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Cobalt-mediated cyclotrimerization and cycloisomerization reactions. Synthetic applications*

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Abstract: This article reviews our contribution in the field of the cobalt(I)-mediated cyclizations. The use of new unsaturated partners such as allenes extend the scope and the utility of the previously developed intramolecular [2+2+2] cyclotrimerization. The presence of chiral auxiliaries induced high level of diastereoselectivity in the enediynes cyclization. The discovery of cobalt(I) catalyzed ene-type reaction allows to propose an efficient route to the basic skeleton of tetracyclic diterpenes *via* a one-pot sequence of cyclizations: [ene-type]/[2+2+2]/[4+2]. This cascade created six carbon-carbon bonds, four rings in a totally stereoselective manner. Finally, a new strategy to the taxoids is proposed.

INTRODUCTION

Cobalt (I) complexes are exceptionally versatile catalysts for the construction of multiple carbon-carbon bonds in a single chemical step [1]. Dramatic examples of their utility in synthesis have been proposed by Peter Vollhardt who successfully developed the cyclopentadienyl dicarbonyl cobalt ($CpCo(CO)_2$) catalysis of the cocyclization of α-ω-diynes with bis(dimethylsilyl)ethyne [2]. Immediately thereafter, this group has been able to achieve very elegant and spectacularly efficient total synthesis of steroid derivatives by illustrating the so-called tandem strategy: [2+2+2]-[4+2] [3]. Moreover, in the early 1980s, the Berkeley's group demonstrated the spectacular synthetic usefulness of the cobalt(I)-mediated intramolecular [2+2+2] of enediynes precursors [4] by its application as a key-step in the total synthesis of various natural products such as steroids [5], tricyclic sesquiterpene [6], tetracyclic diterpene [7] and molecules of theoretical interest [8].

From our side, we anticipate that the potential of the cobalt(I) catalysis could be spectacularly displayed by designing cascade reactions aimed at the construction of complex highly functionalized molecules in a one-pot operation, starting from simple acyclic polyenyne precursors. To reach such a goal, we were interested in the quest for the development of new synthetic tools. We have opted for the finding of new unsaturated partners for the [2+2+2] cyclizations. While we were exploring the scope of the allenediynes cyclizations [9], we disclosed that cobalt(I) complexes could catalyze a formal Alder-ene reaction of allenynes [10] and enynes [11]. By the same way, we discovered that these cobalt(I) species could mediate the ene-type reaction of ω-acetylenic β-ketoesters to form functionalized methylenecyclopentanes in a stereocontrolled manner [12]. Having in hands highly valuable tools, we propose different approaches to the basic skeletons of natural tetracyclic diterpenes in the families of phyllocladanes [13], kauranes [14], taxanes [15], gibbanes [16] and triquinanes [17], based upon the combining of these cyclizations. Finally, the ultimate goal of such strategies is the examination of the asymmetric version of these reactions. This account will review some of the published work involving these cyclotrimerizations and isomerizations and their synthetic applications.

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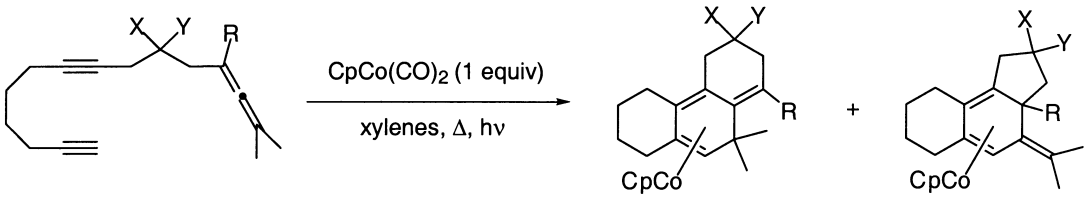
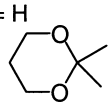
CYCLOTRIMERIZATIONS

Cyclotrimerization of allenediynes

The cobalt(I)-mediated cyclizations of the allenediynes was based on the ability of the allenes, which present cumulated C–C double bond, to be good ligands in organometallic complexes.

Indeed, the [2+2+2] cycloadditions of allenediynes reveal to be quite successful [9]. However, the reaction markedly depends on the position and the substitution of the allene. Thus, the tri- and tetrasubstituted allenes **1** and **2a-c** cyclized in presence of a stoichiometric amount Of $CpCo(CO)_2$ in boiling xylenes under irradiation to provide either the tricyclic [6.6.5] or [6.6.6] compounds as only one diastereomer in high isolated yields (70–87%) (Scheme 1).

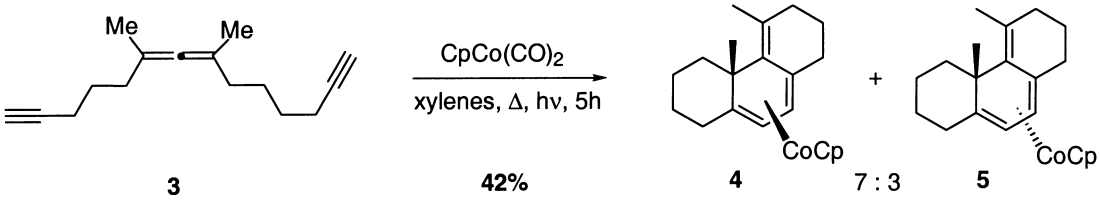


1 X, Y = H	; R = H	**72 %**	0	100
2a X, Y = 	; R = *t*-Bu	**80 %**	0	100
2b X, Y = "	; R = Ph	**87 %**	100	0
2c X, Y = "	; R = Me	**70 %**	100	0

Scheme 1

The substitution of the allene is the determining factor on the regiochemical outcome of the cyclization however, for an identical substitution of the allene, the reaction is significantly influenced by the presence or not of an acetonide substituent on the tether.

Similarly, under the same conditions, the allenediyne **3** having a tetrasubstituted allene at the internal position led to the η^4-complexed tricyclic [6.6.6] structures **4** and **5** as a 7:3 diastereomeric mixture in 42% yield (Scheme 2).



3 **42%** **4** 7 : 3 **5**

Scheme 2

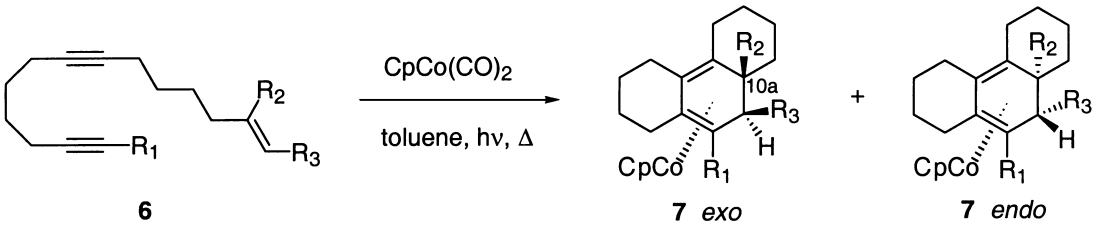
These cyclizations are of great interest for synthetic purposes, since free ligands may be regarded a constituting the BCD and ABC (with an angular methyl at the AB ring junction) moieties of steroids. This is quite useful considering an approach in asymmetric version from an optically pure allene. Based on the results of the cyclization of **1** which represents the simplest substrate, we are currently studying the ability of transferring the axial chirality into the centered one with enantiopure enriched allenediynes.

Cyclotrimerization of chiral linear enediynes

In order to build enantioselective polycyclic compounds, we turned our attention to the selective induction in the [2+2+2] cyclization of chiral substituted linear enediynes. Although one example of [2+2+2] cyclization promoted by chiral cyclopentadienyl cobalt complexes has been reported, albeit

with low diastereomeric excesses [18] as far as we are aware no [2+2+2] reactions with chiral auxiliary on enediynes has been recorded in the literature.

Our initial efforts were focussed on the finding of the more appropriate substituent and the most judicious position of the polyunsaturated precursor. Thus, we showed [19] that the level of the diastereoselectivity of the [2+2+2] cyclization of linear enediynes was improved compared to that reported in the literature [4b,20] 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 3).



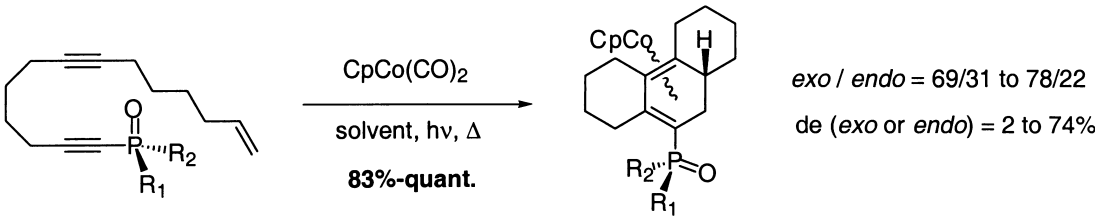
R_1 = CO_2Me, $Ph_2P(O)$, *p*-TolS(O) ; R_2, R_3 = H **31-96 %**; *exo/endo* = 60/40 to 76/24

R_1, R_2 = H ; R_3 = CO_2Et
R_1 = H, R_2 = Me, R_3 = $Ph_2P(O)$ } **32-71 %**; *exo/endo* = 14:86 to 0:100

Scheme 3

The phosphine oxide group at the acetylenic position of the enediynes emerged as the most promising substituent for the asymmetric study in terms of the high stability of the complexed cycloadducts, the yield of the reaction (96%) and the *exo* selectivity (*exo/endo* = 75/25).

Indeed, a highly stereoselective induction in the [2+2+2] cyclization of linear enediynes bearing chiral phosphine oxide was observed [21]. Depending of the substituents on the phosphorus atom especially if the latter is stereogenic, the diastereoselectivity can reach 74% and up to now, this level is the highest observed in such cyclizations (Scheme 4).



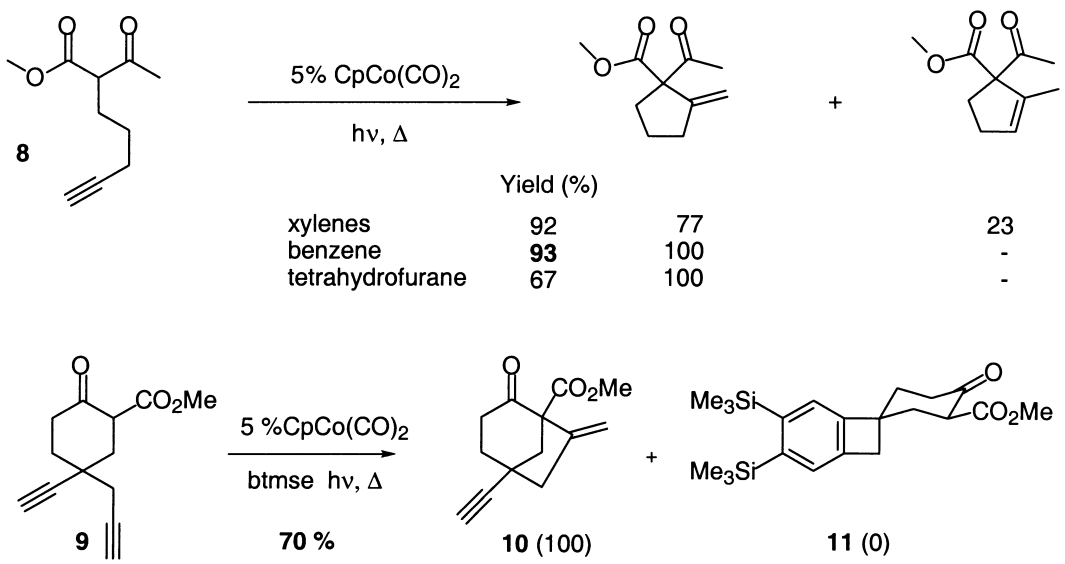
Scheme 4

CYCLOISOMERIZATION OF β-KETOESTERS ω-YNES

In connection with our program designed to the construction of the basic skeletons of natural tetracyclic diterpenes, we checked the behavior of ϵ-acetylenic β-ketoesters in the presence of a catalytic amount of $CpCo(CO)_2$. We found that this cobalt complex was a very efficient catalyst for the Conia-ene type reaction [12a] providing highly functionalized methylenecyclopentanes. Such a result has enhanced the synthetic utility of the thermal and Lewis acid mediated versions of this reaction.

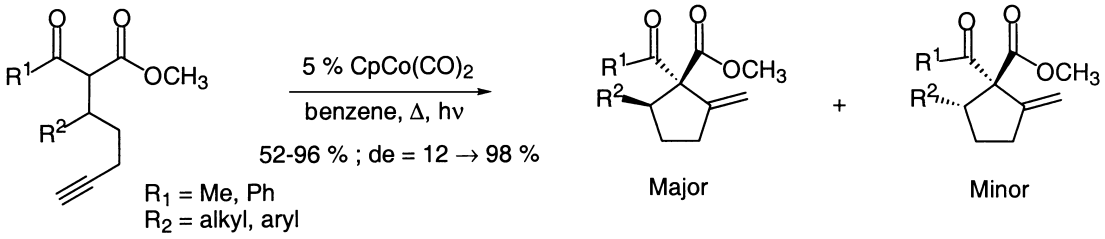
Indeed, studies carried out on the compound **8** showed that the corresponding methylenecyclopentane was obtained in a 93% yield in refluxing benzene. In that case, no double-bond migration was observed, contrary to the case in boiling xylenes. This new catalytic reaction could even be carried out in refluxing tetrahydrofuran, albeit in lower yield. Interestingly, this reaction turned out to be very chemoselective. In the presence of a catalytic amount of $CpCo(CO)_2$ the β-ketoester **9** furnished the bicyclo [3.2.1] octane derivative **10** in 72% yield, indicating the total chemoselectivity of this cycloisomerization. No trace

amounts of the [2+2+2] cycloadduct **11** was detected showing the total selectivity of this new catalysis: cycloisomerization vs. [2+2+2] (Scheme 5).



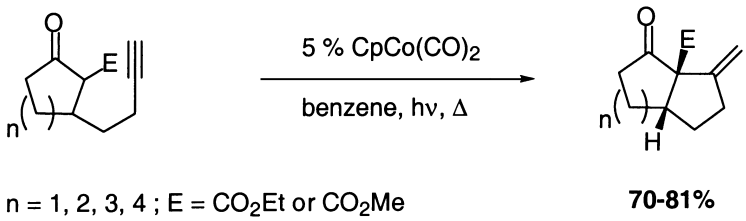
Scheme 5

The investigations into the mechanism and the observed regio-, chemo- and stereoselectivities support a process of an enol-yne cycloisomerization which controls the relative stereochemistry of two contiguous stereogenic centers [12b] (Scheme 6).



Scheme 6

The relative stereochemistry of 1,3- and 1,4-stereogenic centers can be controlled as well with moderate to high level of diastereoselectivity [14,17]. In the same way, this cycloisomerization provides a rapid an totally diastereoselective access to 5,5-, 5,6-, 5,7- and 5,8-ring systems from simple starting material [22] (Scheme 7).

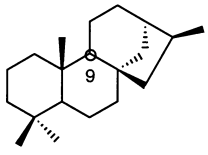


Scheme 7

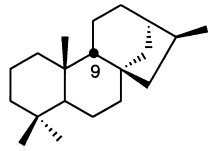
SYNTHETIC APPLICATIONS

Approach to the phyllocladane and kaurane families

In connection, as mentioned above, with our interest in the synthetic development of cobalt-mediated cycloisomerizations, we investigated stereoselective routes to the basic skeletons of tetracyclic diterpenes belonging to the phyllocladane **12** and kaurane **13** families which are widespread in nature [23]. Some representatives display very important biological properties (Scheme 8).



α- H_9 : Phyllocladane (P), **12**



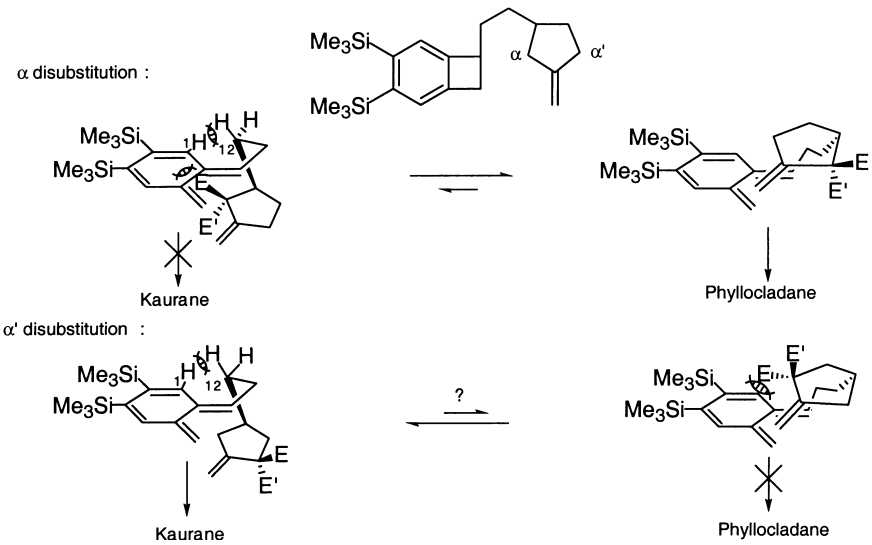
β- H_9 : Kaurane (K), **13**

Scheme 8

For these purposes, we already reported [24] a stereoselective approach to both families, using a common synthetic pathway based upon a sequence of three consecutive cycloadditions reactions: a Pd(0)-assisted [3+2] annulation reaction which led to homoallylic substituted methylenecyclopentanes, a [2+2+2] Co(I)-catalyzed cyclotrimerization and finally an intramolecular [4+2] cyclization.

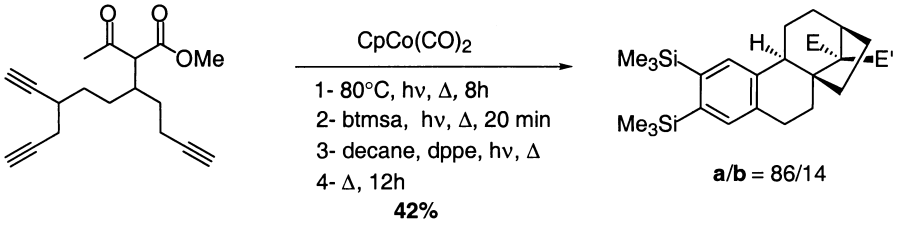
We observed that: (i) the homoallylic substitution on the methylenecyclopentanes was without influence on the stereochemical outcome of this sequence and that (ii) the non-bonding interaction between H_1 of the *o*-quinodimethane and the substituent at C_{12} was the controlling feature for the stereoselectivity of the Diels–Alder reaction. Thus, the presence of a sp^3-hybridized C_{12}, especially a sterically demanding group led stereoselectively to the phyllocladane type tetracycle as a major isomer. A reduction of this steric interaction by the presence of a sp^2-hybridized atom C_{12} markedly changed the proportion of phyllocladane type vs. kaurane type tetracycles (58:42) but still remained useless for further synthetic applications.

Concentrating upon a stereoselective access to the phyllocladane/kaurane families we studied the influence of the presence of substituents in the α or α′ allylic endocyclic position of the methylenecyclopentane unit (Scheme 9).



Scheme 9

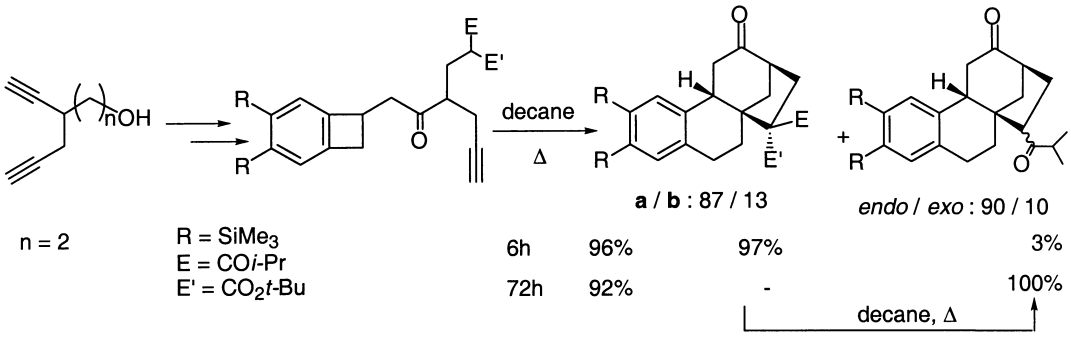
The discovery that cobalt(I) species catalyzed the ene-type reaction of ϵ-acetylenic β-ketoesters to form highly functionalized methylenecyclopentanes in a regio-, chemo- and stereoselective manner allowed us to propose in the case of the α-disubstitution a very short and efficient route to the phyllocladane skeleton by a new cascade: [ene-type], [2+2+2], [4+2] in a one-pot sequence [13]. The complete stereoselectivity in favor of this framework during the intramolecular Diels–Alder reaction resulted from the non-bonding interaction H_1–H_{12} already mentioned with an additional destabilizing interaction between the *gem*-dicarbonyl substituent and the orthoquinodimethane moiety (Scheme 10).



Scheme 10

This remarkable one pot sequence of cascade cyclizations: ene-type [2+2+2], [4+2] allowed the formation of six carbon–carbon bonds and four rings with total regio- and chemoselectivity and with a high level of diastereoselectivity from an acyclic precursor bearing three uncontrolled stereogenic centers.

The totally stereoselective formation of the kaurane framework was achieved, for the first time, by using the synergic influence of the α′-substituent on the methylenecyclopentane partner and the presence of a carbonyl group on the tether (Scheme 11) [14].



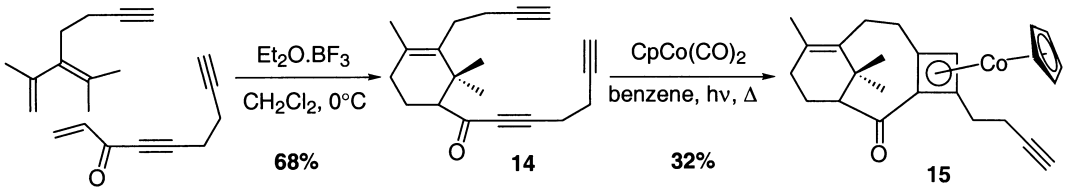
Scheme 11

Thus, by a subtle change in the position of the β-ketoester substituent relative to the tether, we have been able to prepare successfully either the basic skeleton of the phyllocladane in a one-pot sequence or the kaurane one by using a cascade of cyclizations: [ene-type]/[2+2+2]/[4+2].

Approach to the taxane skeleton

Due to their unique structural features as well as their considerable therapeutic potential [25], taxane diterpenoids have been, in recent years, the most challenging synthetic targets. In connection with our research program, we envisioned different approaches to the ABCD taxane framework by using as key steps in these strategies, [4+2] cycloaddition reactions and cobalt(I)-mediated cyclotrimerization. Our preliminary results showed that the AB taxane ring system can be built through a [4+2] reaction and a cobalt(I)-[2+2] cyclization. For the first time, we showed that cobalt(I) species mediate the ring closure of

strained polyunsaturated triynic compound 14 into a more sterically congested eight-membered ring and crowded [6.8.4] fused tricyclic system **15** (Scheme 12).



Scheme 12

The determination of the factors governing this ring closure is under our investigation as well as an easy access to the whole taxoid skeleton.

CONCLUSION

This article has summarized some new developments in cobalt(I)-mediated cyclizations. The stoichiometric cyclotrimerization of allenediynes provides an efficient entry to tricyclic compounds and by extension to the ABC or BCD moieties of steroids. Enantioselective accesses can be easily envisaged by two ways. The catalytic ene-type reaction of ϵ-acetylenic β-ketoesters provides a useful method for the stereoselective preparation of highly functionalized methylenecyclopentanes. The concise strategies to the construction of tetracyclic diterpenes can be viewed as an illustration of the very high performance of cobalt(I) tandem catalyses to the syntheses of complex polycyclic molecules.

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