general. In order to further probe this mode of cyclization, we began an investigation of a set of related substrates, in which an additional carbon atom was placed between the aromatic and acetylenic moieties. We hoped to establish whether this apparently minor modification was tolerated in a general sense, and whether the unusual regiochemistry would be observed in this case.

Our initial investigations began with the elaboration of salicylaldehyde (**3**), by O-alkylation and subsequent reaction with variously substituted acetylenic Grignard derivatives, which provided enynes **5**–**7** in good yields (Scheme 2). These enynes were converted into the corresponding $Co_2(CO)_6$ complex by treatment with $Co_2(CO)_8$ and then subjected to the PK reaction under both oxidative [exposure to *N*-methylmorpholine *N*-oxide, (NMO)][10] and thermal conditions (toluene, ~70 °C).[11] As can be seen in Scheme 2 only the phenyl-substituted enyne **7** undergoes cyclization, providing the cycloadduct **10** in poor yield. Interestingly, it was found that the corresponding silyl ether underwent the cycloaddition somewhat more efficiently, providing **11** in 50% yield.[12] However, despite the fact that this latter example did undergo cyclization, we required a more general solution to cyclizing this type of substrate.[13] In our previous study we had found that the incorporation of buttressing elements (*ortho*-*tert*-butyl groups) increased both the rates and efficiencies of intramolecular PK reactions, and so we decided to explore this tactic with these substrates.[5b,c]

2,4-Di-*tert*-butylsalicylaldehyde (**12**) was O-alkylated with allyl bromide as before (Scheme 3), and then treated with acetylenic Grignard reagents, affording the enynes **14**–**16** in good yield (ca 75%). Initial attempts to engage these substrates in the PK reaction were complicated by the formation of multiple products, and therefore to ease our initial evaluation of these reactions, we decided to remove the propargylic hydroxyl group. This was accomplished readily by treatment of enynes **14**–**16** with Et_3SiH in the presence of TFA leading to the formation of **17**–**19** (Scheme 3). The resulting reduced products were subjected to the PK reaction under both oxidative and thermal conditions (Scheme 4, Table 1). Under both sets of conditions similar results were obtained. The TMS- and Ph-substituted derivatives **18** and **19** both underwent cyclization, providing the expected enones, **21** and **22**, in yields between 45–55% as the only isolable product. An X-ray crystal structure of enone **22** was obtained (Figure 1), confirming the formation of the anticipated tricyclic system. Interestingly, the parent substrate **17** failed to undergo cyclization, providing only decomplexed enyne. We assume

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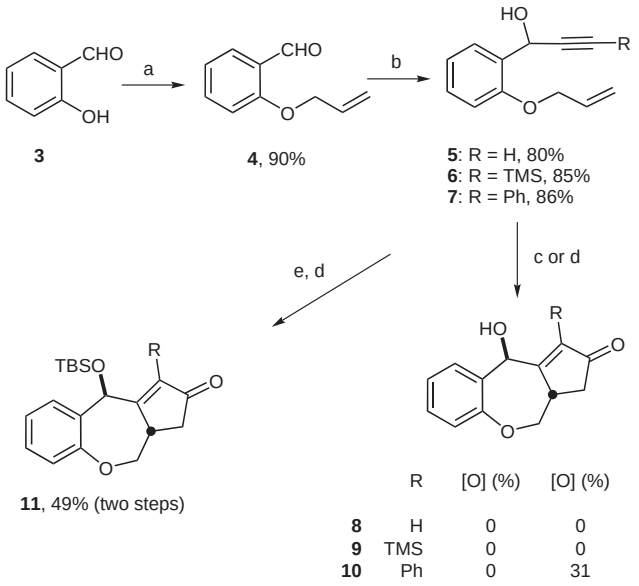
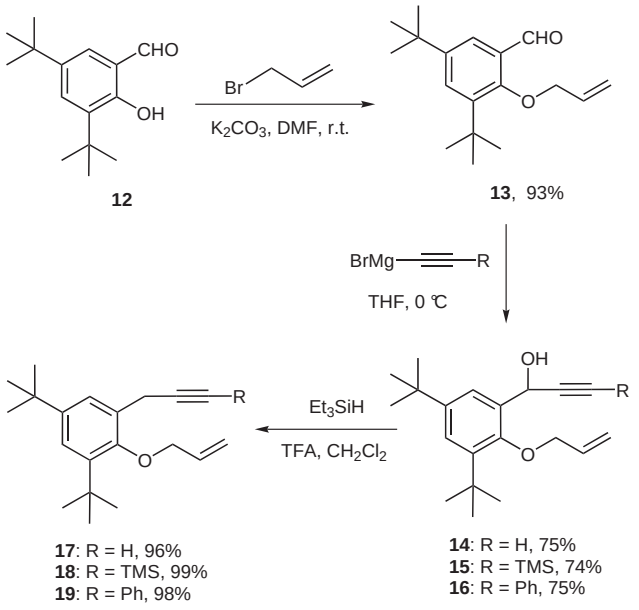


Scheme 2 *Reagents and conditions*: (a) allyl bromide, DMF, K_2CO_3; (b) BrMgC≡CR, THF, 0 °C; (c) $Co_2(CO)_8$, CH_2Cl_2, NMO; (d) $Co_2(CO)_8$, toluene, 70 °C; (e) TBSCl, imidazole, DMF, 55 °C.

that the substituted enyne complexes are somewhat more stable under the PK reaction conditions, whereas the parent substrate complex decomposes faster than it participates in cyclization. We were also able to engage both **15** and **16** in a one-pot, complexation, reduction and cyclization sequence, which provided the enones in comparable yields (Table 1, conditions C), whereas the parent substrate **14** again failed to provide cycloadduct.



Scheme 3

Given this preliminary success with **17**–**19**, we returned our attention to the propargyl alcohols **14**–**16** as substrates, which, after conversion into the $Co_2(CO)_6$ complex, were subjected to both oxidative and thermal

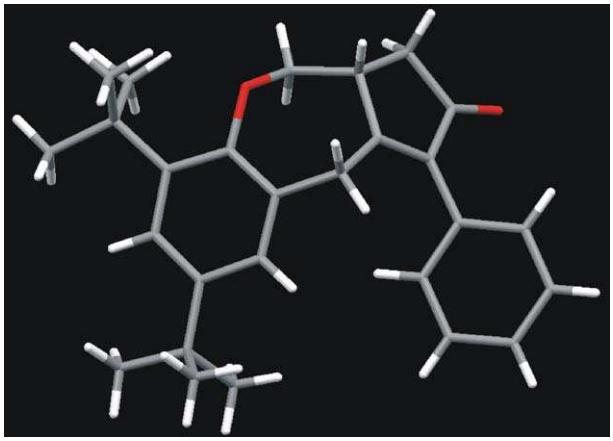
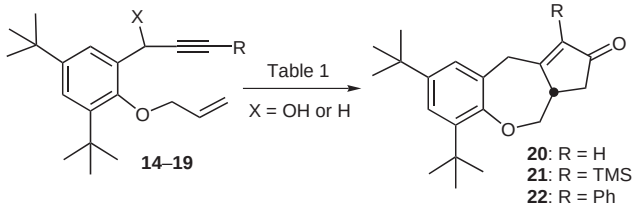


Figure 1 X-ray crystal structure of PK cycloadduct **22**



Scheme 4

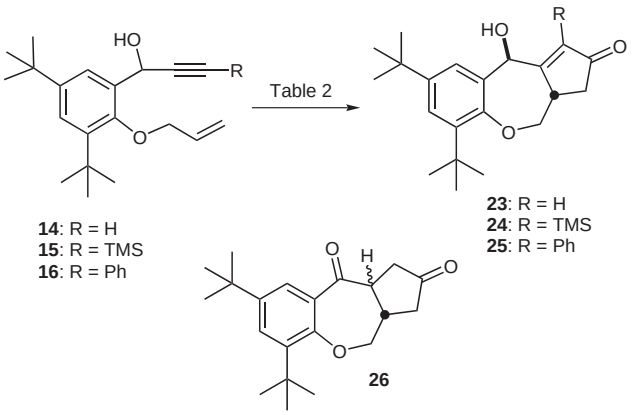
Table 1 PK Reaction of Reduced Enynes

Substrate	Conditions[a]	Product	Yield (%)
17, R = X = H	A	**20**	0
17, R = X = H	B	**20**	0
18, R = TMS, X = H	A	**21**	56
18, R = TMS, X = H	B	**21**	45
19, R = Ph, X = H	A	**22**	43
19, R = Ph, X = H	B	**22**	46
14, R = H, X = OH	C	**20**	0
15, R = TMS, X = OH	C	**21**	48
16, R = Ph, X = OH	C	**22**	50

[a] Conditions A: $Co_2(CO)_8$, toluene, 70 °C; conditions B: $Co_2(CO)_8$, CH_2Cl_2, NMO; conditions C: (i) $Co_2(CO)_8$, CH_2Cl_2; (ii) $NaBH_4$, TFA, (iii) NMO.

conditions. As alluded to above, each of these substrates gave several products (Scheme 5, Table 2), including the expected enones **22**–**25**. In the case of the parent substrate **14**, a total of four cycloadducts were obtained. Under oxidative conditions, the expected cycloadduct **23** was the minor product, obtained in only 17% yield as a 1:1 mixture of diastereomers, the major product was in fact the 1,4-diketone **26**, which was isolated in 80% yield as a 6:1 mixture of diastereomers.[5f] Under thermal conditions the combined yield was somewhat lower, but the same products were obtained.[14] The TMS- and Ph-substituted

derivatives **15** and **16** also provided multiple products under oxidative conditions, both the expected cycloadduct **24** and **25**, as an approximately 2:1 mixture of diastereomers and the reduction products **21** and **22** were obtained. Interestingly, under thermal conditions, none of the reduction product was formed, only the expected cycloadducts. Furthermore, only one diastereomer was obtained from these reactions. An X-ray crystal structure of the product obtained from the Ph-substituted enyne indicated that it was the *exo* alcohol (Figure 2).



Scheme 5

Table 2 Oxidative and Thermal PK Cyclizations of Enynes **12**–**14**

Substrates	Conditions[a]	Product, Yield (%), (Epimer ratio)	Product,Yield (%), (Epimer ratio)
		23	**26**
14, R = H	A	17 (1:1)	80 (6:1)
	B	11 (2:1)	50 (1:1)
		24	**21**
15, R = TMS	A	70 (2:1)	20
	B	58 (1:0)	0
16, R = Ph		**25**	**22**
	A	26 (2:1)	55
	B	94 (1:0)	0

[a] Conditions: A: $Co_2(CO)_8$, CH_2Cl_2, NMO; Conditions B: $Co_2(CO)_8$, toluene, 70 °C.

We assume that the diketone products **26** arise as a result of the insertion of cobalt into the allylic C–H bond and the formation of a π-allyl complex **30** (Scheme 6). Formation of and elimination via the isomeric olefin provides the enol **31**, decomplexation of the cobalt cluster and tautomerization then provides the diketone derivative **26**. We similarly assume that the reduction products arise from ionization of the allylic hydroxyl group forming **32**, in a process reminiscent of Nicholas-type chemistry.[15,16] Loss of the oxygen, presumably as CO_2, then provides the

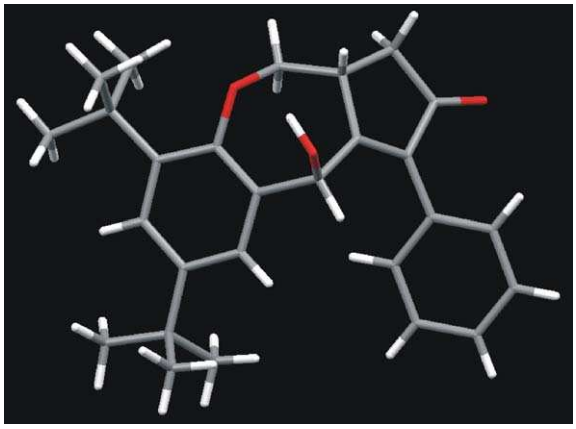
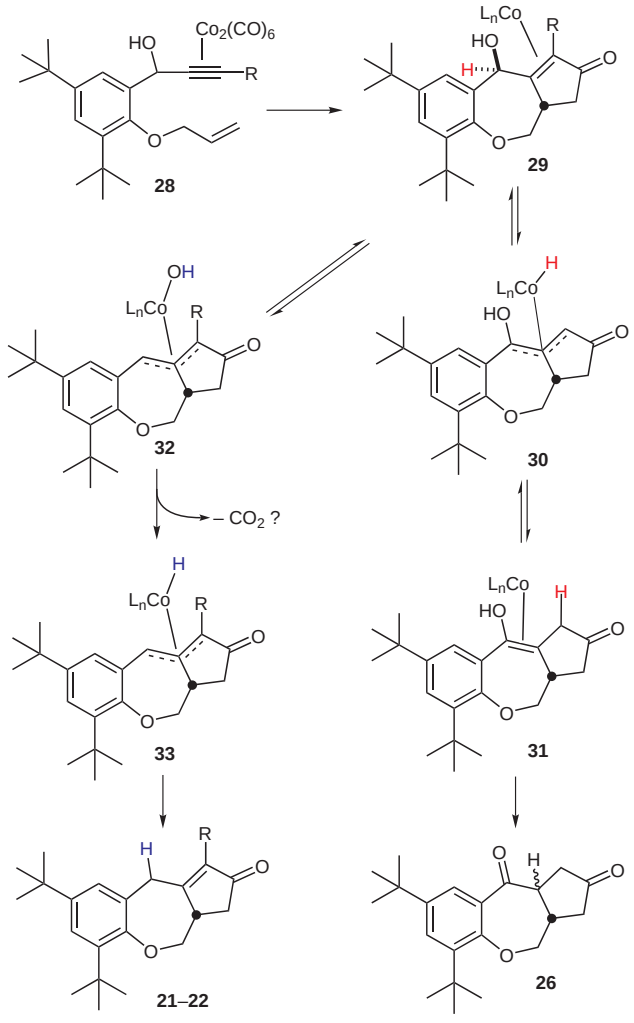
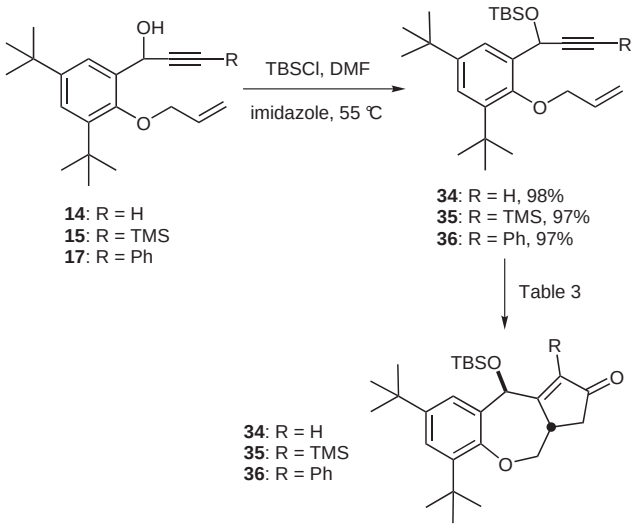


Figure 2 X-ray crystal structure of *exo*-**25**



Scheme 6

cobalt hydride species **33**, which undergoes reductive elimination and decomplexation to provide the reduction products **21** and **22**. While the formation of these products can be rationalized, what is more difficult to understand is the substrate dependence and the product variation as a function of reaction conditions.[17] Once the cobalt complex is formed, the distal substituents exert little electronic



Scheme 7

Table 3 PK Cyclization of Protected Substrate

Substrates	Conditions[a]	Product, Yield (%), (Epimer ratio)	Product, Yield (%)
		37	**20**
34, R = H	A	52 (2:1)	0
	B	80 (1:1)	0
		38	**21**
35, R = TMS	A	61 (1:0)	0
	B	0	0
		39	**22**
36, R = Ph	A	60 (5:1)	11
	B	95 (10:1)	0

[a] Conditions: A: $Co_2(CO)_8$, CH_2Cl_2, NMO; Conditions B: $Co_2(CO)_8$, toluene, 70 °C.

influence toward the propargylic center,[18] although they do provide a steric bias, which frequently leads to the *exo*-type selectivity observed in PK reactions.[5c,19]

Given that under oxidative reaction conditions, and to a limited extent thermal conditions, side reactions involving the free hydroxyl group had been observed, we decided to protect it as a silyl ether. This was readily accomplished under standard conditions providing **34**–**36** (Scheme 7). The resulting enynes were subjected to the PK reaction under both oxidative and thermal conditions (Table 3). In general terms, the cyclizations occurred uneventfully, providing the expected PK products **37**–**39**[20] in good to moderate yields and with good to excellent levels of diastereoselectivity. Some reduction product **22** was still observed under oxidative conditions with the Ph-substituted derivative, but the level was substantially attenuated in comparison to **14**. Similarly, thermal conditions appear to provide greater levels of diastereoselectivity.

In summary our investigation demonstrates that an aromatic ring alone does not sufficiently preorganize the enyne substrate for cyclization leading to medium-sized rings. However, the incorporation of conformational constraints induced by bulky *ortho* substituent enhances both the efficiency and the yield of the enyne cyclization.[21] The PK cyclizations of the substrates reported in this Letter occur with normal regiochemistry and where relevant, proceed with reasonable to high levels of diastereoselectivity. In several examples deoxygenation of the propargylic hydroxyl moiety was observed, but this can be generally attenuated by incorporation of a silyl protecting group. It was also found that these reactions proceed with the typical regioselectivity observed in intramolecular PK reactions, presumably as a result of other orientations requiring unfavorable geometric arrangement of the reacting functional groups. We are continuing to explore the use of buttressing elements in the PK reaction and will report on these in due course.[22]

Acknowledgment

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(7) Congested systems arising from the cyclization of internal alkynes and 2,2-disubstituted olefins were generally poor substrates in this reaction. See ref. 6c for further discussion of this issue.

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(12) Our initial explanation of this change was that bulky silyl ether led to an increase in the reactive conformer population, resulting in enhanced cyclization yields. In other words, the silyl ether was serving as a type of steric buttressing element. However, our subsequent experience with related substrates suggests that this may be only one aspect that contributes to the increased yield. We subsequently observed that substrates containing a free propargylic hydroxyl group were prone to several types of side reactions, and its protection may lead to a reduction of these types of reactions.

(13) For a complementary approach to this type of ring system through the Pauson–Khand reaction, see: Mohamed, A. B.; Green, J. R.; Masuda, J. *Synlett* **2005**, 1543.

(14) Control experiments suggest the diastereomer ratios are kinetically controlled, as the epimeric ketones do not appear to interconvert upon heating in toluene, or on treatment with Et_3N, although at this point, we cannot rule out the possibility of a Co-catalyzed epimerization.

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(16) It is also conceivable that the ionization and reduction take place prior to cyclization, and experiments to address this possibility are currently underway.

(17) It is quite likely that the active complexes (number and type of ligands) are not the same under oxidative and thermal conditions, and thus the differences observed under these two reaction conditions may not only be a result of the temperature differences, but of the precise identity of the active complex.

(18) (a) Thermodynamic study: Connor, R. E.; Nicholas, K. M. *J. Organomet. Chem.* **1977**, *125*, C45. (b) Kinetic study: Kuhn, O.; Rau, D.; Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 900.

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(20) The stereochemistry of the major cycloadducts was determined either through NOE experiments, or in the case of **39**, by desilylation and comparison to *exo*-**23**, to which it was identical.

(21) Selected experimental procedures and selected characterization data. **4,6-Di-*tert*-butyl-2-(-3-phenyl-2-propynyl)-2-propenyloxybenzene (19)**: Triethylsilane (1.24 g, 10.7 mmol) was added at r.t. to a solution of **16** (2.0 g, 5.3 mmol) in CH_2Cl_2 (10 mL) under a N_2 atmosphere. Then trifluoroacetic acid (2.43 g, 21.3 mmol) was added and stirred for 20 min. The reaction mixture was quenched with aq $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 10 mL) to give a yellow liquid. The crude product was purified by flash chromatography (hexane–EtOAc, 95:5) to give **19** as a light yellow liquid (1.87 g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 2.5 Hz, 1 H), 7.44 (m, 2 H), 7.30 (d, *J* = 2.5 Hz, 1 H), 7.29 (d, *J* = 3.0 Hz, 3 H), 6.11 (ddt, *J* = 4.6, 11.0, 17.0 Hz, 1 H), 5.55 (dq, *J* = 1.8, 17.4 Hz, 1 H), 5.32 (dq, *J* = 1.8, 10.5 Hz, 1 H), 4.46 (dt, *J* = 1.8, 4.6 Hz, 2 H), 3.83 (d, *J* = 5.0 Hz, 2 H), 1.46 (s, 9 H), 1.38 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.6, 146.1, 142.0, 134.0, 131.7, 129.9, 128.3, 127.8, 125.5, 124.0, 123.2, 116.5, 88.7, 82.1, 74.1, 35.5, 34.7, 31.6, 31.3, 20.9. IR (neat): 2959, 2870, 1451, 1225, 991, 755 cm^{-1}. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{33}O$: 361.2526; found: 361.2538.

General Procedure for the Oxidative PK Reaction (Procedure A): $Co_2(CO)_8$ (1.1 equiv) was added to a stirred solution of enyne in CH_2Cl_2 and under N_2 at r.t. The reaction mixture was stirred for 5 h at r.t. The reaction mixture was cooled to 0 °C before NMO (12 equiv) was added in three portions at 30 min intervals and then left to stir for 2 h. The reaction mixture was then filtered through a pad of Celite and SiO_2 (ca 1:1) and washed with EtOAc. After rotary evaporation, the crude product was purified by flash chromatography (hexane–EtOAc mixtures).

General Procedure for the Thermal PK Reaction (Procedure B): $Co_2(CO)_8$ (1.1 equiv) was added to a stirred solution of enyne in toluene and under N_2 and stirred for 5 h at r.t. The reaction mixture was then heated at 70 °C under N_2 for overnight. Workup and purification was identical to Procedure A.

6,8-Di-*tert*-butyl-1-phenyl-4,4a-dihydro-3*H*,10*H*-5-oxabenzo[*f*]azulen-2-one (22): The PK cyclization was carried out according to the general Procedures A and B. The enyne **19** (130 mg, 0.36 mmol) was dissolved in the appropriate solvent (10 mL). $Co_2(CO)_8$ (136 mg, 0.40 mmol) and NMO (460 mg, 3.93 mmol) were added according to the general procedure. The crude product was purified by flash chromatography (hexane–EtOAc, 9:1) to afford **22** (60 mg, 43% using Procedure A and 64 mg, 46% using Procedure B) as a yellow solid; mp 160–162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 (t, *J* = 7.8 Hz, 2 H), 7.40 (d, *J* = 2.8 Hz, 1 H), 7.34 (d, *J* = 2.8 Hz, 2 H), 7.30 (s, 1 H), 7.14 (s, 1 H), 4.67 (dd, *J* = 5.5, 11.5 Hz, 1 H), 3.91 (d, *J* = 12.8 Hz, 1 H), 3.76 (d, *J* = 12.8 Hz, 1 H), 3.54 (m, 1 H), 3.35 (t, *J* = 11.5 Hz, 1 H), 2.75 (dd, *J* = 7.1, 18.9 Hz, 1 H), 2.03 (dd, *J* = 2.8, 18.8 Hz, 1 H), 1.41 (s, 9 H), 1.35 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.5, 172.0, 156.8, 146.7, 141.9, 139.7, 131.3, 129.7, 129.6, 128.3, 128.2, 125.3, 123.0, 76.2, 44.1, 36.9, 36.7, 35.2, 34.7, 31.6, 30.7. IR (neat): 2958, 1705, 1474, 758 cm^{-1}. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{32}O_2Na$: 411.2295; found: 411.2266.

6,8-Di-*tert*-butyl-10-hydroxy-1-phenyl-4,4a-dihydro-3*H*,10*H*-5-oxabenzo[*f*]azulen-2-one (25): The PK cyclization of the enyne **16** (250 mg, 0.67 mmol) in the appropriate solvent (10 mL), was carried out following the general Procedures A and B. $Co_2(CO)_8$ (250 mg, 0.73 mmol) and NMO (1.22 g, 10.4 mmol) were added according to the general procedures. The crude product was purified by flash chromatography (silica gel, hexane–EtOAc, 90:10) to afford the reduced PK product **22** (142 mg, 55%) and the expected PK product **25** (70 mg, 26%) as a 1:1 mixture of epimers using Procedure A. Procedure B afforded only *exo*-**25** (255 mg, 94%) as a light yellow solid; mp 171–173 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 (m, 3 H), 7.35 (d, *J* = 2.8 Hz, 1 H), 7.23 (m, 2 H), 7.14 (d, *J* = 2.8 Hz, 1 H), 5.49 (d, *J* = 9.2 Hz, 1 H), 4.61 (dd, *J* = 5.7, 11.5 Hz, 1 H), 4.09 (m, 1 H), 3.51 (t, *J* = 11.9 Hz, 1 H), 3.15 (d, *J* = 8.7 Hz, 1 H), 2.76 (dd, *J* = 6.9, 19.3 Hz, 1 H), 2.03 (dd, *J* = 2.8, 18.8 Hz, 1 H), 1.40 (s, 9 H), 1.32 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.3, 172.3, 156.3, 147.3, 142.8, 139.6, 133.0, 130.7, 129.6, 128.5, 128.3, 125.1, 125.0, 77.9, 73.7, 38.8, 36.7, 35.3, 34.7, 31.5, 30.7. IR (neat): 3435, 2959, 1702, 1598, 756 cm^{-1}. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{33}O_3$: 405.2424; found: 405.2425.

(22) Some initial experiments with olefins with terminal substitution have been successful, but internal substitution is apparently not tolerated.