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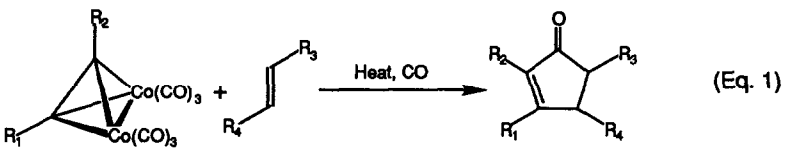
N-OXIDE PROMOTED PAUSON-KHAND CYCLIZATIONS AT ROOM TEMPERATURE

Soroosh Shambayati, William E. Crowe[1] and Stuart L. Schreiber
Department of Chemistry, Harvard University
Cambridge, MA 02138

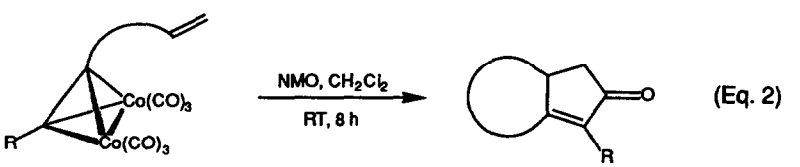
Abstract Tertiary amine oxides have been utilized to effect cobalt-mediated intramolecular cyclizations of enynes (Pauson-Khand reactions) at room temperature. The stereoselectivity, range and limitations of this method are examined.

Cycloaddition of dicobalthexacarbonyl complexes of acetylenes to olefins (Pauson-Khand reaction) is a novel and useful method for the synthesis of cyclopentenone derivatives (Eq. 1).[2,3] The reaction is typically performed at elevated temperatures (60-110 °C) under an atmosphere of carbon monoxide, with the exception of



(Eq. 1)

the procedure of Smit and Caple[4] involving silica gel catalysis and the recently developed ultrasound method of Billington and Pauson.[5] In the former, the reaction occurs under an atmosphere of oxygen at 45 °C, while sonication effects cyclization between room temperature (RT) and 60 °C. In this Letter we report a new and efficient method for the execution of the Pauson-Khand process, which provides a milder and more stereoselective alternative to the corresponding thermal reactions. More specifically, we have found that tertiary amine oxides (e.g. N-methylmorpholine-N-oxide; NMO) readily promote intramolecular Pauson-Khand cyclizations at room temperature, under an inert atmosphere of argon or nitrogen (Eq. 2).

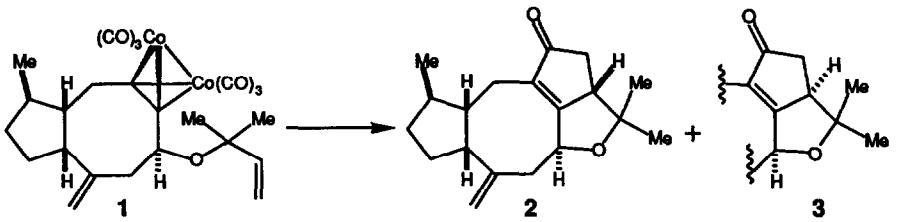


(Eq. 2)

The generality of this method was examined on a number of model substrates as well as on several intermediates for the synthesis of natural products. As outlined in Table I, the N-oxide procedure was successful in the preparation of a variety of fused ring skeletons. For example, both 1,6- and 1,7-enynes can be used to obtain the corresponding fused [3.3.0] and [4.3.0] bicyclic skeletons (entries 1 and 5), although simple 1,8- and 1,9-enynes failed to cyclize. Not surprisingly, substituents on the olefin tether seem to facilitate the intramolecular reactions (cf. entries 1 & 2) and oxygen heteroatoms are also tolerated without complication. The mild conditions required by the reaction allow for the incorporation of various functional groups in the

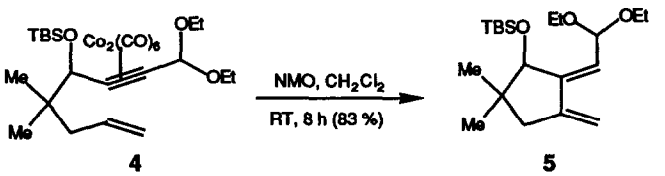
cyclization precursors. Thus far, alcohols, ethers, silyl ethers, acetals and remote olefins have all been found to remain intact during the course of the reaction. More importantly, the lower temperature of the reaction leads to higher levels of stereoselectivity, as compared to the corresponding thermal or ultrasound reactions (Scheme I).

Scheme I



Conditions	Yield (%)	Selectivity (2 : 3)
NMO, CH_2Cl_2, RT	68	11 : 1
CH_3CN, 82 °C	75	4 : 1
CH_3CN,))), 45 °C	45	3 : 1

The reaction with electron deficient alkynes seems to follow a different course. Diene **5** was produced in high yield during an attempted cyclization of the complex **4** (Eq. 3). Diene products have also been observed in



(Eq. 3)

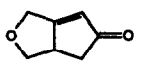
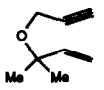
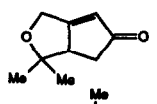
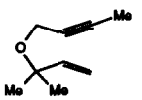
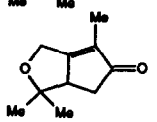
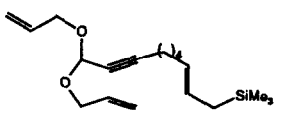
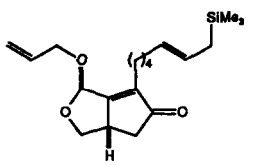
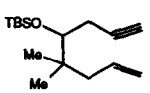
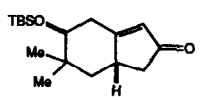
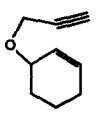
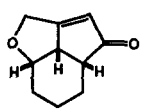
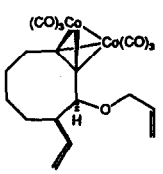
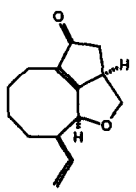
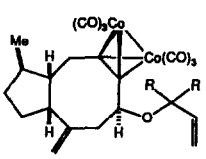
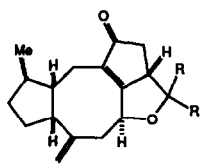
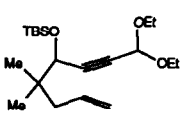
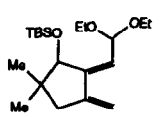
moderate yields (45%) by Khand and Pauson in the intermolecular, thermal reaction of acyl-substituted olefins.[6] Although the generality of this process remains to be established, the reaction is reminiscent of the nickel and palladium catalyzed isomerizations of enynes, recently reported by Trost and coworkers.[7]

It is likely that the mechanism of the N-oxide promoted reaction involves initial oxidation of a cobalt CO ligand to CO_2, thus providing an empty site of coordination for the olefin. However, it is not clear whether or not the N-oxide or the 3° amine, produced during the reaction, can also act as ligands for one of the cobalt-containing intermediates, thereby diverting the steric and electronic course of the reaction away from that of the classical, thermal Pauson-Khand.[8]

Representative Experimental Procedure

A solution of the cobalt complex **1** (30 mg, 0.055 mmol) in CH_2Cl_2 (10 mL) was treated with a single portion of solid N-methylmorpholine-N-oxide (39 mg, 0.33 mmol)[9] at room temperature. After 12 hours stirring at room temperature, a purple precipitate had formed, and TLC analysis indicated the consumption of all starting material with concomitant formation of a more polar, UV active spot (R_f=0.3 in 4:1 hexane/ethyl acetate). The mixture was passed through a small plug of silica gel and the filtrate was concentrated in vacuo.[10] The resulting yellow oil was purified by silica gel chromatography (3:1 hexane:ether) to give 11 mg of a clear oil, shown to be an 11:1 mixture of the diastereomeric enones **2** and **3** by spectral analysis (68%).

Table I. N-Oxide Promoted Pauson-Khand Cyclizations of Enynes[a]

Entry	Substrate[b]	Product[c]	Yield (%)[d]	Selectivity[e]
1			85	-
2			92	-
3			77	-
4			70	4 : 1[f]
5			87	5 : 1[g]
6			98	> 25 : 1[g]
7			90	8 : 1[h]
8			86	5 : 1[h,i]
9	R = H R = Me		68	11 : 1[h]
10			83	-[f]

[a]All reactions were performed according to the procedure reported in the text with reaction times ranging between 8-16 h. All new compounds were fully characterized by ^1H, ^{13}C NMR, IR, and mass spectroscopy. [b]Cobalt complexes of enynes were obtained according to standard procedures reported in ref. 2. [c] Only the major diastereomer is shown. [d]Isolated yields after chromatographic purification. [e]Selectivity refers to the diastereomeric ratios with regards to the newly formed stereocenter. Ratios were determined by ^1H NMR spectroscopy. [f]Stereochemistry deduced only by analogy to related compounds. [g]Stereochemistry deduced from ^1H NMR coupling constants. [h]Stereochemistry deduced from NOEDS experiments. [i]Stereochemistry determined by X-ray crystallographic analysis of crystalline derivatives.

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References and Footnotes

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8. For a study of the effect of phosphines and phosphine oxides as additives in the Pauson-Khand reaction see ref. 5a.
9. Use of a pre-dried (4 Å sieves) solution of NMO, instead of the solid form of the reagent, did not have a noticeable effect on the efficiency of the reaction.
10. For substrates that may be sensitive to high concentrations of a 3° amine, the workup procedure can be modified to include a $CuSO_4$ wash (5-10 % solution) of the organic layer to remove any excess N-methylmorpholine.

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