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A Dual-Function, Highly Efficient Chiral Controller for Stereoselective Intermolecular Pauson-Khand Reactions

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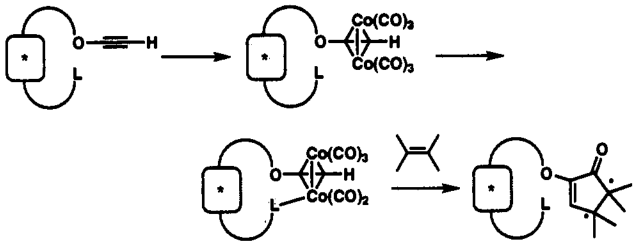
Pauson–Khand and related cyclopentenone-forming reactions, in particular those that can be applied to bicyclization, are presently experiencing considerable scrutiny and application in synthesis.[1] The potential of these transition-metal-mediated transformations for the preparation of complex natural products[1,2] prompted us to examine a few years ago a novel strategy for Pauson–Khand intramolecular bicyclization, which resulted in an effective, enantioselective approach.[3,4]

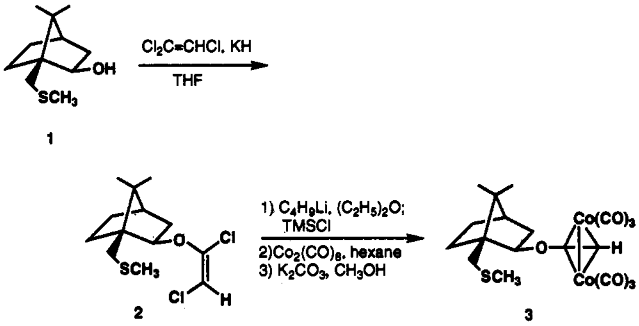
Quite recently, we have extended our interest to the intermolecular version of the Pauson–Khand reaction, which offers the additional advantages of simplicity and ready availability of starting materials. Stereochemical control in this mode of the reaction, although more challenging than in the intramolecular one, has also been addressed with encouraging results through the use of alkoxy acetylenes derived from conventional, purely sterically based chiral auxiliares.[5]

Seeking to enhance stereocontrol in this intermolecular process, we have now examined several chiral auxiliares that bear an appropriately positioned group able to interact with the metal center along the reaction pathway and thus potentially improve the diastereoselection of the reaction (Scheme 1). In this communication we report that the auxiliary 10-methylthioisoborneol[6] (**1**), selected for study on the basis of our previous results with camphor-derived inductors[4,5] and the known ability of alkylthio groups to interact with cobalt clusters,[7] appears to function within this conceptual design and serves as a highly effective chiral controller for stereoselective intermolecular Pauson–Khand reactions.

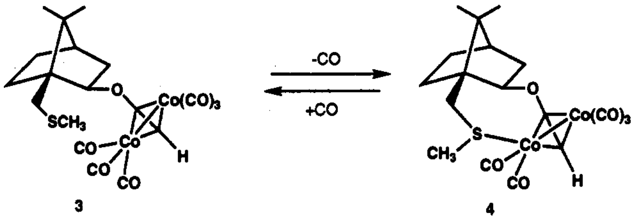
Scheme 1



Scheme 2



Scheme 3



The requisite alkoxy acetylene hexacarbonyl complex **3** could be prepared from this readily available alcohol by using a novel, recently developed procedure[8] (Scheme 2). The alkoxy dichloro olefin **2**, obtained from **1** in 78% yield,[9] was transformed to the hexacarbonyl complex **3** in 80% yield through the trimethylsilylated alkoxy acetylene derivative.

Concordant with our expectations, when **3** in hexane was allowed to stand at near ambient temperature under a current of dry nitrogen (for CO evacuation), it indeed underwent transformation to give a more polar substance, whose spectroscopic data were consistent with the formulation in **4** (Scheme 3). Interestingly and in support of this structure, **4** reverted completely to **3** when the above solution was stirred under a CO atmosphere.[10,11]

The feasibility of the interconversion of **3** and **4** established, our first interest was to determine if the nature of the initial species, **3** or **4**, had a definite effect on the course of the Pauson–Khand reactions (see Table 1). With norbornene as the substrate, the transformation was first carried out under typical thermal conditions and with a CO atmosphere (conditions A), which was intended to minimize conversion to **4**. At 20 °C, the reaction

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(1) For reviews on the Pauson-Khand reaction, see: Pauson, P. L.; Khand, I. U. *Ann. N. Y. Acad. Sci.* **1977**, *295*, 2–14. Pauson P. L. *Tetrahedron* **1985**, *41*, 5855–5860. Schore, N. E. *Org. React.* **1991**, *40*, 1–90. Schore, N. E. In *Comprehensive Organic Synthesis;* Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, pp 1037–1064.

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(9) Moyano, A.; Charbonnier, F.; Greene, A. E.*J. Org.Chem.* **1987**, *52*, 2919–2922.

(10) While this manuscript was in preparation, a report appeared (Krafft, M. E.; Scott, I. L.; Romero, H. R.; Feibelmann, S.; Van Pelt, C. E. *J. Am. Chem. Soc.* **1993**, *115*, 7199–7207) describing a related equilibrium between two achiral cobalt complexes.

(11) By ^1H NMR and TLC analysis, the new compound **4** appears to be a single diastereomer, probably as the result of thermodynamic control. It is worth noting that the absolute configuration of the Co_2(alkyne) tetrahedron is not known.

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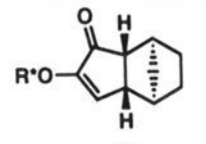
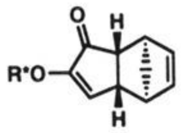
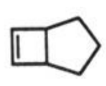
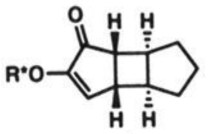
Table 1. Enantioselective Pauson–Khand Reactions of Cobalt Complexes **3**/**4**

alkene	major product	conditions,[a] t (°C)	yield (%)	ratio of diastereomers
	 **5a**	A, 20 B, 50 B, 0 C, 0 C, –20	65 69 99 66 77	70/30[b] 60/40[c] 80/20[b] 88/12[c] 92/8[c]
	 **5b**	A, 20 C, –20	95 82	60/40[d] 96/4[d]
	 **5c**[e]	A, 50 C, –20	70 91	72/28[d] 93/7[d]

[a] Conditions A: stirring of the hexane solution of complex **3** and the alkene at the specified temperature under CO. Conditions B: thermal preparation of complex **4** in hexane and subsequent addition of the alkene at the specified temperature under N_2. Conditions C: chemical generation of complex **4** in CH_2Cl_2 at 20 °C by reaction of **3** with 6 equiv of NMO and subsequent addition of the alkene at the specified temperature under N_2. [b] By ^1H NMR. [c] ^{13}C NMR. [d] By HPLC (Nucleosil 120 C18; CH_3OH/H_2O). [e] Tentative assignment by analogy with **5a** and **5b**.

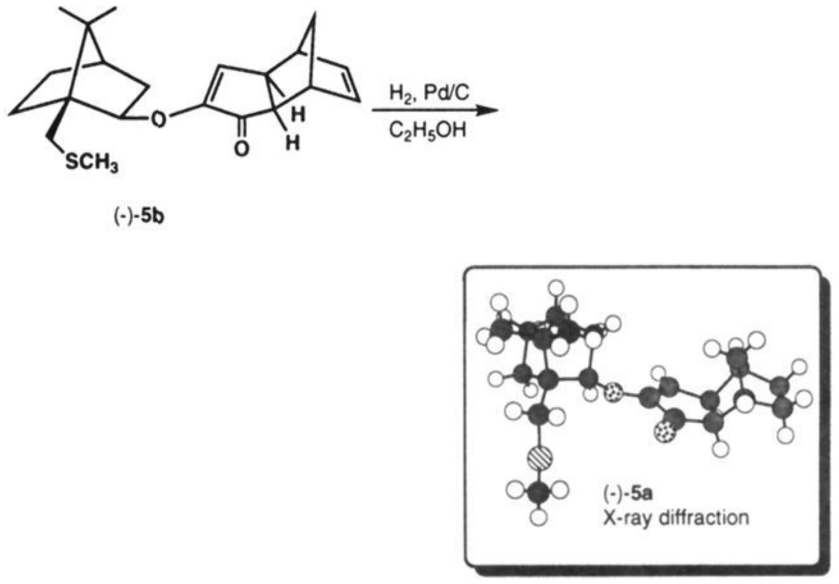
required 20 h for completion and afforded regioselectivity, albeit in moderate yield and with a low degree of asymmetric induction, the tricyclic enones having the expected[1] exo stereochemistry. In an attempt to involve **4** in the transformation, a hexane solution of **3** was heated at 50 °C for 30 min under a N_2 stream (conditions B), which produced, according to ^1H NMR analysis, >85% conversion to **4**. When norbornene was subsequently added at this temperature, the reaction occurred in minutes, though once again with disappointing diastereoselectivity. Notable improvement in selectivity could be achieved, however, by cooling the above thermally generated mixture to 0 °C prior to olefin addition.

Complete conversion of **3** to **4** could be effected by oxidation with N-methylmorpholine N-oxide[12,13] in CH_2Cl_2 at 20 °C (conditions C). While Pauson–Khand reaction of this complex with norbornene at 0 °C as before afforded in 66% yield the same tricyclic ketones as a separable 88:12 mixture, more impressively, at –20 °C the enones were generated in 77% yield and in a 92:8 diastereomeric ratio.

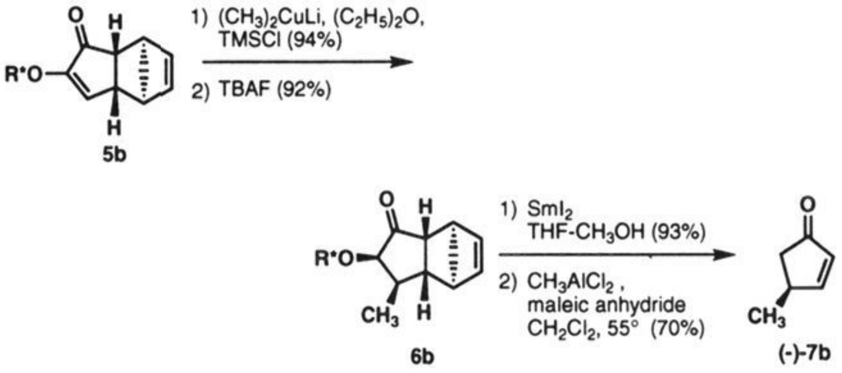
Norbornadiene and bicyclo[3.2.0]hept-6-ene were also subjected to both the purely thermal and the oxidative conditions (see Table 1). The former procedure at 20 °C as well as 50 °C gave high yields of the corresponding cyclopentenones but with poor diastereoselectivity; the latter, in contrast, provided at –20 °C the adducts not only in excellent yield but also with unprecedented diastereoselectivities: 96:4 and 93:7, respectively! *The chelated complex **4**, formed effectively by oxidation and reactive at unusually low temperature, thus appears to offer a unique solution to the problem of intermolecular Pauson–Khand diastereoselection.*

The absolute configuration of the major stereoisomers of **5a** and **5b** has been established by X-ray diffraction[14] and chemical correlation, respectively, as shown in Scheme 4.

Scheme 4



Scheme 5



The excellent yield and diastereoselectivity in the reaction of **4** with norbornadiene is of particular interest in that it provides, through coupling with the retro-Diels–Alder reaction, the basis for an enantioselective cyclopentenone synthesis. For example, *(S)-(–)-4-methyl-2-cyclopentenone* (**7b**)[15] *could be prepared from* tricycle **5b** in high yield and enantiopurity as outlined in Scheme 5. Lithium dimethylcuprate conjugate addition to **5b** gave after fluoride treatment exclusively the cis stereoisomer **6b**.[16] This adduct on reduction with SmI_2 in $THF–CH_3OH$[17] followed by Lewis acid-catalyzed retro-Diels–Alder reaction[18] provided (–)-**7b**.[19]

In summary, we have developed a conceptually new, very efficient chiral controller for the intermolecular Pauson–Khand reaction and have illustrated its applicability for enantioselective cyclopentenone synthesis. Although a full mechanistic discussion would be premature at this point, the variation with temperature of the diastereoselectivity in the experiments with norbornene[20] tends to support the idea that a common intermediate **4**, extremely reactive toward olefin coordination, is involved under all sets of experimental conditions. Mechanistic studies as well as applications of this conceptually new and effective approach to diastereoselective Pauson–Khand cycloaddition are in progress in our laboratories and will be reported in due course.

Acknowledgment. We thank DGICYT (PB 89-0255) and the CNRS (UA 332) for financial support.

Supplementary Material Available: X-ray diffraction data (crystallographic parameters, atomic coordinates, thermal parameters, and intramolecular distances and angles) for (–)-**5a** (7 pages); listing of observed and calculated structure factors (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(14) Crystals of **5a** were grown from cold pentane. Crystallographic data are available as supplementary material.

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(20) ln(diastereomeric ratio) is linearly correlated with $1/T$.