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Diastereoselective Formation of 5-Vinylcyclopentenes from 1,6-Enynes: Cobalt-Mediated C–H Allylic Activation and Formal 5-Endo-Dig Cyclization

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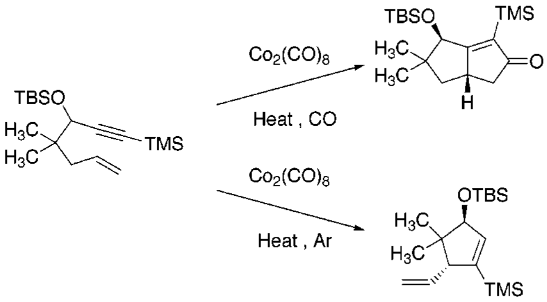
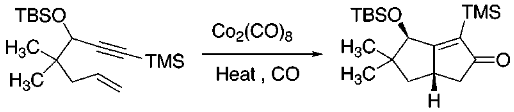
ABSTRACT



A novel intramolecular cyclization reaction mediated by dicobalt octacarbonyl ($Co_2(CO)_8$) is reported. Thermolysis in an argon atmosphere transforms the cobalt complex of 1-trimethylsilyl-6-hepten-1-ynes into 1-trimethylsilyl-5-vinylcyclopentenes in good yield and in a highly diastereoselective manner. This formal 5-endo-dig cyclization is proposed to proceed via an allylic C–H oxidative addition.

The utility of cobalt−alkyne complexes has been demonstrated in organic synthesis. They may be used for facilitating S_N1 reactions at propargylic sites and for the formation of carbocycles through cycloadditions with alkenes and alkynes.[1] One such process, the Pauson-Khand reaction, involves the reaction of dicobalt hexacarbonyl−alkyne complexes with alkenes to form cyclopentenones.[1a,b,2] In particular, the intramolecular variant (e.g., Scheme 1) is very useful for the formation of bicyclic structures and is often highly diastereoselective.[3] Several methods have been developed

Scheme 1



1 2

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[1] For reviews see: Schore, N. E. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stowe, F. G. A., Wilkinson, G., Eds.; 1995; Vol. 12, p 703. (b) Geis, O.; Schmalz, H.-G. *Angew. Chem., Int. Ed. Eng.* **1998**, *37*, 911. (c) Caffyn, A. J. M.; Nicholas, K. M. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stowe, F. G. A., Wilkinson, G., Eds.; 1995; Vol. 12, p 685. Selected examples in synthesis: (d) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc. **1980***, 102, *5253*. (e) Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749. (f) Montaña, A.-M.; Nicholas, K. M.; Khan, M. A. *J. Org. Chem.* **1988**, *53*, 5193. (g) Iwasawa, N. *Synlett* **1999**, *1*, 13.

[2] (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977.

[3] (a) Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477. (b) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851. (c) Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetetrahedron.* **1985**, *41*, 5861. (d) Clive, D. L. J.; Cole, D. C.; Tao, Y. *J. Org. Chem.* **1994**, *59*, 1396. (e) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1998**, *63*, 3346. (f) Kowalczyk, B. A.; Smith, T. C.; Dauben, W. G. *J. Org. Chem.* **1998**, *63*, 1379. (g) Alcaide, B.; Polanco, C.; Sierra, M. A. *J. Org. Chem.* **1998**, *63*, 6786. (h) Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **1999**, *121*, 7411.

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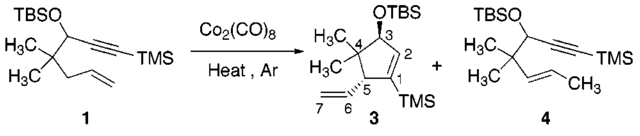
for efficiently promoting the Pauson-Khand reaction under both stoichiometric[4] and catalytic conditions.[5] One of the most common protocols involves thermolysis of the substrate in an apolar solvent and a CO atmosphere.[1a,b] In this letter we report that, for certain substrates, modification of the reaction conditions can lead to an alternative carbocyclization pathway (Scheme 2) in which 1,6-enynes are converted to 5-vinyl-1-trimethylsilylcyclopentenes. This reaction, which involves an apparent allylic C−H insertion and a formal 5-endo-dig cyclization, affords densely functionalized products in good yield and with excellent diastereoselectivity.

Scheme 2



As described by Magnus,[3a−c] enyne **1** readily forms a cobalt complex upon exposure to $Co_2(CO)_8$ in toluene, and subsequent thermolysis of this intermediate in a CO atmosphere results in clean transformation to the cyclopentenone **2**. We have found that if the reaction is conducted in an argon atmosphere, only a small amount of **2** is formed. Instead, the major product is cyclopentene **3** (Scheme 2), which is obtained in good yield along with lesser amounts of isomerized alkene **4** (75:25 ratio of **3**:**4**). Separation of **3** from **4** by either chromatography or distillation proved difficult. However, selective degradation of **4** with potassium carbonate in methanol allowed **3** to be isolated and fully characterized by common techniques. The structure of **3** is fully supported by ^1H, ^{13}C, COSY, HMQC, and HMBC NMR experiments. In particular, the HMBC spectrum reveals correlations between the H5 proton and the C1, C2, C3, and C4 carbons, providing clear evidence for the C1−C5 σ bond formation. Importantly, only a single cyclopentene diastereomer is produced. The trans stereochemistry of the product was assigned by observation of an NOE from H3 to H6 and further substantiated by the lack of an NOE between H3 and H5. The structure of the minor isomerized enyne **4** was confirmed by independent synthesis from 2,2-dimethyl-3-pentenal.

A close examination of the reaction conditions showed that the product yields are dependent upon the nature of the solvent, the reaction temperature, and the level of CO present (Table 1). Conducting the reaction in polar solvents can lead to promotion of the Pauson-Khand pathway (butyronitrile, entry 8),[4d] increased isomerization (2-pentanone, entry 7), or even complete deactivation of the cobalt complex (DMF, entry 9). Of the low polarity solvents investigated, conversion of **1** to **3** was most efficient in toluene at reflux (entry 1). Raising the temperature of the reaction by using a higher boiling point solvent (*p*-xylene) resulted in an increased amount of isomerization to **4** at the expense of **3** (entry 6). Alternatively, the cobalt complex of **1** fails to react at 80 °C in benzene (entry 5). The outcome of the reaction is not affected by varying the duration of the thermolysis or by the presence of a large excess of $Co_2(CO)_8$. The yield of cyclopentene **3** was improved by active removal of CO from the medium (entry 1 vs 10). Formation of Pauson-Khand product **2** was completely inhibited by bubbling argon through the reaction mixture. Using this optimized protocol, the cyclopentene **3** could be isolated in 70% yield.[6]

Table 1. Optimization of Conditions for Carbocyclization of Enyne **1**

entry	solvent	temp (°C)	$Co_2(CO)$ (equiv)	time (h)	ratio **3**:**4**:**2**
1	PhMe	110	1.2	12	70:20:10
2	PhMe	110	1.2	36	70:20:10
3	PhMe	110	2.0	12	70:20:10
4	PhMe	110	0.9	12	50:20:10[a]
5	PhH	80	1.2	12	NR
6	*p*-xylene	135	1.2	12	65:20:15
7	2-Pentanone	101	1.2	12	0:50:0[b]
8	*n*-PrCN	115	1.2	12	0:0:100
9	DMF	110	1.2	12	NR
10[c]	PhMe	110	1.2	12	75:25:0

[a] Ratio reflects 20% recovered starting material. [b] Ratio reflects 50% recovered starting material. [c] Conducted with constant bubbling of argon through the reaction medium.

We propose that the first mechanistic steps in the formation of both **3** and **4** mirror those previously invoked for the Pauson-Khand reaction (Scheme 3).[1a,b,7,8] Thus, in the presence of $Co_2(CO)_8$, the enyne substrate **1** forms a cobalt complex (**5**) at room temperature. Heating induces loss of one CO ligand, which is replaced by coordination of the alkene (complex **6**).[9] In the normal Pauson-Khand process, migratory insertion leads to metallocycle **7** and subsequent CO insertion and reductive elimination give rise to the

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(4) (a) Simonian, S. O.; Smit, W. A.; Gybin, A. S.; Shashkov, A. S.; Mikaelian, G. S.; Tarasov, V. A.; Ibragimov, I. I.; Caple, R.; Froen, D. E. *Tetrahedron Lett.* **1986**, *27*, 1245. (b) Billington, D. C.; Helps, I. M.; Pauson, P. L.; Thomson, W.; Willison, D. *J. Organomet. Chem.* **1988**, *354*, 233. (c) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetetrahedron Lett.* **1990**, *31*, 5289. (d) Hoye, T. R.; Suriano, J. A. *J. Org. Chem.* **1993**, *58*, 1659. (e) For comparison of various stoichiometric protocols, see ref 3d.

(5) See ref 1b and (a) Pagenkopf, B. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, *118*, 2285. (b) Kim, J. W.; Chung, Y. K. *Synthesis* **1998**, 142.

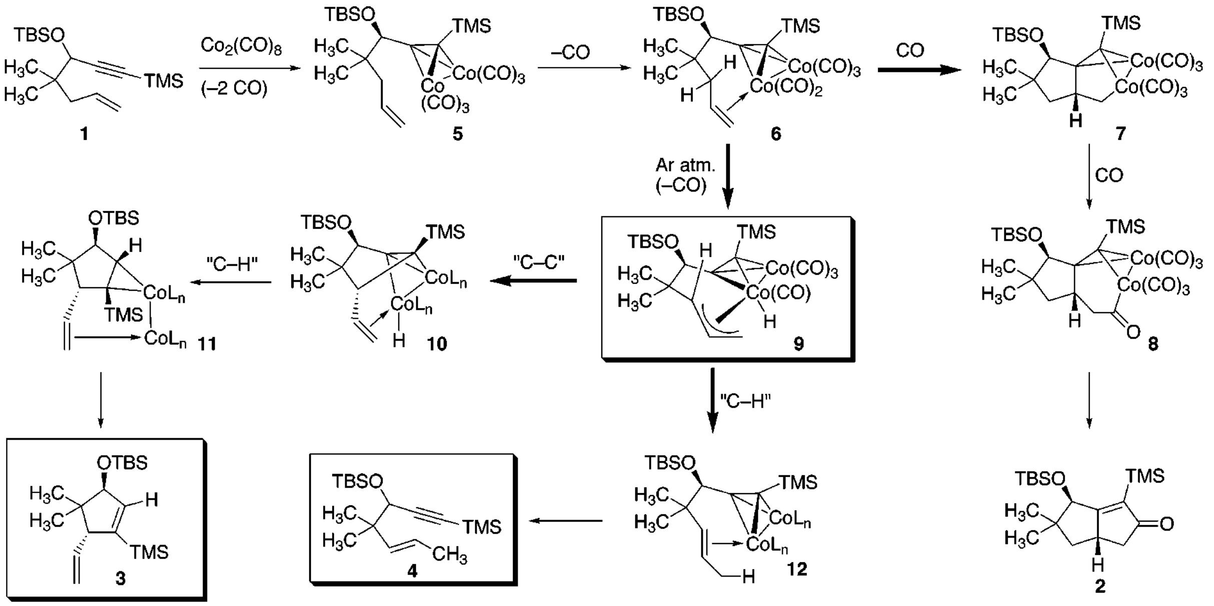
(6) **Representative Experimental Procedure.** In a round-bottom flask fitted with a condenser, a magnetic spin-bar, and a glass tube that permits constant bubbling of argon through the reaction medium, $Co_2(CO)_8$ (632 mg, 1.85 mmol, 1.20 equiv) is added to a solution of the eneyne **1a** (500 mg, 1.54 mmol, 1.00 equiv) in anhydrous toluene (40 mL). After stirring at 21 °C for 2 h, the black solution is heated at reflux for 12 h, during which time a suspension forms and a cobalt(0) mirror coating is observed on the sides of the flask. After cooling to 21 °C, the black suspension is concentrated, and the products are separated using chemical derivatization and flash chromatography techniques. For full details see Supporting Information.

(7) LaBelle, B. E.; Knudsen, M. J.; Olmstead, M. M.; Hope, H.; Yanuck, M. D.; Schore, N. E. *J. Org. Chem.* **1985**, *50*, 5215.

(8) This reaction appears to be mechanistically different from the interrupted Pauson-Khand reaction reported by Krafft. See: Krafft, M. E.; Wilson, A. M.; Dasse, O. A.; Shao, B.; Cheung, Y. Y.; Fu, Z.; Bonaga, L. V. R.; Mollman, M. K. *J. Am. Chem. Soc.* **1996**, *118*, 6080.

(9) As with the Pauson-Khand reaction, it has not been possible to detect any intermediates other than the initial cobalt complex **5.** Evidence for the initial ligand loss exists. See: Krafft, M. E.; Scott, I. L.; Romero, R. H.; Feibelmann, S.; Van Pelt, C. E. *J. Am. Chem. Soc.* **1993**, *115*, 7199.

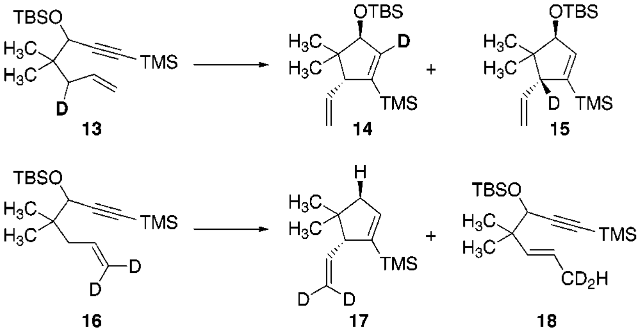
Scheme 3



cyclopentenone product **2**. We propose that this migratory insertion process (**6** → **7**) is driven by recomplexation of a CO ligand and that in the absence of added CO, an allylic C−H oxidative addition forms η^3-allylcobalt hydride **9**.[10] This complex can partition between reductive elimination to form a C−H bond (complex **12**), leading to isomerized alkene **4**, and reductive elimination to form a C−C bond between C5 and C1 (complex **10**). In the latter case, subsequent reductive elimination to form a C−H bond gives rise to complex **11**, which after decomplexation provides the cyclopentene **3**. The notion that CO is required for driving the migratory insertion process is at present limited to this particular class of substrates, as there are cases where the Pauson-Khand pathway occurs in the absence of a CO atmosphere (vide infra). We suggest that the facial selectivity of the formation of the η^3-allylcobalt species, presumably the stereodefining step of the entire sequence, is determined by minimization of nonbonded interactions between the allyl group and the *tert*-butyldimethylsilyloxy group.

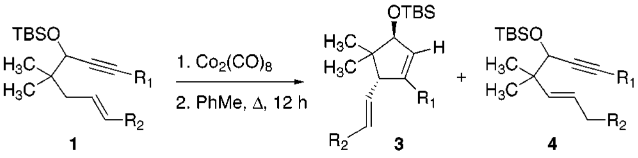
The proposed mechanisms are consistent with two deuterium labeling experiments that were conducted (Scheme 4). Submission of **13** to the standard reaction conditions led to deuterium enrichment at C2 of the cyclopentene. When **16** was subjected to the same reaction conditions, no migration of the deuterium label was observed in either the cyclopentene or the isomerized olefin. These results are consistent with the formation of allyl cobalt species **9** and subsequent reductive elimination to give **10** and **12**. Furthermore, they are inconsistent with a mechanism by which the alkene first isomerizes to internal olefin **4** prior to cyclopentene ring formation.[11] That **4** is a byproduct and not an intermediate was confirmed by the fact that **4** remains unchanged when resubmitted to the reaction conditions.

Scheme 4



A series of substrates were submitted to the optimized reaction conditions to investigate the scope of the rearrangement (Table 2). Internal alkynes ($R_1 = CH_3$, ^{t}Bu, phenyl;

Table 2. Cobalt-Mediated Cyclopentene Formation



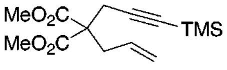
entry	R_1	R_2	product ratio[a] **3**:**4**	isolated yield of **3**
a	Me_3Si	H	75:25	70%
b	Me_3Ge	H	80:20	72%
c	*t*-$BuMe_2Si$	H	15:10[b]	
d	Me_3Si	CO_2Et	95:0[c]	92%
e	Me_3Si	CH_2OTBS	*d*	71%

[a] Determined by ^{1}H NMR. [b] Ratio reflects 75% of **1** remaining. [c] Ratio reflects 5% of **1** remaining after third iteration; 58% conversion observed after first iteration. [d] Several unidentified minor products were observed in this reaction.

R_2 = H) gave complex mixtures with no evidence of cyclization to cyclopentenes of form **3**. The trimethylgermyl derivative **1b** underwent clean reaction, and an improved ratio of cyclopentene to isomerized olefin was realized.[12] Interestingly, an increase in steric bulk of the silyl group is detrimental to the efficiency of the reaction. With the *tert*-butyldimethylsilyl alkyne **1c**, only 25% of the starting material is consumed during the reaction, and the incorporation of a larger TIPS substituent at R_1 gives a completely unreactive substrate. A comparison of the reactivities of R_1 = ^{t}Bu, TMS, and $GeMe_3$ hints toward an inductive electronic effect in which the relative electron density of the cobalt complex is an important factor in promoting the product-determining C−H insertion step.

In addition to the variations at the terminal alkyne position, functional groups were introduced at the alkene terminus of the substrate. Under the above reaction conditions, α,β-unsaturated ester **1d** afforded exclusively cyclopentene **3d** and recovered starting material (58% conversion), with no evidence of alkene migration (entry 12). Reiterating the reaction process twice before purification resulted in nearly complete conversion of **1d** and a 92% isolated yield of **3d**. In contrast, silyloxymethyl-substituted **1e** underwent cyclization to form cyclopentene **3e** in 74% yield with no starting material recovered. This indicates that the lower reactivity of **1d** is most likely due to electronic rather than steric factors.

Finally, it is important to note that the normal Pauson-Khand reaction does occur for some 1-trimethylsilyl-hept-6-en-1-ynes under the described reaction conditions. For instance, the simple malonate-derived enyne **19** formed only the Pauson-Khand product when submitted to the reaction conditions. Furthermore, there are numerous reports where other substrates undergo normal Pauson-Khand reactions under nitrogen atmosphere.[3g,9]



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In conclusion, we have shown that a variation in the Pauson-Khand protocol can produce novel cylopentenes through a proposed cobalt-mediated C−H allylic activation and formal 5-endo-dig cyclization of 1,6-enyne substrates. Single diasteroisomers of highly functionalized compounds are synthesized in good to excellent yields. The reaction is tolerant of ester and silyl ether groups. Although the reaction appears to be limited to trimethylsilyl and trimethylgermyl alkynes, it should be possible to transform the vinyl silanes and germanes into other functional groups. Further studies in this area will include the extension of this methodology to cyclic ethers and amines as well as a delineation of the factors that induce different substrates to follow either the Pauson-Khand or cyclopentene-forming pathway.

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Supporting Information Available: Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The formation of η^3-allylcobalt hydrides were postulated by Serratosa et al. as a potential mechanism for isomerization of bicyclo[3.3.0]-oct-2-enes to bicyclo[3.3.0]oct-1-enes during intermolecular Pauson-Khand reactions. See: Montaña, A.-M.; Moyano, A.; Pericàs, M. A.; Serratosa, F. *Tetrahedron Lett.* **1985**, *41*, 5995.

(11) A related, albeit mechanistically different, reaction has been reported wherein 7-trimethylsilyl-6-hepten-1-ynes undergo 5-endo-dig cyclizations under the influence of halfnium (IV) chloride. Imamura, K.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5339.

(12) The corresponding alkynyltin substrate (R_1 = $SnMe_3$; R_2 = H) proved to be too unstable to the reaction conditions and gave only decomposition products.