Acetylene−Dicobaltcarbonyl Complexes with Chiral Phosphinooxazoline Ligands: Synthesis, Structural Characterization, and Application to Enantioselective Intermolecular Pauson−Khand Reactions

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Received March 31, 2000

Abstract: The reaction of the phenylacetylene−dicobalthexacarbonyl complex (**2**) with the 4-R-2-(2-diphenylphosphinophenyl)oxazolines **1** (R = Ph) and **4** (R = $CH_2CH_2SCH_3$) leads to the selective formation of the chelated complexes **3** and **5**, respectively. On the other hand, the *tert*-butyl-substituted phosphinooxazoline **6** acts as a monodentate ligand, and its reaction with several 1-alkyne-derived complexes (**2**,**7**−**10**) affords readily separable mixtures of the diastereomer nonchelated complexes **11a**,**b**−**15a**,**b**. The interconversion rate between diastereomeric pairs is dependent on the steric bulk of the alkyne substituent, and neither **3** nor **5** epimerize at room temperature. The structures of both kinds of complexes have been ascertained by a combination of spectroscopical (IR, NMR), X-ray diffraction, and chiroptical methods; this has allowed the development of a practical procedure for the establishment of the absolute configuration of the chiral alkyne−dicobaltcarbonyl complexes obtained by the selective substitution of a carbon monoxide on one of the diastereotopic cobalt atoms. The intermolecular Pauson−Khand reaction of the chelated complexes **3** and **5** with norbornadiene respectively affords the (+) and (−) enantiomers of expected enone adduct **25**, but in low enantiomeric excesses. Contrary to that, the tertiary amine *N*-oxide-promoted intermolecular Pauson−Khand reactions of nonchelated complexes **11a**,**b**−**13a**,**b** give the corresponding norbornadiene- or norbornene-derived adducts both in high yields (85−99%) and enantioselectivities (93−97% enantiomeric excess), in what constitutes a substantial improvement over preexisting procedures for this reaction. The possibility of achieving chiral induction in the Pauson−Khand reaction of symmetrical alkynes (via the corresponding dicobaltpentacarbonyl complexes with ligand **6**) has been demonstrated for the first time. An enantioselectivity mnemonic rule and a mechanistic model that explains the observed asymmetric sense of induction have been developed, and have been found to be in agreement with the results of model semiempirical molecular orbital calculations.

Introduction

The substitution of one or more carbonyl groups by phosphines and related compounds in acetylene−dicobaltcarbonyl complexes[1] has been shown to have significant effects in both the structure and the reactivity of these synthetically useful compounds. Thus, it is well-known that trialkyl- and triarylphosphines can readily displace a carbon monoxide molecule from alkyne−dicobalthexacarbonyls, occupying an axial coordination position in the tetrahedral Co_2C_2 core, trans to the cobalt−cobalt bond (Figure 1a), and that this substitution is accompanied by an appreciable shortening of the cobalt−carbonyl distances, a fact that is usually ascribed to the poorer π-acceptor character of phosphines relative to that of carbonyl ligands.[2] In the case of bidentate phosphines, both chelated (Figure 1b) and bridged (Figure 1c) complexes[2a,3] in which the ligand occupies equatorial coordination positions about the metal atoms have been obtained.

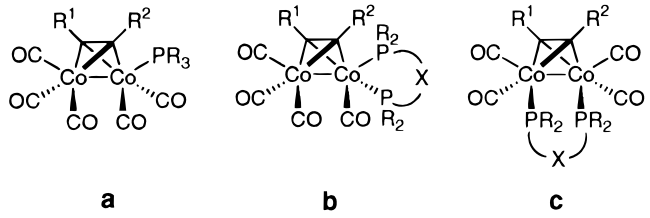

Figure 1. Phosphine-substituted alkyne−dicobaltcarbonyl complexes.

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10.1021/ja001143o CCC: $19.00
Published on Web 08/08/2000

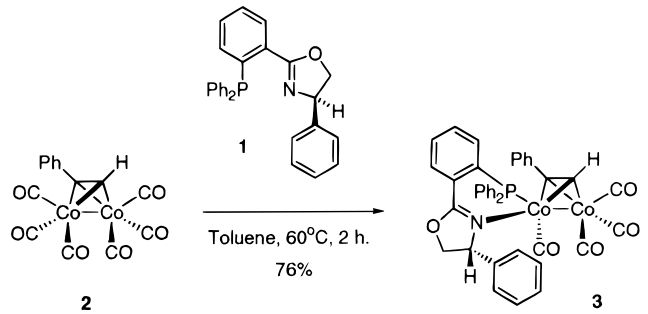
With regard to reactivity, phosphine-substituted acetylene−dicobaltcarbonyl complexes have been studied in connection to both the Nicholas[4] and the Pauson−Khand reactions,[5,6] mainly with the aim of developing enantioselective versions of these processes. Up to now, however, complexes of this type have not found extensive use in synthesis, due to several reasons:

(a) In several instances, because of the stereoheterotopic nature of the two cobalt atoms, phosphine substitution on acetylene−dicobalthexacarbonyl complexes leads to the formation of diastereomer pairs, which are often hardly separable. This happens for example in complexes of the type shown in Figure 1a (with R^1 different from R^2), either when the phosphine ligand or the alkyne moiety is chiral. Even when obtained stereoisomerically pure, the absolute configuration of such substituted complexes is difficult to ascertain by methods other than X-ray diffraction. Thus, lack of crystallinity has prevented the complete characterization of the (*R*)-Glyphos-derived complexes used in enantioselective Pauson−Khand reactions.[6a,d]

(b) Thermally induced phosphine dissociation processes, leading to the interconversion between stereoisomeric complexes and to the loss of the stereochemical integrity of the tetrahedral C_2Co_2 moiety, take place at relatively low temperatures. This phenomenon strongly limits the use of enantiopure chiral phosphine-substituted alkyne complexes in asymmetric Pauson−Khand and Nicholas reactions.

(c) The electrophilicity of dicobaltcarbonyl-stabilized propargyl cations, which are the reactive intermediates in the Nicholas reaction, is greatly diminished upon substitution of a carbon monoxide by a triaryl- or trialkylphosphine.[7] In a similar way, the Pauson−Khand reactivity of phosphine- or phosphite-substituted complexes is lower than that of the parent unsubstituted compounds.[6f,8]

Scheme 1



We have recently found[9] that the reaction of (*R*)-2-(2-diphenylphosphinophenyl)-4-phenyloxazoline **1** with the phenylacetylene−dicobalthexacarbonyl complex (**2**) gives rise to a 85:15 mixture of two diastereomer complexes. The structure of the major one (**3**), elucidated by X-ray diffraction analysis, revealed an unprecedented P,N-chelation of the ligand with one cobalt atom (Scheme 1).

Contrary to nonchelated, phosphine-substituted alkyne−dicobaltcarbonyl complexes, **3** was very stable toward isomerization, but showed only moderate enantioselectivities [up to 51% enantiomeric excess (ee)] in the intermolecular Pauson−Khand reaction with norbornadiene. On the basis of these findings, we decided to further investigate the use of 4-substituted-2-(2-diphenylphosphinophenyl)oxazolines as chiral ligands for alkyne−dicobaltcarbonyl complexes. We disclose here in full detail the results of this study, which has led to the development of both a highly enantioselective, practical version of the intermolecular Pauson−Khand reaction and a facile method for the determination of the absolute configuration of chiral, phosphine-substituted acetylene−dicobaltcarbonyl complexes.

Results and Discussion

Synthetic and Structural Studies on Alkyne−Dicobalt-(phosphinooxazoline)carbonyl Complexes. First, we studied the reaction of the methionine-derived phosphinooxazoline **4** [prepared from (*S*)-methioninol according to the procedure reported by Helmchen and co-workers[10]] with the phenylacetylene−dicobalthexacarbonyl complex **2**. The oxazoline residue was chosen to ascertain the effect of the replacement of the phenyl group in **1** by a less bulky alkyl chain, as well as to investigate the possibility of additional chelation by the sulfide moiety.[11] The treatment of **2** with 1 equiv of **4** in hot toluene led to the isolation of a new complex **5** in 78% yield after chromatographic purification (Scheme 2).

This complex appears to be a single diastereomer, according to physical data (melting point), chromatographic behavior

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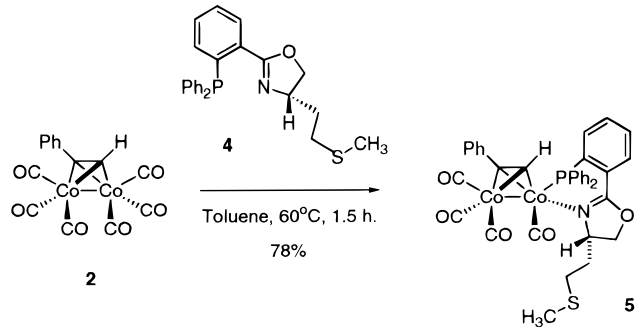
Scheme 2



(HPLC), and spectroscopic studies (^{1}H and ^{13}C NMR). Because we were not able to obtain single crystals suitable for X-ray diffraction analysis, the structural characterization of **5** was carried out in the following way. First, the 1:1 stoichiometry of the new complex was readily apparent both from the NMR spectra and from mass spectroscopic data. Next, the fact that the phosphinooxazoline **4** acts as a bidentate ligand in complex **5** could be established by inspection of infrared (IR) spectrum of **5**, both in the carbonyl (see later) and in the C═N stretching zones; in effect, a shift of this band from 1655 (in the free ligand **4**) to 1625 cm^{-1} (in the complex) is strongly indicative of the presence of a chelated structure, as previously observed by us[9] and by other authors.[12] On the other hand, complexation of the cobalt by the sulfur atom of the chain does not take place in **5**, as revealed by the coincidence of the ^{1}H and ^{13}C NMR signals corresponding to methylthioethyl group in both **4** and **5**.

Finally, the absolute configuration of **5** was ascertained by analysis of its chiroptical properties. Previously, Kajtàr et al.[13] have shown that the circular dichroism (CD) spectra of the dicobalthexacarbonyl complexes of chiral acetylenes show several bands in the 300−600-nm zone that can be assigned to chirally perturbed transitions of the $C_2Co_2(CO)_6$ core of the molecule. We reasoned that the CD spectra of complexes such as **3** and **5**, in which the local C_{2v} symmetry of the C_2Co_2 tetrahedral moiety is broken by the substitution of one cobalt atom, would exhibit a direct correlation with the absolute configuration of the molecule. After checking that the free ligands **1** and **4** did not present any significant absorption in the CD between 300 and 700 nm, we recorded the spectra of the corresponding complexes **3** and **5**, which as anticipated showed relatively intense bands ascribable to transitions of the intrinsically chiral C_2Co_2 chromophore (Figure 2).

As can readily be seen, the two spectra present a clear pseudoenantiomeric relation. Because the X-ray analysis of **3** established that the phosphinooxazoline ligand is chelating the pro-*R* cobalt atom, we conclude that in complex **5** the coordination of the ligand takes place at the pro-*S* cobalt, as depicted in Scheme 2. It is thus clear that the stereochemistry of these chelated complexes is dictated by the absolute configuration of the chiral oxazoline moiety: the phosphinooxazoline ligand **1** [derived from (*R*)-phenylglycinol] leads to an (*R*)-configuration of the C_2Co_2 moiety in complex **3**, whereas the (*S*)-ligand **4** affords the corresponding (*S*)-complex **5**.

To further clarify the influence of the steric bulk of the oxazoline substituent, we next studied the reaction of **2** with the (*S*)-*t*-leucinol-derived[10] phosphinooxazoline **6** (Scheme 3 and

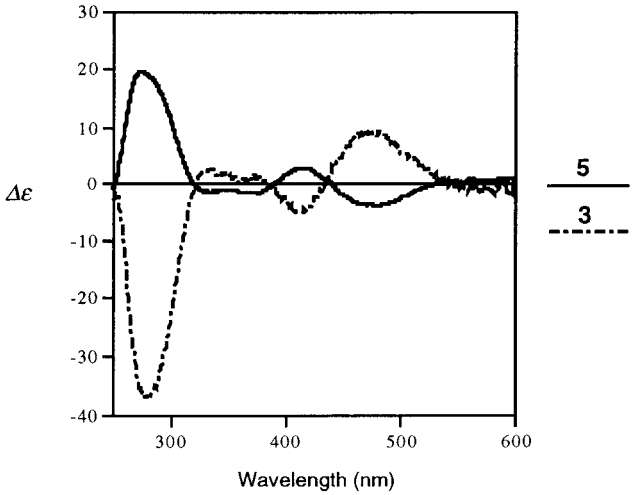


Figure 2. CD spectra of pseudoenantiomeric complexes **3** and **5**.

Scheme 3

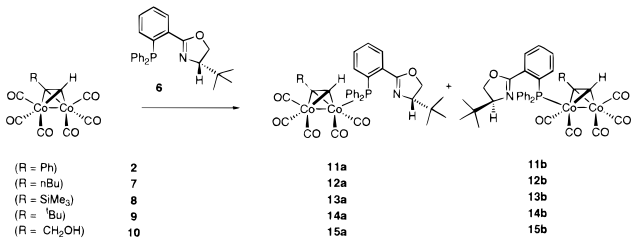


Table 1. Synthesis of Dicobalt Pentacarbonyl Complexes **11a**,**b**−**15a**,**b**

entry	starting complex	reaction conditions[a]	product (yield, %)[b]	d.r.[c]
1	Ph (**2**)	60 °C, 2.5 h	**11a** (38), **11b** (39)	1:1.02
2	nBu (**7**)	55 °C, 1 h	**12a** (34), **12b** (47)	1:1.24
3	$SiMe_3$ (**8**)	60 °C, 2 h	**13a** (14), **13b** (16)	1:1.33
4	*t*-Bu (**9**)	70 °C, 3 h	**14a** (16), **14b** (21)	1:1.25
5	CH_2OH (**10**)	55 °C, 2.5 h	**15a** (28), **15b** (16)	1.87:1

[a] Stirring the preformed complex in toluene solution at the specified temperature in the presence of 1 molar equiv of the phosphinooxazoline **6** under nitrogen. [b] Yield of diastereomerically pure, isolated complexes after column chromatography (SiO_2). [c] Determined by HPLC analysis of the reaction mixture.

entry 1 of Table 1). After heating a 1:1 mixture of **2** and **6** at 60 °C in toluene for 2.5 h, thin-layer chromatography (TLC) analysis showed the complete disappearance of complex **2** and the presence of two more polar, dark-colored spots of similar intensity. After chromatographic purification, the two monosubstituted complexes **11a** and **11b** were isolated as burgundy-colored, crystalline solids in 38 and 39% yield, respectively. The spectral data of both **11a** and **11b** clearly showed their diastereomeric nature. The structure of the more polar complex **11b** was unambiguously determined by X-ray diffraction of a single crystal, and is shown in Figure 3.

Contrary to what we had observed for complexes **3** and **5**, in this case the phosphinooxazoline behaves as a monodentate ligand, in which the phosphorus atom is bound to the pro-*R* cobalt atom in an axial (i.e., trans to the cobalt−cobalt bond) coordination position. The cobalt−cobalt and cobalt−carbon bond lengths of the C_2Co_2 core are similar to those of unsubstituted complexes,[14] whereas the cobalt−phosphorus bond length and the Co−Co−P and C−Co−P bond angles are

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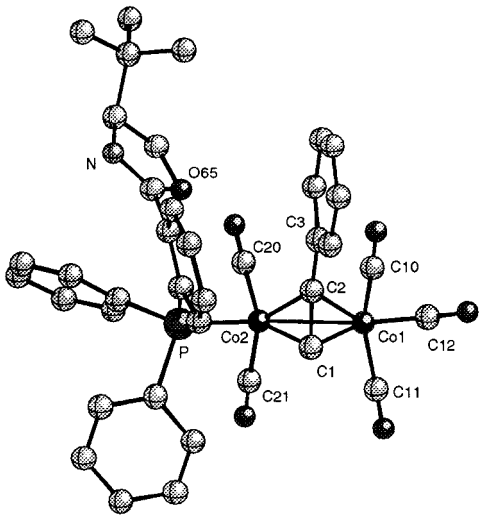


Figure 3. Molecular structure of **11b** in solid state. Hydrogen atoms have been omitted for clarity.

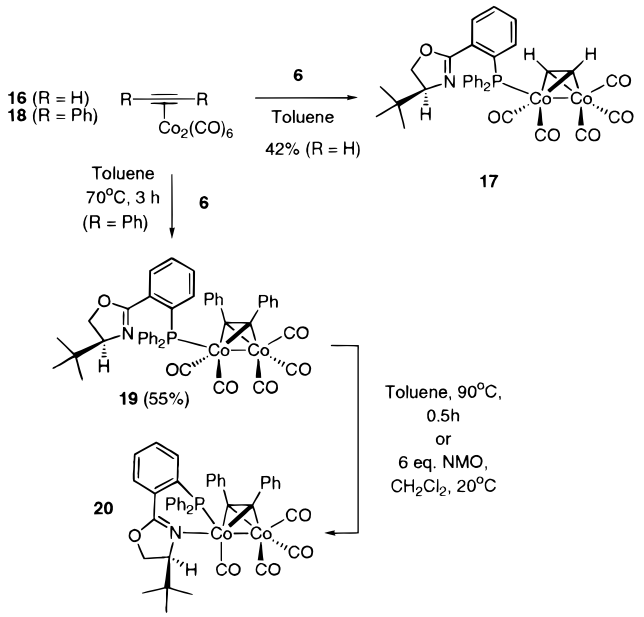
analogous to those recorded for other phosphine-substituted complexes.[2,3] On the other hand, the usual decrease of the cobalt−carbonyl distances upon substitution of a carbonyl ligand by a poorer π-acceptor one[2c] is also observed in this case. As we will see later, the structure of the less polar complex **11a** is totally parallel to that of **11b**, except for the fact that the ligand is bound to the pro-*S* cobalt atom.

On the basis of this result, we explored the effect of the alkyne substituent by reacting **6** with the alkyne−dicobalthexacarbonyl complexes **7**−**10** (Scheme 3 and entries 2−5 in Table 1). In all instances, an easily separable mixture of two monosubstituted, nonchelated diastereomer complexes (**12a**,**b**−**15a**,**b**) was obtained. This demonstrates that the presence of the bulky *tert*-butyl substituent in the oxazoline moiety strongly hinders the formation of a chelated complex, the ligand **6** acting as a monodentate chiral phosphine, but with the additional bonus that the two diastereomers can be separated by standard column chromatography, being readily obtained in high diastereomeric purity (checked by HPLC).[15] The nature of the acetylene substituent has some effect both in the yield and in the stereoselectivity of the process. Thus, in the case of the phenylacetylene (**2**)- and of the 1-hexyne (**7**)-derived complexes, the reaction was not diastereoselective (entries 1 and 2 in Table 1). Increasing the steric bulk of the alkyne substituent (complexes **8** and **9**) strongly diminished the yield of the reaction, whereas the isomer ratio remained essentially the same (entries 3 and 4 in Table 1). A reversal of the diastereoselectivity of the process was observed with the 1-propynol-derived complex **10**, which gave a ca. 1.9:1 mixture in which the less polar complex was the major component (entry 5 of Table 1). In this case, the relatively low global yield (44%) was due to the competing formation of other complexes that were too unstable to be characterized.

The easy availability of the complexes in stereochemically pure form allowed us to investigate their stability toward epimerization processes. To this end, all of the isolated complexes were dissolved in hexane at room temperature immediately after chromatographic purification and the diastereomeric purity of the resulting solutions was monitored by HPLC (see Supporting Information). The rate of epimerization is dependent on the steric bulk of the alkyne substituent. Thus,

(15) The separation of the diastereomer alkyne−dicobaltpentacarbonyl complexes obtained by substitution with (*R*)-Glyphos has only been achieved either by fractional crystallization[6a,b] or by preparative HPLC.[6d,e]

Scheme 4



both diastereomers of complex **11** appear to be remarkably stable, since the diastereomeric purity of a hexane solution of **11b** remained essentially unchanged after 2 days at room temperature, whereas that of **11a** was slightly disminished (6% loss). Complexes **12a** and **12b** interconvert slowly at room temperature (a 11% loss of the diastereomeric purity of a solution of **12a** was observed after 2 days). The behavior of **15a**,**b** is very similar to that of **12a**,**b**, except that the stability of these complexes in solution is much more limited. The trimethylsilyl-substituted complexes **13a**,**b** epimerize more readily, and a 6% loss of diastereomeric excess is observed after 1 h. In sharp contrast to this, the *tert*-butyl-substituted complexes **14a**,**b** undergo a very fast interconvertion, and their diastereomeric excesses fall down to ca. 70% after 1 h at room temperature. On the other hand, the chelated complex **3** does not epimerize at room temperature.[9] As we will see later, the relative rates of epimerization of these complexes are closely related to the enantioselectivities of their Pauson−Khand reactions.

The behavior of symmetrical alkyne−dicobalthexacarbonyl complexes toward the substitution reaction was also investigated. In this case, given the homotopic nature of the two cobalt atoms, only one monosubstituted complex can be obtained. The reaction of the ethyne complex **16** with 1 equiv of the phosphinooxazoline **6** gave a four-component mixture (TLC) from which the monosubstituted complex **17** could be isolated in 42% yield by column chromatography (Scheme 4). The nonchelated nature of **17** was deduced from its spectroscopic properties (see below). The diphenylacetylene-derived complex **18** reacted more sluggishly with **6**, and gave, after heating in toluene at 70 °C over 3 h, a mixture of the nonchelated, monosubstituted complex **19** with an unstable, less polar complex **20** to which we assigned a chelated structure (Scheme 4). Although the unstability of **20** precluded its spectroscopic characterization, this structural assignment comes from the fact that pure complex **19**, isolated in 55% yield by column chromatography, could be completely converted into **20** either by heating at 90 °C or by treatment by *N*-methylmorpholine-*N*-oxide.[11]

Whereas the structure of **11b** was unambiguously established by X-ray diffraction, those of the remaining complexes derived from phosphinooxazoline **6** (**11a**, **12a**,**b**−**15a**,**b**, **17**, and **19**)

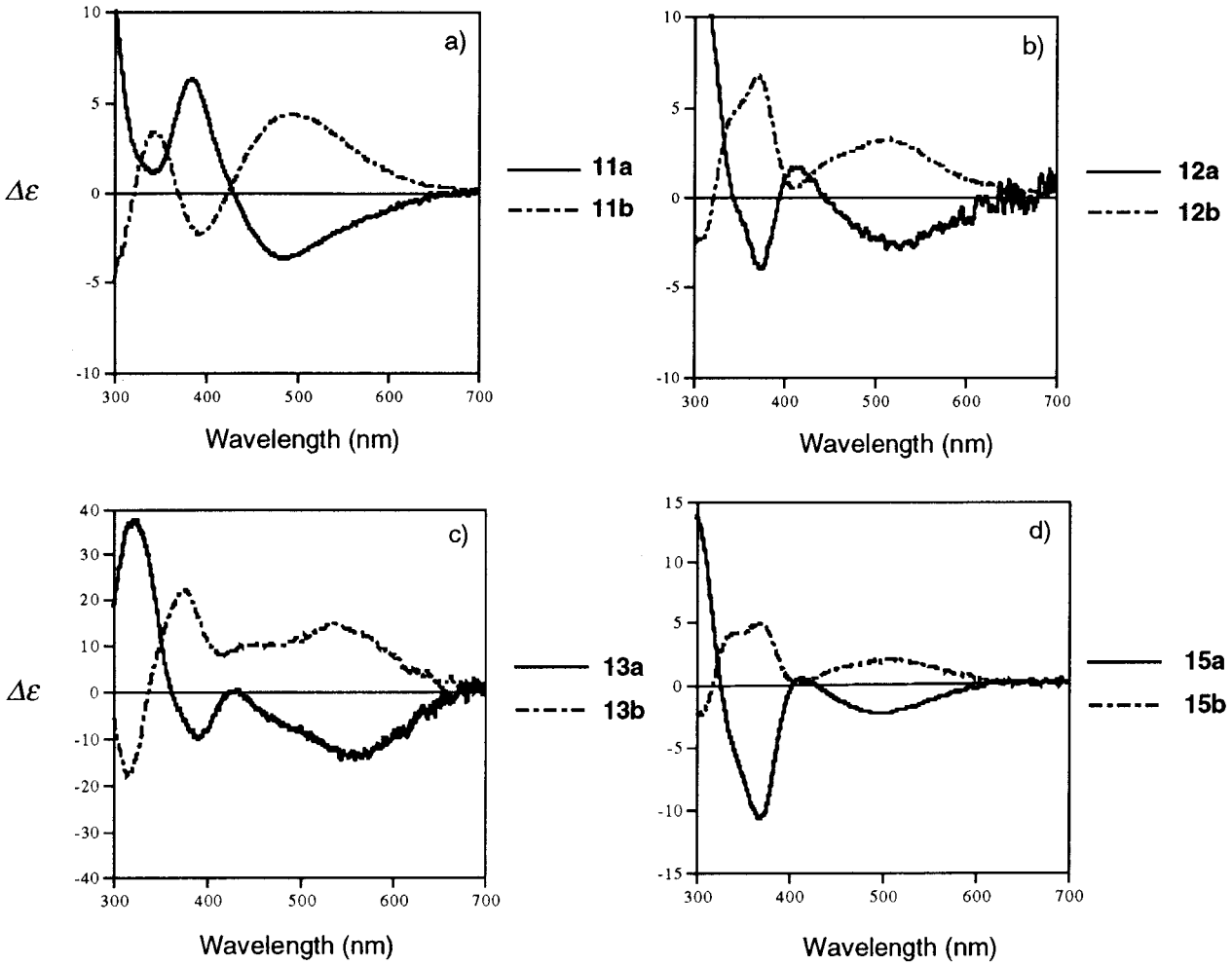


Figure 4. CD spectra of diastereomer complexes (a) **11a**,**b**; (b) **12a**,**b**; (c) **13a**,**b**; and (d) **15a**,**b**.

were ascertained by indirect methods. In the course of the structure determination process, three questions have to be answered: (a) Is the phosphinooxazoline **6** acting as a mono- or as a bidentate (chelated or bridged) ligand? (b) Is the phosphorus atom placed in an axial or in an equatorial coordination site? (c) In the case of complexes derived from nonsymmetrical alkynes, which of the two enantiotopic cobalt atoms has been substituted?

The nonchelated nature of the complexes could be readily ascertained by inspection of their IR spectra. Because the structures of both **3** and **11b** are known from X-ray diffraction studies, we can conclude that the intramolecular coordination of one cobalt by the oxazoline nitrogen is accompanied by a decrease of ca. 40 cm^{-1} of the frequencies associated with CO stretching vibrations. These experimental observations are moreover in good accordance with theoretical calculations on the normal vibration models of model complexes, performed with the PM3(tm) semiempirical method[16] as implemented in the SPARTAN 5.1.1 package of programs[17] (see Supporting Information). Moreover, as we have already stated when discussing the structure of complex **5**, the position of the C═N stretching band is also indicative of the coordination mode of the phosphinooxazoline ligand. Thus, all of the nonchelated complexes (**11a**,**b**−**15a**,**b**, **17**, **19**) present an IR absorption at 1655 cm^{-1} that corresponds to the C═N stretching frequency of the free ligand.

Chiroptical Method for Assigning Absolute Configuration of the C_2Co_2 Moiety in Chiral Phosphine-Substituted Alkyne−Dicobaltcarbonyl Complexes. The absolute configuration of the chiral alkyne−dicobaltcarbonyl complexes obtained by the selective substitution of a carbon monoxide on one of the diastereotopic cobalt atoms has been ascertained only in the cases in which the X-ray diffraction analysis has been possible.[9] Our finding that the sign of several bands of the CD spectra of the chelated complexes **3** and **5** appeared to present a clear correlation with their absolute configurations paved the way for the development of a practical alternative to X-ray diffraction. In particular, in the case of complex **3**, in which the configuration of the C_2Co_2 moiety is (*R*), the CD spectrum presents a maximum ($\Delta\epsilon = +7.9$) at a wavelength of 475 nm, whereas the (*S*)-complex **5** showed a minimum negative absorption ($\Delta\epsilon = -3.8$) at a very similar wavelength (Figure 2). We surmised that in the case of the monosubstituted (1-alkyne)−dicobalt-pentacarbonyl complexes the sign of a CD absorption at ca. 500 nm, if observed, could also be directly related to the topicity (i.e., to the pro-*R* or the pro-*S* character) of the substituted cobalt.

To verify this hypothesis, we measured the CD spectra of the complexes **11a**,**b**−**13a**,**b** and **15a**,**b** (Figure 4). All of them presented several bands in the 300−700-nm zone. Most importantly, we were pleased to find that the complex **11b**, whose (*R*) configuration at the C_2Co_2 moiety had been unambiguously established by X-ray diffraction analysis (Figure 3),

(16) Which incorporates a parametrization for transition metals to the original PM3 method: Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209−220.

(17) SPARTAN, version 5.1.1. Wavefunction, Inc.; 18401 Von Karman Ave., Suite 370, Irvine, CA 92612.

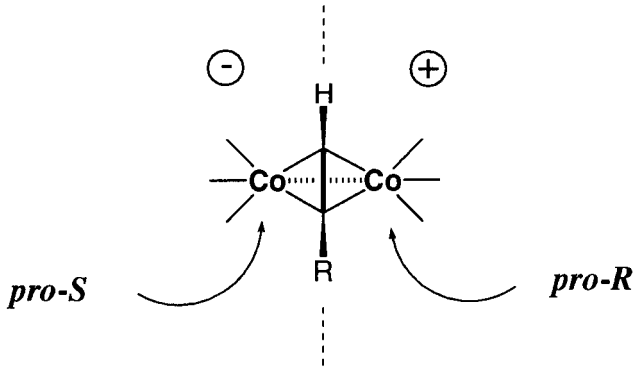
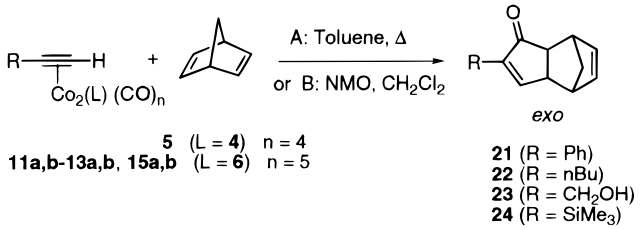


Figure 5. Empirical rule for determination of the absolute configuration of chiral phosphine-substituted 1-alkyne−dicobaltcarbonyl complexes using their chiroptical properties.

Scheme 5



showed a maximum positive dichroism at 492 nm ($\Delta\epsilon = +4.4$), and that its diastereomer **11a** had a CD spectrum pseudoenantiomeric to that of **11b** (Figure 4a), with a minimum at 480 nm ($\Delta\epsilon = -3.8$). In all of the remaining complex pairs, the more polar ones (**12b**, **13b**, **15b**) have a positive CD in the 450−650-nm region that presents a mirror-image relation with the CD spectra of the corresponding less polar diastereomers (**12a**, **13a**, **15a**, Figure 4b−d). In this way, we have shown for the first time that the absolute configuration of chiral, phosphine-substituted 1-alkyne−dicobaltcarbonyl complexes can be directly ascertained from their chiroptical properties according to the following empirical rule: *A positive (negative) CD absorption in the 450−650-nm region implies that the phosphine ligand is bound at the pro-R (pro-S) cobalt atom* (Figure 5).

Enantioselective Intermolecular Pauson−Khand Reactions of Chiral Phosphinooxazoline-Substituted Alkyne−Dicobaltcarbonyl Complexes. Having successfully solved the problem of the structure elucidation of the phosphinooxazoline-substituted complexes, we turned our attention to their intermolecular Pauson−Khand reactions. In the first place, we studied their reaction with norbornadiene (Scheme 5 and Table 2).

The reaction of complex **5** with norbornadiene gave, under thermal conditions (entry 1 of Table 2), the levorotatory *exo*-enone (−)-**21** in a low enantiomeric excess (12% ee). When the reaction was run in the presence of *N*-methylmorpholine-*N*-oxide,[18] essentially racemic **21** was obtained (entry 2 of Table 2). This behavior is entirely parallel to that observed in the case of **3**,[9] and underscores the fact that chelated complexes, although being very stable toward epimerization processes, give low enantioselectivities in the Pauson−Khand reaction.

The reaction took a very different course in the case of the nonchelated complexes. The thermal reaction (toluene, 60 °C) of the phenylacetylene-derived complex **11a** (entry 3) afforded the adduct (−)-**21** in high yield (86%) and with moderate enantioselectivity (61% ee). Lowering the reaction temperature to 45 °C (entry 4) gave slightly better yield and optical purity. A substantial improvement took place when the reaction was promoted by *N*-methylmorpholine-*N*-oxide: at 0 °C, enone (−)-**21** was obtained in 85% yield and in high enantiomeric purity (94% ee, entry 6). Under these optimized conditions (entry 9), the diastereomer complex **11b** produced the dextrorotatory adduct (+)-**21**, again with high optical purity (97% ee) and in essentially quantitative yield. The use of thermal activation (entries 7 and 8) diminished the enantiomeric excess of the product. Thus, both enantiomers of the exo-tricyclic ketone **21** can be obtained from the same starting materials (**2**, **6**, and norbornadiene).

Table 2. Intermolecular Pauson−Khand Reaction of Complexes **5**, **11a**,**b**, **13a**,**b**, and **15a**,**b** with Norbornadiene

entry	starting complex	reaction conditions[a]	**26**[b]	product	yield[c]	ee[d]
1	Ph (**5**)	A, 60 °C, 18 h	-	(−)-**21**	93	12
2	Ph (**5**)	B, 20 °C, 24 h	n.d.	**21**	90	0
3	Ph (**11a**)	A, 60 °C, 18 h	-	(−)-**21**	86	61
4	Ph (**11a**)	A, 45 °C, 18 h	-	(−)-**21**	98	66
5	Ph (**11a**)	B, 20 °C, 24 h	n.d.	(−)-**21**	85	87
6	Ph (**11a**)	B, 0 °C, 24 h	87	(−)-**21**	85	94
7	Ph (**11b**)	A, 80 °C, 15 min	-	(+)-**21**	95	70
8	Ph (**11b**)	A, 45 °C, 18 h	-	(+)-**21**	98	74
9	Ph (**11b**)	B, 0 °C, 24 h	n.d.	(+)-**21**	99	97
10	nBu (**12a**)	B, 20 °C, 24 h	88	(−)-**22**	73	82
11	nBu (**12b**)	B, 20 °C, 24 h	85	(+)-**22**	89	93
12	CH_2OH (**15a**)	B, 20 °C, 24 h	70	(−)-**23**	54	83
13	CH_2OH (**15b**)	B, 20 °C, 24 h	94	(+)-**23**	92	95
14	$SiMe_3$ (**13a**)	B, 20 °C, 24 h	92	(−)-**24**	33	30
15	$SiMe_3$ (**13b**)	B, 20 °C, 24 h	85	(+)-**24**	50	19

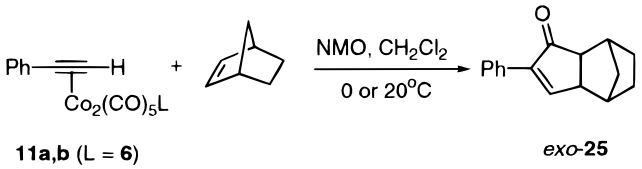
[a] (A) stirring the preformed complex in toluene solution at the specified temperature in the presence of 10 equiv of olefin under nitrogen; (B) chemical activation of the complex by *N*-methylmorpholine-*N*-oxide in dichloromethane solution under nitrogen. [b] Yield (%) of phosphine oxide **26** (see text). [c] Yield (%) of isolated product after chromatographic purification. [d] Determination of the enantiomeric purity (% ee) of **21** and **23** by HPLC analysis. Determination of the enantiomeric purity (% ee) of **22** and **24** by GC analysis.

These excellent results could be extended to other alkyne complexes. Thus, the two diastereomer complexes derived from 1-hexyne (**12a** and **12b**) gave rise, respectively, to the levo- and dextrorotatory enantiomers of the *exo*-enone **22** in high optical purity (entries 10 and 11). In a similar way, the reaction of the diastereomer complexes derived from propargyl alcohol (**15a** and **15b**) took place in a highly enantioselective fashion (entries 12 and 13), affording the two enantiomers of the tricyclic *exo*-keto alcohol **23**. For these complexes, the reaction was run at 20 °C, because lowering the temperature at 0 °C resulted in very low conversions. On the other hand, the Pauson−Khand reaction of the two complexes derived from trimethylsilylethyne (**13a** and **13b**) was very slow, and the levo- and dextrorotatory enantiomers of the expected *exo*-adduct **24** were obtained in both low yields and enantiomeric excesses (entries 14 and 15). In this case, TLC monitoring of the reaction mixture showed that epimerization processes compete with the Pauson−Khand reactions, in accordance with the epimerization behavior observed by HPLC. It is thus clear that, as was originally suggested,[6a] the intermolecular Pauson−Khand reactions of the pure diastereomers are stereospecific, and that the only requisite for attaining good enantioselectivities is that the rate of cycloaddition must be much higher than that of epimerization.

The reaction of complexes **11a**,**b** with norbornene, under *N*-methylmorpholine-*N*-oxide-promoted conditions, was also investigated (Scheme 6 and Table 3). Optimization of the temperature (0 °C) led to the formation of the two enantiomers

(18) (a) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289−5292. (b) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, 204−206.

Scheme 6



11a,b (L = **6**) *exo*-**25**

Table 3. Intermolecular Pauson−Khand Reaction of Complexes **11a**,**b** with Norbornene

entry	starting complex	reaction conditions[a]	**26**[b]	product	yield[c]	ee[d]
1	Ph (**11a**)	20 °C, 18 h	n.d.	(−)-**25**	91	68
2	Ph (**11a**)	0 °C to 20 °C, 24 h	90	(−)-**25**	89	74
3	Ph (**11b**)	20 °C, 18 h	n.d.	(+)-**25**	83	67
4	Ph (**11b**)	0 °C to 20 °C, 24 h	79	(+)-**25**	77	87
5	Ph (**11b**)	0 °C, 24 h	86	(+)-**25**	85	94

[a] Chemical activation of the complex **11a**,**b** by *N*-methylmorpholine-*N*-oxide in dichloromethane solution under oxygen. [b] Yield (%) of phosphine oxide **26** (see text). [c] Yield (%) of isolated product after chromatographic purification. [d] Determination of the enantiomeric purity (% ee) of **25** by HPLC analysis.

of the expected *exo*-enone **25** with yields and enantiomeric purities only slightly inferior to those obtained when using norbornadiene (compare entries 2 and 5 of Table 3 with entries 6 and 9, respectively, of Table 2).

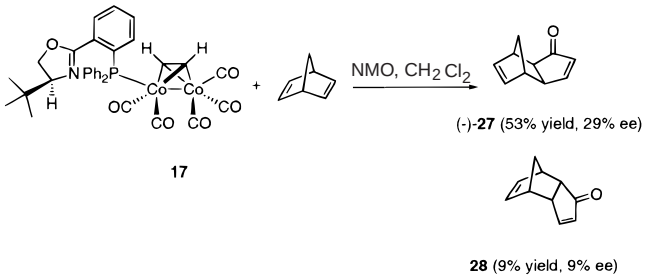
Another interesting feature of this reaction lies in the fact that the ultimate source of chirality [(*S*)-*tert*-leucinol] can be recovered at the end of the process in good yield. In effect, when the Pauson−Khand reaction was run in the presence of *N*-methylmorpholine-*N*-oxide, the phosphine oxide **26** derived from **6** could be isolated by column chromatography (70−94% yields; see Tables 2 and 3). Subsequent acidic hydrolysis of **26** afforded pure (*S*)-*tert*-leucinol in 85% yield. It is worth noting that under thermal conditions the phosphinooxazoline ligand appears to be strongly bonded to the cobalt residues, and was not recovered from the reaction mixture.

In conclusion, the above results show that the (*S*)-phosphinooxazoline **6** is an exceptionally good chiral ligand in the enantioselective intermolecular Pauson−Khand reactions of relatively unhindered 1-alkynes that nicely complements the chiral auxiliary-based strategies previously developed in our laboratories.[11,19] Moreover, the use of **6** presents several clear-cut advantages over the preexisting methods also based on the use of chiral phosphines:[6]

(a) The diastereomer complex pairs resulting from the reaction of **6** with 1-alkynes can be readily separated by standard column chromatography on silica gel.[15]

(b) The enantiomeric excesses obtained in the reactions of the isolated diastereomers with norbornene or norbornadiene, under tertiary amine *N*-oxide-mediated conditions, are uniformly high (93−97%ee) for nonhindered alkynes.

Scheme 7



17

(c) The ultimate source of chirality (*tert*-leucinol) can be recovered at the end of the process.

(d) Because the absolute configurations of both the starting complexes and (as we will see in the next section) of the reaction products can be ascertained, the stereochemical course of the reaction can be determined.

Finally, we set out to investigate the hitherto unexplored possibility of performing an enantioselective Pauson−Khand reaction with symmetrical alkynes. The *N*-methylmorpholine-*N*-oxide-promoted reaction of the acetylene complex **17** with norbornadiene (Scheme 7) gave a readily separable mixture of the *exo*- and *endo*-adducts[20] (−)-**27** and **28** in 53 and 9% yield, respectively. Most significantly, the major adduct was obtained in nonracemic form (29% ee, as determined by chiral GC).[21]

Even if the recorded enantioselectivities are only moderate, the above results stand out as the first examples of an enantioselective Pauson−Khand reaction with symmetrically substituted alkynes.

Determination of Absolute Configuration of Reaction Products. 1. Enantioselectivity Mnemonic for Intermolecular Pauson−Khand Reaction of Phosphine-Substituted Alkyne Complexes. In previous reports on chiral phosphine-mediated enantioselective Pauson−Khand reactions,[6a−e] not only were the absolute configurations of the starting complexes unknown, but those of the adducts do not appear to have been investigated. As a result of that, the stereochemical course of these reactions remained totally unclear.

In the course of our studies on the Pauson−Khand reaction of chiral 1-alkynylsulfoxides, we had established that the absolute configuration of enones (−)-**22** was (1*R*,2*R*,6*R*,7*S*) and that (+)-**25**[22] had the opposite (1*S*,2*S*,6*S*,7*R*) configuration. In the present work, we were able to assign the absolute stereochemistry of enones (−)-**24** and (−)-**27** in the following way (Scheme 8): Catalytic hydrogenation of (−)-**24** (30% ee) afforded the levorotatory α-trimethylsilyl ketone (−)-**29**, which after desilylation gave the levorotatory *exo*-tricyclic ketone (−)-**30**. This compound showed a negative Cotton effect for the n-π^* transition in the CD spectrum. According to the octant rule,[23] this unequivocally establishes an (1*R*,2*R*,6*S*,7*S*) configuration to (−)-**24** (Figure 6). Catalytic hydrogenation of (+)-**24** (19% ee) followed by desilylation gave a dextrorotatory sample of (+)-**30**. On the other hand, (−)-**27** (29% ee) was

(19) Intermolecular Pauson−Khand reactions: (a) Bernardes, V.; Verdaguer, X.; Kardos, N.; Moyano, A.; Pericàs, M. A.; Riera, A.; Greene, A. E. *Tetrahedron Lett.* **1994**, *35*, 575−578. (b) Fonquerna, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **1995**, *14*, 4239−4254. (c) Bernardes, V.; Kann, N.; Riera, A.; Moyano, A.; Pericàs, M. A.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 6670−6671. (d) Fonquerna, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Am. Chem. Soc.* **1997**, *119*, 10225−10226. (e) Fonquerna, S.; Ríos, R.; Moyano, A.; Pericàs, M. A.; Riera, A. *Eur. J. Org. Chem.* **1999**, 3459−3478. Intramolecular Pauson−Khand reactions: (f) Castro, J.; Sörensen, H.; Riera, A.; Morin, C.; Moyano, A.; Pericàs, M. A.; Greene, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 9388−9389. (g) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1994**, *5*, 307−310. (h) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A.; Greene, A. E.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1996**, *61*, 9016−9020. (i) Tormo, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4851−4856, and refs. cited therein.

(20) The reaction between complex **2** and norbornadiene has been reported to give a mixture of the racemic *exo*- (*rac*-**27**) and *endo*- (*rac*-**28**) adducts: Billington, D. C.; Helps, I. M.; Pauson, P. L.; Thomson, W.; Willison, D. *J. Organomet. Chem.* **1988**, *354*, 233−242.

(21) Under the same reaction conditions, complex **19** decomposed and gave diphenylacetylene as the sole identifiable product. However, when the reaction was run under very mild thermal conditions (room temperature, 5 days) an optically active (38% ee) adduct was formed, although in very low yield.

(22) Montenegro, E.; Moyano, A.; Pericàs, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J.-F. *Tetrahedron: Asymmetry* **1999**, *10*, 457−471.

(23) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 1022−1033.

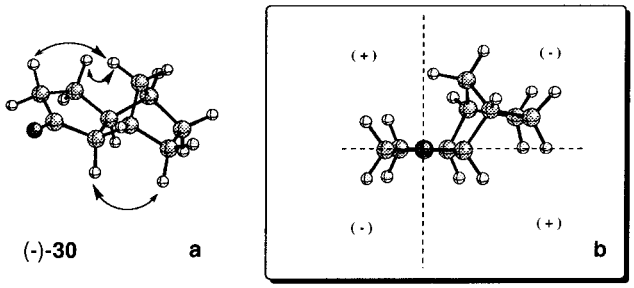
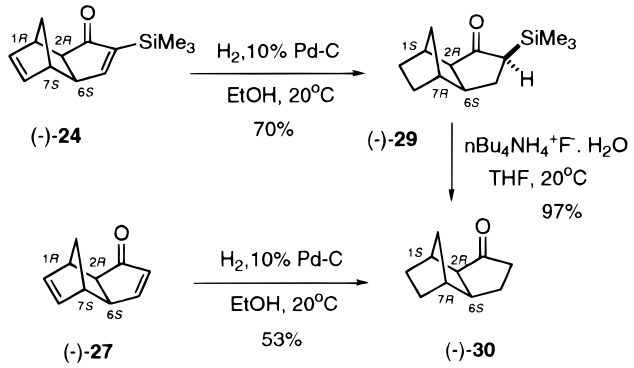


Figure 6. AM1-calculated lowest-energy conformation of compound (−)-**30** and selected nuclear Overhauser enhancement spectroscopy correlations (a). Octant rule projection (rear sector) of ketone (−)-**30** (b).

Scheme 8



hydrogenated to (−)-**30**, so that an (1*R*,2*R*,6*S*,7*S*) configuration was also assigned to (−)-**27**.

All in all, these results offer compelling evidence that in general the levorotatory enantiomers of the Pauson−Khand enone adducts obtained in this work have the same (2*R*) configuration, irrespective of the starting alkyne substituent, and that therefore the dextrorotatory enantiomers have the opposite (2*S*) configuration. Most importantly, this conclusion allows us to establish for the first time a correlation between the absolute configurations of the chiral phosphine-substituted alkyne complexes and those of the corresponding Pauson−Khand adducts: *In their intermolecular Pauson−Khand reactions either with norbornene or norbornadiene, 1-alkyne−dicobaltcarbonyl complexes with mono- or bidentate phosphinooxazoline ligands coordinated at the pro-S cobalt predominantly afford enones with a (2R) absolute configuration. Conversely, the diastereomer complexes with ligands coordinated at the pro-R cobalt give rise predominantly to the (2S) enantiomers.*

This enantioselectivity mnemonic rule can be readily accounted for on the basis of the usually accepted mechanism of the Pauson−Khand reaction, initially proposed by Magnus et al.[24] and largely corroborated by subsequent theoretical[14] and experimental[11a−c,25] studies. According to this mechanistic sequence of events, the reaction is initiated by the displacement of a carbon monoxide from the starting alkyne−dicobaltcarbonyl complex by the olefin, leading to an intermediate species in which both the alkyne and the alkene moieties are bonded to cobalt. Further evolution of this complex (insertion of the complexed olefin into a carbon−cobalt bond giving a five-membered cobaltacycle, insertion of carbon monoxide, and reductive elimination of a dicobaltcarbonyl moiety) leads to the final cyclopentenone product. Within this mechanistic scheme,

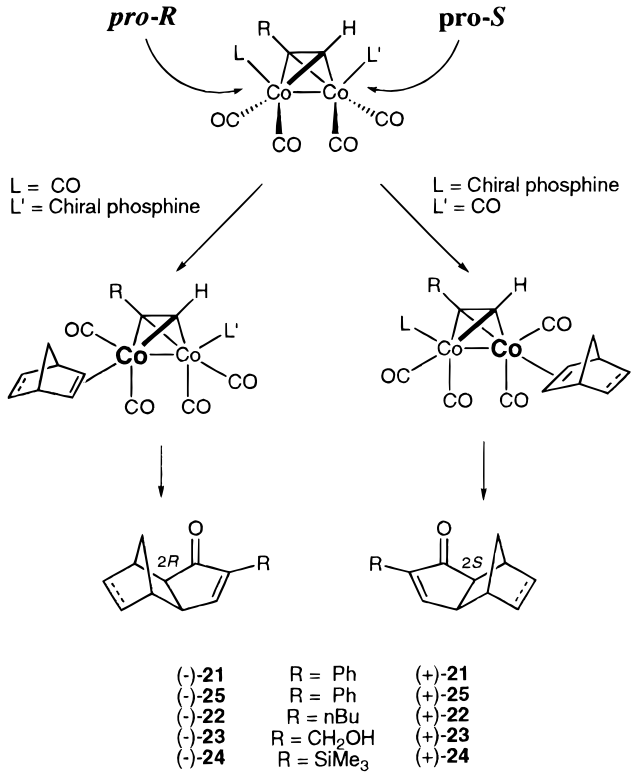


Figure 7. Enantioselectivity mnemonic for the intermolecular Pauson−Khand reaction of phosphine-substituted alkyne complexes.

the stereochemical outcome of the reactions of the monodentate, phosphinooxazoline-substituted complexes can then be explained by assuming the following: (a) The substitution of a cobalt atom by a phosphine ligand largely directs the coordination of the olefin to the unsubstituted cobalt; (b) the olefin (norbornene or norbornadiene) is bonded to the cobalt by the more accessible exo-face, and (c) the olefin is oriented in a way that minimizes the steric interactions of the methylene bridge with the tetrahedral C_2Co_2 cluster. In this way, as depicted in Figure 7, the predominant formation of the (2*R*) or (2*S*) products from the substituted (*S*)- or (*R*)-complexes, respectively, can be easily rationalized. It should furthermore be pointed out that PM3(tm) calculations,[16,17] performed on model systems, give support to this rationalization of the stereochemical outcome of the reaction (see Supporting Information).

The reduced enantioselectivity shown by the chelated complexes **3** and **5** can also be accommodated within this mechanistic model, assuming that in this case, because of the lability of the nitrogen−cobalt bond,[26] coordination of the olefin can also take place at the substituted cobalt and leads therefore to the competing formation of both enantiomers of the product.

(24) (a) Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861−5869. (b) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851−4854.

(25) (a) La Belle, B. E.; Knudsen, M. J.; Olmstead, M. M.; Hope, H.; Yanuck, M. D.; Schore, N. E. *J. Org. Chem.* **1985**, *50*, 5215−5222. (b) Montaña, A.-M.; Moyano, A.; Pericàs, M. A.; Serratosa, F. *Tetrahedron* **1985**, *41*, 5995−6003. (c) Casalnuovo, J. A.; Scott, R. W.; Harwood, E. A.; Schore, N. E. *Tetrahedron Lett.* **1994**, *35*, 1153−1156. (h) Thommen, M.; Veretenov, A. L.; Guidetti-Grept, R.; Keese, R. *Helv. Chim. Acta* **1996**, *79*, 461−476. (d) Corlay, H.; James, I. W.; Fouquet, E.; Schmidt, J.; Motherwell, W. B. *Synlett* **1996**, 990−993. (e) Kowalczyk, B. A.; Smith, T. C.; Dauben, W. G. *J. Org. Chem.* **1998**, *63*, 1379−1389. (f) Krafft, M. E.; Wilson, A. M.; Dasse, O. A.; Bonaga, L. V. R.; Cheung, Y. Y.; Fu, Z.; Shao, B.; Scott, I. L. *Tetrahedron Lett.* **1998**, *39*, 5911−5914. (g) Corlay, H.; Fouquet, E.; Magnier, E.; Motherwell, W. B. *Chem. Commun.* **1999**, 183−184.

(26) PM3(tm) calculations on the relative energies of the chelated and nonchelated forms of complexes **3** and **11a**, **b** indicate that the oxazoline nitrogen−cobalt bond is ca. 20 kcal mol^{-1} weaker than a cobalt−carbonyl one.

In summary, the results described in this article exemplify the use of the chiral phosphinooxazoline[27] **6** as a highly efficient and practical ligand for the enantioselective intermolecular Pauson−Khand reactions of 1-alkynes with norbornadiene.

Experimental Section

Ligands **1**, **4**, and **6**[10] and complexes **2**, **7**−**10**, **16**, and **18**[2,28] were prepared according to standard procedures.

General Procedure for Preparation of Alkyne−Dicobaltpentacarbonyl Complexes Substituted by (−)-[2-[(4*S*)-4-(*tert*-Butyl)(1,3-oxazolin-2-yl)]phenyl]diphenylphosphino 6: Preparation of Complexes 11a,b. To a solution of phenylacetylene−dicobalthexacarbonyl complex **2** (297 mg, 0.765 mmol) in toluene (10 mL) was added phosphinooxazoline **6** (210 mg, 0.54 mmol). The dark-red solution was heated to 60 °C for 2 h 30 min. The reaction mixture was cooled to room temperature and filtered through Celite, which was thoroughly washed with methylene chloride. The solvents were eliminated under reduced pressure, and the dark-brown residue was purified by column chromatography on silica gel (previously washed with ether and hexane), eluting with hexanes−ethyl acetate mixtures of increasing polarity, to afford 155 mg (38%) of **11a** and 159 mg (39%) of **11b**. The global yield was 77%. Each diastereomer was recrystallized from hexane/methylene chloride and then kept in the freezer. One crystal of **11b** has been X-ray diffracted. **Complex 11a:** Brown-red crystals; mp 105−106 °C; R_f 0.24 (hexane:ethyl acetate, 5:1); $[\alpha]^{25}_D$ −968 (*c* 0.006); CD [λ_{max}, nm ($\Delta\epsilon$)] 287 (+12.0), 383 (+6.2), 480 (−3.8) (*c* 8.57 × 10^{-5}); IR (cm^{-1}) 2060, 2010, 1997, 1960, 1655, 1479; ^{1}H NMR (300 MHz) δ 8.10−8.00 (m, 1H), 7.60−7.45 (m, 2H), 7.43−7.30 (m, 1H), 7.25−6.60 (m, 16H), 5.54 (d, J = 3.9 Hz, 1H), 3.80−3.30 (m, 3H), 0.62 (s, 9H); ^{13}C NMR (75.4 MHz) δ 207.0 (b, CO), 206.0 (b, CO), 202.5 (b, 3CO), 162.6 (C_q), 139.8 (C_q), 138.0−126.0 (complex signal, $4C_q$ and 19CH), 88.2 (C_q), 76.7 (CH), 73.2 (CH), 69.1 (CH_2), 34.2 (C_q), 26.4 ($3CH_3$); ^{31}P NMR δ +55.23; MS [FAB(+)] *m*/*e* = 748.1 (M^+ + 1, 1%), 691.1 (M^+ − 2CO, 5%), 663.1 (M^+ − 3CO, 8%), 636.2 (M^+ − 4CO, 3%), 607.1 (M^+ − 5CO, 60%), 474.1 (20%), 446.1 (100%); HRMS (FAB+) calcd for $C_{33}H_{32}Co_2NOP$ (M − 4CO)$^+$ 607.089, found 607.085. **Complex 11b:** Brown-red crystals; mp 95−96 °C; R_f 0.10 (hexane:ethyl acetate, 5:1); $[\alpha]^{25}_D$ = + 637 (*c* 0.017); CD [λ_{max}, nm ($\Delta\epsilon$)] 342 (+3.03), 392 (−2.4), 492 (+4.4) (*c* 2.25 × 10^{-4}); IR (cm^{-1}) 2060, 2010, 1647, 1593, 1479; ^{1}H NMR (200 MHz) δ 7.8−7.5 (m, 5H), 7.2−6.6 (m, 14H), 5.59 (d, J = 4 Hz, 1H), 3.52−3.65 (m, 1H), 3.27−3.39 (m, 1H), 2.82−2.98 (m, 1H), 0.69 (s, 9H); ^{13}C NMR (75.4 MHz) δ 207.6 (b, CO), 206.5 (b, CO), 202.7 (b, 3CO), 163.7 (C_q), 139.2 (C_q), 138.0−126.0 (complex signal, $4C_q$ and 19CH), 90.0 (C_q), 75.8 (CH), 72.6 (CH), 69.2 (CH_2), 34.4 (C_q), 26.4 ($3CH_3$); ^{31}P NMR δ +58.27; MS [FAB(+)] *m*/*e* = 748.1 (M^+ + 1, 1%), 691.1 (M^+ − 2CO, 7%), 663.2 (M^+ − 3CO, 10%), 607.1 (M^+ − 5CO, 65%), 474.1 (35%), 446.1 (100%); HRMS (FAB+) calcd for $C_{33}H_{32}Co_2NOP$ (M − 4CO)$^+$ 607.089, found 607.085. Conditions for the determination of the diastereomeric purities of **11a** and **11b** by HPLC analysis: CHIRALCEL OD (25 cm) column, 1% 2-propanol 99% hexane, 0.5 mL/min, 30 °C, λ = 254 nm, P = 14 bar. t_R(**11a**): 9.71 min. t_R(**11b**): 11.24 min.

General methods, preparation, and spectroscopic and analytical data of complexes **3**, **5**, **12a**,**b**−**15a**,**b**, **17**, and **19**, procedures for their intermolecular Pauson−Khand reactions, and characterization data of the resulting adducts can be found in the Supporting Information.

Acknowledgment. Financial support from DGES (PB96-0376 and PB97-0939) is gratefully acknowledged.

Supporting Information Available: Tables of crystal data, structure solution and refinement, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for **11b**. Evolution of the diastereomeric purity of complexes **11a**,**b**−**15a**,**b** in solution. Semiempirical molecular orbital (MO) studies on phosphinooxazoline-substituted alkyne−dicobaltcarbonyl complexes. Semiempirical MO studies on the intermolecular Pauson−Khand reactions of phosphine-substituted alkyne−dicobaltcarbonyl complexes. Complete Experimental Section (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA001143O

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