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Practical Asymmetric Version of the Intermolecular Pauson-Khand Reaction

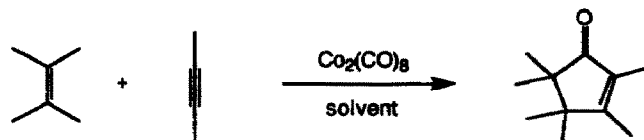
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Abstract: The first practical asymmetric version of the intermolecular Pauson-Khand reaction has been developed based on novel chiral (non-racemic) alkoxy acetylene dicobalt hexacarbonyl complexes. The major adduct from (1R, 2S)-2-phenylcyclohexyloxyethyne and norbornadiene, isolated in 58% yield, is shown to be useful for obtaining chiral 4-substituted 2-cyclopentenones.

The intermolecular Pauson-Khand reaction, which joins an olefin, an acetylene, and carbon monoxide to form a cyclopentenone, is attractive due to its operational simplicity and broad applicability (Scheme 1).¹ Since its discovery some 20 years ago, this reaction has been extensively studied by several research groups and has found application for the racemic preparation of natural as well as non-natural products.¹ It is thus surprising that, in contrast to the intramolecular version,² there have been virtually no attempts to date to render this impressive reaction asymmetric.³ In this paper we wish to disclose our initial efforts in this area.



Scheme 1

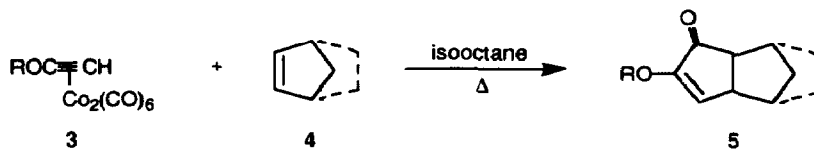
Our interest in chiral (non-racemic) O-alkyl enol ethers and O-alkyl acetylenic ethers⁴ prompted us to consider these compounds in the context of the intermolecular Pauson-Khand reaction. The only literature example of the use of an enol ether as a substrate in the intermolecular Pauson-Khand reaction, however, was not encouraging,⁵ and as our results in related systems also were not promising, attention was quickly focused on O-alkyl acetylenic ethers as possible substrates.

The requisite dicobalt hexacarbonyl complexes **3** were efficiently obtained by a recently developed procedure⁶ from the trimethylsilylated derivatives **2**, which could be prepared generally in one pot^{4c} from the corresponding chiral alcohols **1** (Scheme 2).



Scheme 2

The results of the Pauson-Khand reactions of several complexes (3a-i) with norbornene and cyclopentene (Scheme 3), representative olefins of considerably different reactivity, are collected in Table I.⁷



Scheme 3

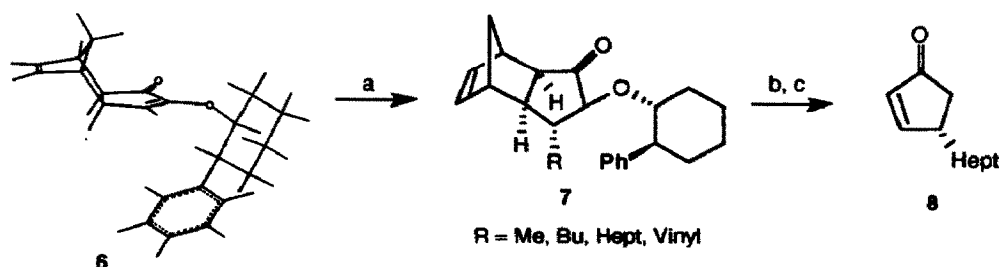
Table I. Yields^a and Diastereomeric Ratios^b in The Pauson-Khand Reactions of Alkoxy Acetylene Complexes 3a-i with Norbornene and Cyclopentene

RO- in complex 3	olefin		
	norbornene	cyclopentene	
	a, R ¹ = phenyl	62 (3:1)	52 (2:1)
	b, R ¹ = 9-phenanthryl	51 (>10:1)	25 (>10:1)
	c, R ¹ = 2, 4, 6-trimethylphenyl	40 (3:1)	-
	d	50 (2:1)	-
	e ^c R ¹ = O-; R ² = OCH ₂ Bu ^t	100 (1:1)	40 (1:1)
	f ^d R ¹ = OCH ₂ Bu ^t ; R ² = O-	93 (1:1)	30 (3:1)
	g X =	88 (2.5:1)	46 (1.6:1)
	h X =	75 (1:1)	64 (1:1)
	i	68 (1.2:1)	46 (2:1)

^aCombined yield after purification. ^bBy ¹H NMR. ^cReaction with 2,5-dihydrofuran proceeded in 37% yield (1.6:1 dr). ^dReaction with 2,5-dihydrofuran proceeded in 40% yield (2.1:1 dr).

In keeping with the usual tendencies associated with the Pauson-Khand reaction,¹ the 2-alkoxy-substituted cyclopentenones **5** were the only regioisomers detected and, where endo-exo annelation was possible, the exo diastereomers were the only ones found. While the phenanthrylcyclohexanol derivative **3b** afforded the best diastereoselection, the difficult preparation of the inductor in enantiopure form led us to consider in this preliminary study *trans*-2-phenylcyclohexanol⁸ as the chiral auxiliary of choice. The advantages of this compound over the other chiral controllers examined in this study are particularly significant: both enantiomers are easily and inexpensively available on a multigram scale, the diastereomeric Pauson-Khand products can invariably be separated by simple open-column SiO₂ chromatography, and its derivatives tend to be crystalline. It is relevant to point out that *on a practical level, good yields of separable diastereomers can more than counterbalance unspectacular diastereoselections.*

With these results in hand, we examined the annelation of norbornadiene, which presents a particular interest because of the possibility of effecting a Pauson-Khand-retro Diels-Alder tandem to obtain chiral cyclopentenones.⁹ The absolute stereochemistry of the preponderant diastereomer formed with the alkoxy acetylene complex **3a**, isolated in 58% yield, is that shown in **6** ($[\alpha]_D -65^\circ$, CHCl₃) (Scheme 4), a determination made by conversion (H₂, Pd-C; SmI₂) to the levorotatory tricyclodecanone of known absolute stereochemistry.^{10,11} The representation **6** (Scheme 4) also depicts the lowest-energy ground state conformation of the enone, as discerned by molecular mechanics calculations (Insight II Discover, Biosym Technologies), and suggests that conjugate addition should take place predominantly on the exo face, which is in fact what was exclusively found. Boron trifluoride etherate-promoted conjugate addition reactions of methyl, butyl, heptyl, and vinylcopper reagents¹² provided only the exo adducts **7** in 52-80% yields. Samarium (II) iodide was clearly the reagent of choice for the reductive removal^{2a,b} of the chiral auxiliary from these molecules. With this easily prepared reagent,¹³ the enantiopure ketones could be rapidly and cleanly obtained (80-89%), and the intact auxiliary readily recovered for reuse. The Lewis acid-catalyzed retro Diels-Alder reaction⁹ applied to the ketone derived from **7** (R=Hept) produced known (*S*)-(-)-4-heptyl-2-cyclopentenone (**8**, ee 95%¹⁴) in 71% yield.



Scheme 4 Reagents and conditions: a, RCu, BF₃·Et₂O, Et₂O, -78 to -50 °C; b, SmI₂, MeOH-THF, -78 °C; c, MeAlCl₂, maleic anhydride, ClCH₂CH₂Cl, 55 °C.

Extensions and applications of this asymmetric version of the intermolecular Pauson-Khand reaction are currently being studied in our laboratories.

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EXPERIMENTAL

Pauson-Khand Cyclization of Complex 3a with Norbornadiene. A stirred solution of 3a (3.00 g, 6.17 mmol) and norbornadiene (5.68 g, 61.7 mmol) in 2,2,4-trimethylpentane (140 mL) under argon was heated at 60–65 °C for 18 h. The resulting mixture was filtered through celite and the solvent was evaporated to give the crude product, which was subjected to dry SiO₂ chromatography first with 10% AcOEt in hexane to give a 2.5:1 mixture of the two diastereomers (1.83 g, 93%), and then with 4% AcOEt in hexane to afford the more polar minor product (500 mg, 25%) and the less polar major product (1.15 g, 58%) 6: mp 120–122 °C; $[\alpha]_D^{25}$ -65 (c 1.2, CHCl₃); ¹H NMR (200 MHz, CDCl₃) δ 7.30–7.10 (m, 5H), 6.22 (dd, *J* = 2.4, 5.5 Hz, 1H), 6.13 (dd, *J* = 2.5, 5.5 Hz, 1H), 6.04 (d, *J* = 3.0 Hz, 1H), 4.10 (m, 1H), 2.83 (m, 2H), 2.54 (s, 1H), 2.41 (ps t, 1H), 2.06 (d, *J* = 5.0 Hz, 1H), 1.95–1.15 (m, 10H); ¹³C NMR (75.2 MHz, CDCl₃) δ 202.8, 159.1, 144.0, 138.2, 136.4, 130.2, 128.2, 127.8, 126.4, 82.2, 50.2, 43.3, 43.1, 40.8, 32.2, 32.0, 25.7, 24.9; IR (Nujol) 3075, 3040, 1710, 1620, 760, 700 cm⁻¹; mass spectrum (EI), *m/z* 320 (M⁺), 91 (100%). Anal. Calcd for C₂₂H₂₄O₂: C, 82.46; H, 7.49. Found: C, 82.36; H, 7.49.

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