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Improvement of the Diastereoselectivity of the Cobalt-Mediated [2+2+2] Cycloaddition of Substituted Linear Enediynes

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Abstract : The level of the diastereoselectivity of the cobalt-mediated [2+2+2] cyclization of linear enediynes was improved compared to that reported in the literature by substituting the triple or the double bond with ester, phosphine oxide or sulfoxide groups. © 1999 Elsevier Science Ltd. All rights reserved.

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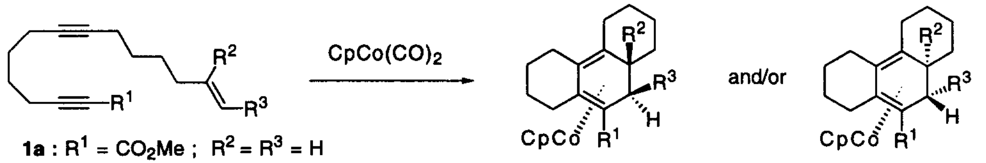
In the last decades, the cobalt(I)-mediated [2+2+2] cyclizations of triynes[1] or linear achiral enediynes containing di-, tri- and tetrasubstituted double bond[2] have emerged as one of the most useful synthetic tools. Remarkable selectivity and high yields have been observed and have allowed the synthesis of a range of complex molecules of medicinal[3] and theoretical[4] interest.

As part of our continuing effort to exploit cobalt-catalyzed [2+2+2] cyclization in the synthesis of polycyclic natural products,[5] we turned our attention to the asymmetric version of this reaction. Though one example of asymmetric [2+2+2] cycloaddition promoted by chiral cyclopentadienylcobalt complexes has been reported,[6] as far as we are aware no [2+2+2] reactions with chiral auxiliary on enediynes have been recorded in the literature. Aiming at an efficient transfer of chirality, we focused our initial study on the more appropriate substituent and the most judicious position of the polyunsaturated precursor. We report in this communication the improvement of the observed *endo/exo* diastereoselectivity of the [2+2+2] cyclization of linear enediynes compared to that reported in the literature[1b] by introducing substituents such as an ester, a sulfoxide or a phosphine oxide at the terminal position of either the triple or the double bond partner (Scheme 1).



1a : R^1 = CO_2Me ; $R^2 = R^3$ = H
1b : R^1 = $Ph_2P(O)$; $R^2 = R^3$ = H
1c : R^1 = *p*-TolS(O) ; $R^2 = R^3$ = H
1d : R^1, R^2 = H ; R^3 = CO_2Et
1e : R^1 = H ; R^2 = Me ; R^3 = $Ph_2P(O)$

2a-e *exo*

2a-e *endo*

Scheme 1

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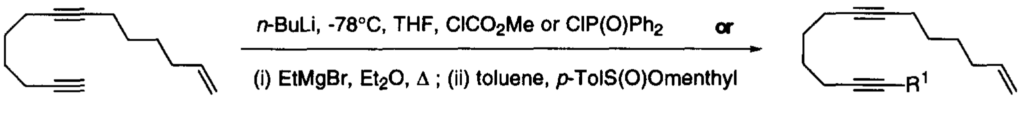
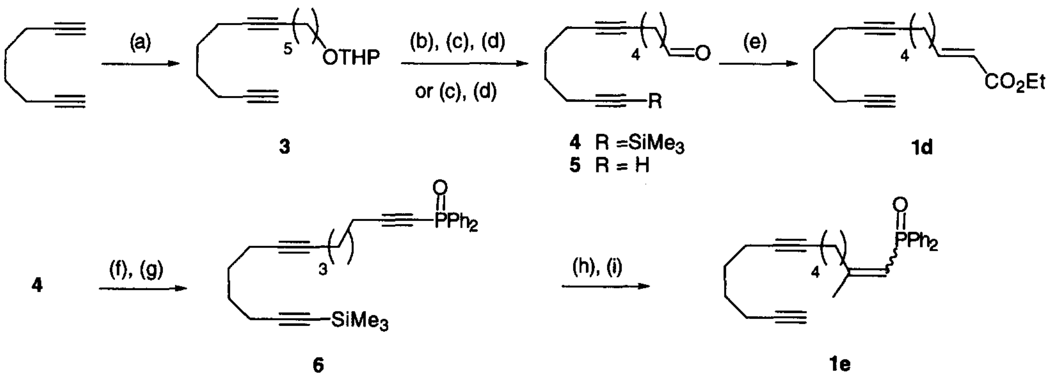
The enediynes **1a-c** were prepared as outlined in Scheme 2 from the 1-tetradecene-7,13-diyne. Deprotonation of the latter either with *n*-BuLi or ethyl Grignard reagent followed by addition of methylchloroformate or chlorodiphenylphosphine oxide or *p*-tolylmenthyl sulfinate provided **1a-c** in 73%, 57% and 26% yields respectively.



1a-c

Scheme 2

The precursors **1d** and **1e** were obtained from the trideca-6,12-diynal **4** and **5** which were prepared from the commercially available 1,7-octadiyne (Scheme 3).



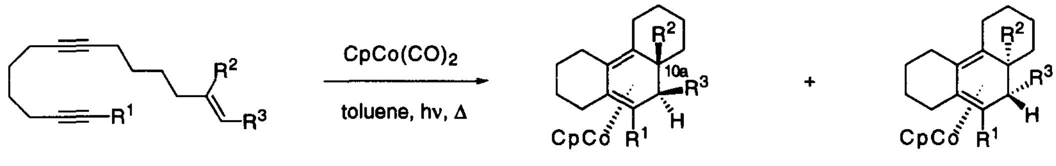
(a) *n*-BuLi , -78°C, THF, HMPA, $Br(CH_2)_5OTHP$, 75%. (b) *n*-BuLi, THF, -78°C, Me_3SiCl, 98 %. (c) cat. PTSA, MeOH, 95%. (d) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, quant. (e) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, NEt_3, CH_3CN, r.t., overnight, 88%. (f) 1. CBr_4, PPh_3, CH_2Cl_2, 96 % ; 2. *n*-BuLi, THF, -78°C, quant. (g) 1. EtMgBr, Et_2O, Δ ; 2. toluene, Δ, $ClP(O)Ph_2$, 61 %. (h) MeMgBr, Et_2O, Cu_2Cl_2, Δ, (*E*)-**7** : 48 % ; (*Z*)-**7**: 32 %. (i) KF, DMSO, r.t., (*E*)-**1e** : 99 % ; (*Z*)-**1e** : 95 %.

Scheme 3

The monoalkylation of the 1,7-octadiyne with 2-(5-bromo-pentyloxy)-tetrahydropyran[7] provided the ether **3**, accompanied by the dialkylated compound (12%). Compound **3** was subsequently acid-catalyzed deprotected and oxidized to afford the aldehyde **5**. This latter was submitted to the mild alkenylation procedure of Masamune *et al.*[8] to provide the (*E*)-α,β-unsaturated ester **1d** in 88% yield. The aldehyde **4** was obtained by the same sequence as described for **5** after the protection of the triple bond and it was transformed by chain extension to the corresponding alkyne by Corey's procedure.[9] Alkylation of the resulting triyne with chlorodiphenylphosphine oxide led to the compound **6** in 61% yield. Michael addition of the methyl Grignard reagent to **6** in ether occured in presence of cuprous chloride[10] and furnished the vinylphosphine oxides as a mixture of separable diastereomers (*E*)-**7** and (*Z*)-**7** in 48 % and 32 % yields respectively. Removal of the trimethylsilyl group by using potassium fluoride in aqueous DMSO achieved the preparation of the enediynes (*E*)-**1e** and (*Z*)-**1e**.

Exposure of the enediynes **1a-e** to a stoichiometric amount of $CpCo(CO)_2$ in refluxing toluene and under irradiation afforded the red-brown complexes as a mixture of inseparable diastereomers **2a-e** *exo*/*endo* in very high yields (see table 1), except for **1c** whose cyclization led to the corresponding [2+2] compound (24%), beside **2c** *exo* and **2c** *endo*, each as a mixture of diastereomers (de_{exo} = 15% ; de_{endo} = 18%). In the case of (*E*)-**1e**, longer reaction time (36 h) was required and involved decomposition either of the starting material or the complexes ; the cyclization was carried out with (*Z*)-**1e** as well but untractable materials were obtained. On the contrary to **2c-e**, the complexes **2a** and **2b** were particularly stable to the air and can be easily handled.

Table 1 : Cobalt-Mediated [2+2+2] Cycloadditions of **1a-e**



1a-e **2a-e** *exo* **2a-e** *endo*

Entry	R^1	R^2	R^3	Yield %	**2a-e** *exo*	**2a-e** *endo*
1a	CO_2Me	H	H	94	60	40
1b	$Ph_2P(O)$	H	H	96	75	25
1c	*p*-TolS(O)	H	H	31	76	24
1d	H	H	CO_2Et	71	14	86
1e	H	Me	$Ph_2P(O)$	32	0	100
1f(1b)	$SiMe_3$	H	H	92	50	50
1g(1b)	H	H	H	76	66	33

The ratio of the diastereomers was determined by ^{1}H-NMR based on the integration of the cyclopentadienyl hydrogens. The stereochemical assignments of **2a-e** *exo* and *endo* relied on similar spectral interpretation[1b] of the parent compounds **1f** and **1g**. They are based on the characteristic chemical shifts of the angular hydrogen H-10a (for **1a-d**) or the methyl (for **1e**), which are highly shielded for the diastereomer *exo* relatively to the *endo* one. Similarly, the ^{13}C resonance at the *endo* methyne carbon C-10a (for **2a-d**) occurs 8-9 ppm downfield from the analogous *exo* methyne carbon.

In all cases, the level of the diastereoselectivity was improved compared to that reported for **1f** and **1g**. Interestingly the cyclization of (*E*)-**1e** is totally selective, albeit proceeding in moderate yield. Thus, the *exo* selectivity increased when the triple bond is substituted with an ester, a phosphine oxide or a sulfoxide relatively to a trimethylsilyl group. On the contrary, it is the *endo* selectivity that improved when the double bond in the *E* configuration is substituted.

These results could be explained by the most probable mechanisms of the [2+2+2] cyclization which may involve either a cobaltacyclopentadiene or -pentene. But whatever the mechanism is, the predominant directing effect is the chelation between the oxygen atom of the electronwithdrawing group and the metal. If we assume that the metal initially binds to the heteroatom, the resulting chelation could control the stereochemistry of the reaction. Thus, a chelation might be expected and efficient for the cyclization only with a double bond in the *E* configuration and in an *endo* approach. Similarly, in the case of the substitution of the triple bond, the chelation would favor the initial formation of cobaltacyclopentadiene and furthermore explaining the *exo* selectivity.

In summary, we have shown that the selectivity of the cobalt-mediated [2+2+2] cyclization of linear enediynes can be significantly improved by introducing substituents such an ester, a phosphine oxide or sulfoxide at the terminal position of the polyunsaturated precursor. The phosphine oxide group seems a quite promising substituent in view of the study of the asymmetric [2+2+2] cycloadditions which are currently under active progress in our laboratories.

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