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Highly Stereoselective Induction in the Cobalt-Mediated [2+2+2] Cycloaddition of Chiral Phosphine Oxides Substituted Linear Enediynes

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Abstract : The cobalt(I)-catalyzed highly stereoselective [2+2+2] cyclization has been realized for the first time with chiral phosphine oxides substituted linear enediynes. Depending the substituents on the phosphorus atom, the cycloaddition was achieved with a level of diastereoselectivity of 74%.

Keywords : cobalt and compounds ; diynes ; cyclisation ; diastereoselection

The intramolecular cobalt-mediated [2+2+2] cyclizations of triynes,[1] enediynes[2] and allenediynes[3] have attracted much attention as useful synthetic tools.[4,5] As part of our program designed to exploit this cyclization in the synthesis of polycyclic natural products,[6] we were interested in examining the asymmetric version of this reaction. Though one example of [2+2+2] cyclization promoted by chiral cyclopentadienyl cobalt complexes has been reported albeit with low diastereomeric excess,[7] as far as we were aware, no cobalt(I) cyclizations with chiral auxiliary on enediynes have been recorded in the literature. In the last years, nickel(0)-promoted asymmetric [2+2+2] cocyclizations have been realized based upon a strategy which involves conceptually a new enantiotopic group selective formation of a nickelacyclopentadiene.[8] Recently, our initial efforts[9] showed that the phosphine oxide at the acetylenic position of the enediynes seemed to be a promising substituent for an asymmetric study of this reaction in terms of the high stability of the complexed cycloadducts, the yield of the reaction and the *exo* selectivity. Numerous synthetic routes of optically active phosphine oxides have been accomplished because those are widely used as chiral ligands in organometallic catalysts for asymmetric synthesis. Despite this fact only few examples of asymmetric induction involving chiral phosphine oxides have been reported in the 1,3 dipolar cycloadditions,[10] Diels-Alder and Pauson-Khand reactions and conjugate additions.[11]

In this communication, we report that a highly stereoselective induction in the [2+2+2] cyclizations of linear enediynes bearing chiral phosphine oxides is obtained by the proper choice of the substituent on phosphorus and we show that the phosphines oxides turn out to be highly valuable auxiliaries for stereoselective synthesis.

The enediynes **1a-f** bearing the chiral phosphine oxide either in enantiomerically pure form for **1a-d** or as a racemic mixture for **1e** and **1f** were prepared as outlined in Scheme 1 from 1-tetradecene-7,13-diyne. Deprotonation of the latter with *n*-BuLi followed by the addition of the chlorophosphine oxide[12] **2a-e** provided

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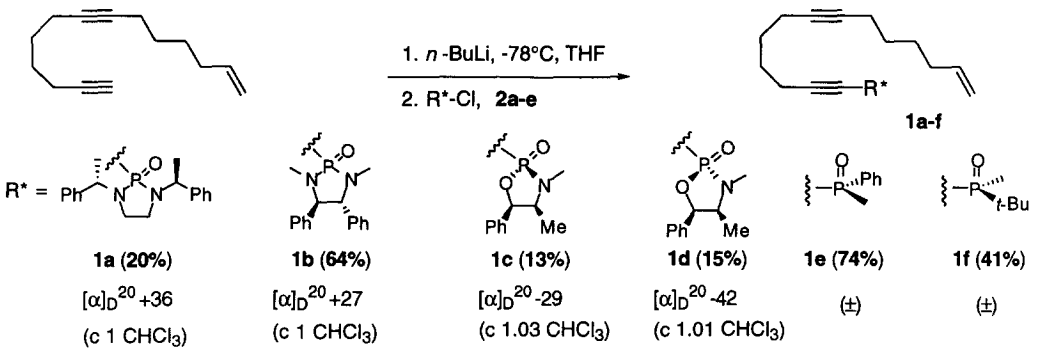
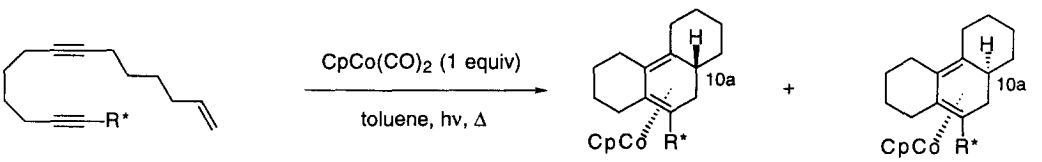
1a -f in moderate yields. The compounds **1c** and **1d** arose from the reaction with the 1, 3, 2-oxazaphospholidine derived from (-)-ephedrine **2c** and were obtained as a 1:1 separable mixture.



Scheme 1

Exposure of the enediynes **1a-f** to a stoichiometric amount of $CpCo(CO)_2$ in refluxing toluene and under irradiation (using a sun lamp) led to the red-brown complexes **3a-f** *exo/endo* in very high yields (see table 1). Interestingly, these complexes are quite air-stable and can be handled without any special care (their purifications were runned on silica without degassed solvents).

Table 1 : Cobalt-mediated [2+2+2] Cyclizations of **1a-f**



Enediynes	Yield (%)	**3a-f** *exo* (de %)	**3a-f** *endo* (de %)
1a	94	76 (6)	24 (2)
1b	quantitative	78 (15)	22 (25)
1c	83	67 (29)	33 (24)
1d	88	69 (36)	31 (34)
1e	80	69 (30)	31 (42)
1f	99	71 (**60**)	29 (**58**)

In all cases except for **1f**, all the diastereomers were obtained as an inseparable mixture and their ratio were determined by ^1H NMR based on the integration of the cyclopentadienyl hydrogens or by ^{31}P NMR. The

stereochemical assignment of *exo/endo* diastereomers relied on the same spectral interpretation of the parent compounds and the ratio *exo/endo* observed was consistent in all cases with our previous findings.[9]

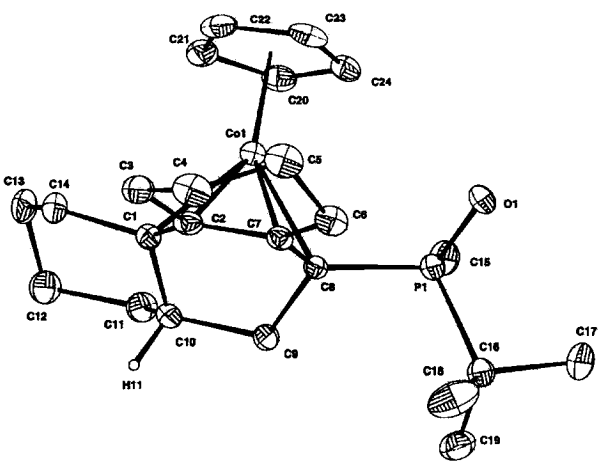
These results showed that the diastereomeric excess either for the *exo* diastereomer or the *endo* one is higher when the stereogenic centers are close to the triple bond. The best excesses were observed when the phosphorus atom is stereogenic especially in the case of **1f** which exhibits a bulky *tert*-butyl group on the phosphorus atom. We also checked the influence of the solvent ; the cyclizations were carried out, with **1f**, as usual in refluxing solvent and under irradiation. The results are summarized in the table 2.

Table 2 : Influence of the solvent in the cyclization of **1f**

Solvent	Time	Yield (%)	**3f** *exo* (de %)	**3f** *endo* (de %)
toluene	30 min	99	71 (60)	29 (58)
benzene	30 min	quantitative	70 (64)	30 (64)
dioxane	90 min	quantitative	72 (60)	28 (66)
THF	60 min	quantitative	71 (**74**)	29 (**72**)

We noticed an improvement of the diastereomeric excesses only in refluxing THF, probably due to its lower boiling point ; however when the reaction was carried out at lower temperature (0°C), the reaction did not proceed.

The major **3f** *exo* diastereomer, isolated as a pure compound,[13] crystallized and the assigned structure was unambiguously confirmed by a X-ray analysis. The ORTEP representation (Scheme 2) showed the relative configuration between H-10a (H11 on the ORTEP) and the phosphorus substituent and the *anti* relationship between the angular H-10a and the cobalt moiety. The data revealed that the oxygen of the phosphine oxide is *syn* to the cobalt, meaning that the transition state of the cyclization involves a chelation between the oxygen atom of the phosphine oxide and the metal which is probably the controlling feature of the stereochemistry of the reaction.



Scheme 2

In summary, the first examples of the cobalt(I)-catalyzed asymmetric [2+2+2] cyclization have been realized with chiral phosphine oxides substituted linear enediynes. Depending of the substituents on the phosphorus atom especially if the latter is stereogenic, the diastereoselectivity can reach 74% ; up to now, this level is the highest observed in such cyclizations. Work is still currently under active progress in our laboratories.

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12. **2a**, **2b**, **2c** and **2d** were obtained by heating in toluene, the diamine, prepared in our hands, or commercial aminoalcohol and $POCl_3$ in presence of NEt_3. For **2a** (83%): see (+)-N, N'-Bis[(*R*)-1-phenylethyl]-1,2-ethylendiamine Horner, L.; Dickerhof, K. *Liebigs Ann. Chem.* **1984**, 1240-1257. For **2b** (94%): see N, N'-dimethyl-1,2-diphenylethane-1,2-diamine Alexakis, A.; Aujard, I.; Kanger, T.; Mangeney, P. *Organic Synthesis* in press. For **2c** (28%) see Cooper, D.B.; Hall, C. R.; Harrison, J. M.; Inch, T. D. *J. Chem. Soc. Perkin Trans. I* **1977**, 1969-1980. For **2d** (66%) : see Korpiun, O.; Lewis, R. A.; Chickos, J. Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4842-4846. For **2e** (86%) : Crofts, P. C.; Parker, D. M. *J. Chem. Soc. (C)* **1970**, 332-335.
13. **Spectral data for 3f *exo***: ^{1}H-NMR (400 MHz, C_6D_6) δ 4.85 (s, 5H), 3.99 (m, 1H), 2.45 (ddd, J = 16.3, 11.2, 4.1 Hz, 1H), 2.24-2.07 (m, 3H), 1.98-1.68 (m, 7H), 1.49 (d, J = 11.2 Hz, 3H), 1.19 (d, J = 13.2 Hz, 9H), 1.59-1.08 (m, 4H), 0.69 (m, 1H), 0.44 (quint d, J = 8.6, 1.5 Hz, 2H) ; ^{13}C-NMR (100 MHz, C_6D_6) δ 97.0 (J_{CP} = 12.1 Hz), 89.1 (J_{CP} = 12.1 Hz), 83.3 (5C), 72.3, 53.4 (J_{CP} = 80.9 Hz), 41.9 (J_{CP} = 10.1 Hz), 36.4, 35.3 (J_{CP} = 60.7 Hz), 33.9 (J_{CP} = 8.1 Hz), 33.5, 29.1, 26.8 (3C), 26.6, 26.4 (2C), 23.9, 23.4, 13.4 (J_{CP} = 66.7 Hz) ; ^{31}P-NMR (162 MHz, C_6D_6) δ 55.2 ; IR ($CHCl_3$) 2920, 2850, 2800, 1440, 1360, 1285, 1140, 1125, 875, 865, 810 cm^{-1} ; Anal. Calcd for $C_{24}H_{36}OPCo$: C, 66.97 ; H, 8.43. Found : C, 66.89 ; H, 8.49.