Tetrahedron Letters, Vol.31, No.51, pp 7505-7508, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

ASYMMETRIC INDUCTION STUDIES IN THE INTRAMOLECULAR PAUSON-KHAND CYCLIZATION OF 7-ALKOXY-1-HEPTEN-6-YNES

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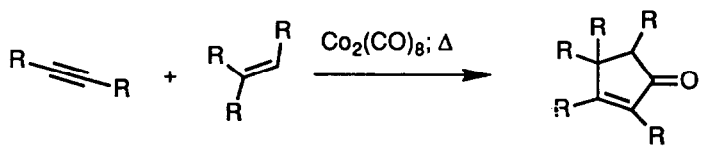
Summary: *Asymmetric induction has been achieved in the intramolecular Pauson-Khand reaction of 7-alkoxy-1-hepten-6-ynes derived from chiral alcohols. The stereochemical outcome of the reaction can be explained by the intermediacy of a cis-cobaltabicyclooctane.*

Among the several published[1-3] transition metal-mediated syntheses of cyclopentenones from alkenes, alkynes, and carbon monoxide, the cobalt-induced process (the Pauson-Khand reaction, eq 1)[1] is arguably the most powerful. It is therefore surprising that there have been no reports to date of efforts directed toward making this transformation enantioselective by using a chiral auxiliary.[1] In this communication we describe some of our initial results in this area.[4]



Equation 1

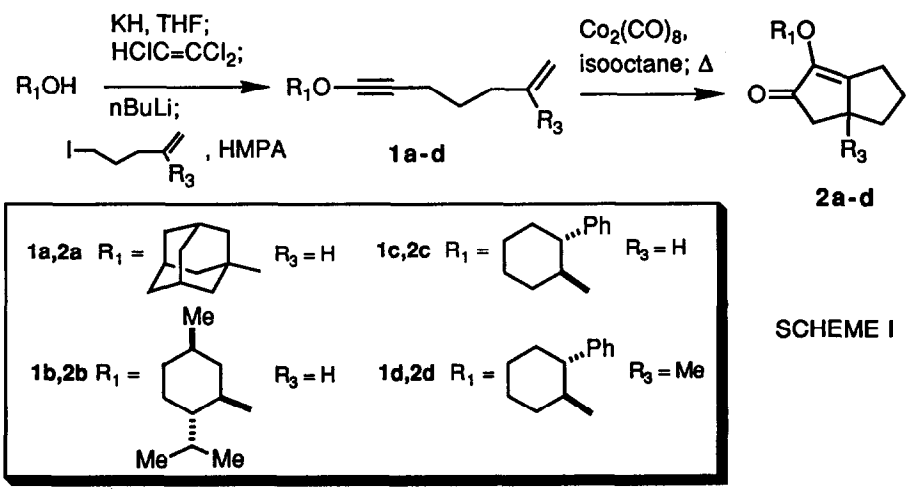
Nearly all types of acetylenes readily enter into the Pauson-Khand reaction, a notable exception, though, being ethoxyacetylene. The rather unstable dicobalt hexacarbonyl complex of ethoxyacetylene on reaction with norbornene has been reported to give only a trace amount of an unidentified ketone.[5] In that previous experience had shown that well-substituted acetylenic diethers afford relatively stable dicobalt hexacarbonyl complexes,[6] it seemed worthwhile to investigate the possibility that acetylenic monoethers composed of alkoxyl groups bulkier than ethoxyl could in fact be suitable for use in the Pauson-Khand reaction. *If so, an asymmetric version of the Pauson-Khand reaction might then be possible through the use of readily available homochiral acetylenic ethers.*

In order to dissociate the complexation and cyclization components of the Pauson-Khand reaction, first the dicobalt hexacarbonyl complexes of a series of representative acetylenic ethers were prepared (through treatment of the alkyne with 1.1 equiv of dicobalt octacarbonyl in a hydrocarbon solvent at ambient temperature) and isolated. The yields of the isolated complexes are given in Table I. While increasing the steric bulk of the alkoxyl group, as expected, improves the yield of the complex, the presence of an additional acetylenic substituent produces a far more meaningful amelioration. Through appropriate substitution of the acetylenic ether (e.g., entries 7,8), synthetically useful yields of the dicobalt hexacarbonyl complexes can indeed be realized; however, the yields of the complexes are, in general, lower than those obtained with "normal" acetylenes.

Table I. Dicobalt Hexacarbonyl Complexes from Acetylenic Ethers $R_1OC{\equiv}CR_2$

Entry	R_1	R_2	Solvent	Yield (%)
1	n-decyl	H	Pet. ether	38
2	2,6-dimethylphenyl	H	Pet. ether	88
3	cyclohexyl	H	Pet. ether	98
4	*trans*-2-phenylcyclohexyl	H	Pentane	10
5	*tert*-butyl	H	Pentane	12
6	1-adamantyl	H	Benzene	17
7	*tert*-butyl	trimethylsilyl	Pentane	36-55
8	*trans*-2-phenylcyclohexyl	methyl	Isooctane	77

With these results in hand, the intramolecular Pauson-Khand reaction of several 7-alkoxy-1-hepten-6-ynes (**1a-1d**, Scheme I) was investigated. It was hoped that advantage could be taken of the positive effect in the Pauson-Khand reaction of both alkyne substitution (complexation efficiency) and intramolecularity (cyclization yield).[7] The requisite enynes could readily be prepared from the corresponding acetylenic ethers by alkylation[8] (**1a**, 64%) or directly from the corresponding alcohols through an efficient one-pot procedure[9] previously developed in our laboratories (**1b**, 76%, **1c**, 90%, **1d**, 89%).[10] When the alkoxyenynes were first treated with dicobalt octacarbonyl in isooctane or xylene and then heated at reflux in the same solvent, the corresponding 2-alkoxybicyclo[3.3.0]oct-1-en-3-ones **2a-d** were obtained in the yields shown in Table II. It is interesting to note that the efficiency of these complexation-cyclizations is similar to that observed with 1-hepten-6-yne, which produced bicyclo[3.3.0]oct-1-en-3-one in 31% yield.[7]



SCHEME I

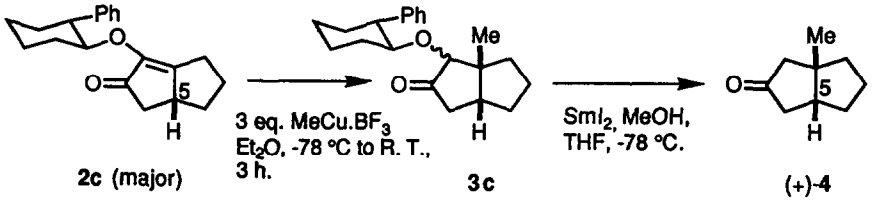
Table II. Intramolecular Pauson-Khand Cyclization of Alkoxyenynes **1a-d.**

Enyne	Solvent, Reflux Time (h)	Product	Yield(%)	Diast. ratio
1a	xylene, 2	**2a**	24	
1b	xylene,4	**2b**	30	1.1 : 1
1c	isooctane, 16	**2c**	38	3.2 : 1
1d	isooctane, 15	**2d**	28	1.2 : 1

In the case of the (-)-menthol derivatives **2b**, the ^{13}C NMR spectrum clearly indicated that the reaction had proceeded with a small, but real, diastereoselection, even though menthol is generally considered to be a rather inefficient chiral auxiliary, and the newly created chiral center is four bonds away from the first asymmetric carbon atom in the alkoxyl group. The more stereodiscriminating chiral auxiliary, *trans*-2-phenylcyclohexanol,[11] was found to

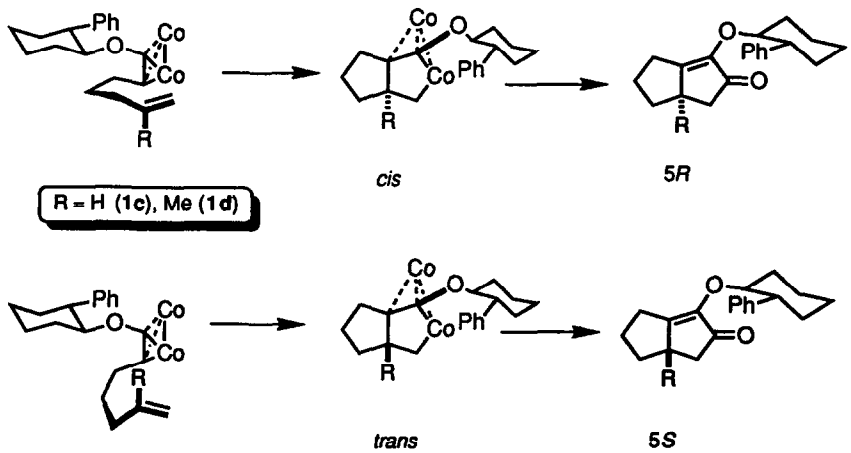
give **2c** with a sizable 52% diastereomeric excess[12]. *Thus, a significant level of induction can clearly be achieved in the intramolecular alkoxyacetylene-olefin Pauson-Khand cyclization.* The extent of the diastereoselection, however, was observed to be a function of the olefin substitution: the 2-methyl derivative **1d** afforded the corresponding bicyclooctenones **2d** with considerably lower diastereoselectivity.

The configuration of the newly created center in the major diastereomer of **2c** could be established as shown in Scheme II. The major isomer of **2c**, derived from optically pure[11] (1*S*, 2*R*)-(+)-2-phenylcyclohexanol and obtained in diastereomerically pure form by chromatography, was exposed to Yamamoto's methylcopper-boron trifluoride reagent[13] to give the conjugate addition product **3c** (epimeric at C-2). Reductive cleavage of the auxiliary in **3c** with samarium diiodide[14] then cleanly produced the known[15] (+)-*cis*-1-methylbicyclo[3.3.0]octan-3-one (**4**) (enantiomerically pure, as evidenced by the ^{13}C NMR spectrum of the acetal derived from (2*R*,3*R*)-2,3-butanediol[16]). Since the absolute configuration at C-5 of (+)-**4** is known to be *R*, that at C-5 of the major diastereomer of **2c** is also *R*.



SCHEME II

This stereochemical outcome can be explained on the basis of the currently accepted Pauson-Khand mechanism.[17] A PCMODEL calculation of the dicobalt hexacarbonyl complex of 1-((1*S*,2*R*)-2-phenylcyclohexyloxy)propyne (taken as a model for enynes **1c** and **1d**), shows that the most stable conformation is that in which the bulky dicobalt hexacarbonyl group is disposed as far as possible from the cyclohexane ring. The analogous conformation in the case of enynes **1c** and **1d** (see Figure below) places the pro-*S* diastereotopic cobalt atom so as to be more accessible to the olefin than the pro-*R* cobalt due to appreciable shielding by the phenyl group. Assuming that metallocycle formation is the step that controls the diastereoselectivity of the process,[17] the major diastereomer of the Pauson-Khand cyclization of enyne **1c** would arise then principally from the transient *cis* cobaltabicyclooctane (see Figure below, R=H) that is the product of coordination of the pro-*S* cobalt with the *Si* face of the olefin.The minor diastereomer would be formed either by *Re* face olefin coordination with the pro-*R* cobalt or, possibly, by coordination of the same pro-*S* cobalt with the *Re* face of the olefin, which would produce a transient *trans* cobaltabicyclooctane.



It is interesting to note that the loss of stereoselectivity observed with **1d** can be accounted for through this same interpretation by assuming that the energy difference between the *cis* and *trans* cobaltabicyclooctanes diminishes due to the steric interaction between the methyl and the exocyclic cobalt tricarbonyl group in the *cis* diastereomer (see Figure above, R=Me).

A general and efficient asymmetric approach to the Pauson-Khand reaction, based on the use of a removable chiral controller, would serve to make this powerful cyclopentenone synthesis yet more useful. The insight provided by these initial results should facilitate the design of alkoxyenyne systems to meet this objective.

Acknowledgments We thank Dr. A. Riera for helpful discussions, and the DGICYT (Grant PB86-0510) and the CNRS (UA 332) for financial support. A FPI fellowship (to J.C.) is gratefully acknowledged.

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(Received in UK 24 October 1990)