Intramolecular [2+2+2] Cyclization of Triynes and Enediynes Catalyzed by CoI_2-Mn-Phosphine Ligand

Franck Slowinski, Corinne Aubert,* Max Malacria*

Université Pierre et Marie Curie (Paris 6), Laboratoire de Chimie Organique de Synthèse associé au CNRS, Tour 44–54, Case 229; 4, place Jussieu 75252 Paris Cedex 05, France
Fax: +33-1-44-27-73-60; e-mail: aubert@ccr.jussieu.fr; malacria@ccr.jussieu.fr

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The use of transition metal catalysis for promoting cycloaddition reactions is growing at an exponential rate. [1] These reagents are used to perform carbon-carbon bond forming reactions in a selective manner. Furthermore, they provide new opportunities to enhance the efficiency of the synthesis of complex organic molecules and to reduce the generation of waste as well.[2]

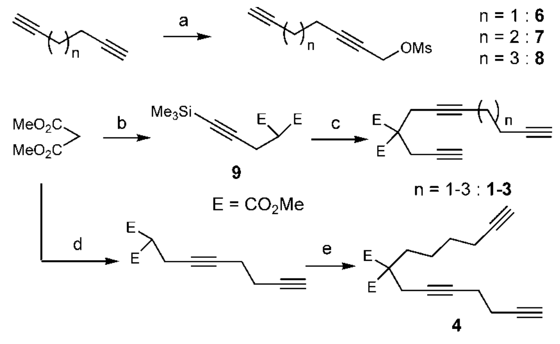
Cobalt(I) complexes are quite versatile catalysts and fulfill these criteria: they allow the construction of several carbon-carbon bonds in a single chemical step in a highly regio-, chemo-, and stereoselective fashion.[3] Various examples of their utility have been proposed by Vollhardt,[4] ourselves,[5] and others[6] who successfully developed the cyclopentadienylcobalt dicarbonyl, $CpCo(CO)_2$, catalysis for the cyclotrimerization of alkynes and the [2+2+2] cyclization of various polyunsaturated systems.

In order to construct polycyclic compounds enantioselectively, we turned our attention to the asymmetric version of the [2+2+2] cyclization. Having observed a highly stereoselective induction in the [2+2+2] cyclization of linear enediynes bearing a chiral phosphine oxide,[7] we anticipated that the potential of the cobalt(I) catalysis could be spectacularly displayed by designing a chiral cobalt catalyst.

To our knowledge, only one example of [2+2+2] cyclization mediated by a chiral cyclopentadienylcobalt complex has been reported, although giving η^4-cobalt complex adducts with quite a low diastereomeric excess.[8] Thus, we were interested to develop a catalytic system which can be easily prepared and, more particularly, which does not necessitate harsh requirements for the preparation of the chiral ligand. However, the first step was to develop a suitable catalyst.

Thus, we focused on the system which combines CoX_2/reductive metal/phosphine ligand in which the cobalt salt, in the presence of phosphine, is reduced *in situ* with zinc or manganese powder in suspension. These catalysts present the advantages of being economical, safe, environmentally benign, and easy to handle. The efficiency of such catalytic systems has been demonstrated in homo-Diels-Alder reactions,[9] particularly for the enantioselective syntheses of monofunctionalized deltacyclenes.[10] The combination $CoCl_2$/Mn has also been efficiently used in the partially intramolecular [2+2+2] cyclizations of 1,6- or 1,7-diynes with monoalkynes or nitriles;[11] however, it has been found to be ineffective in the partially intramolecular diyne-olefin reactions.[12] As far as we are aware, no intramolecular cyclizations of triynes and enediynes have been recorded.

To assess the synthetic potential of such catalytic systems, associated to the possibility to achieve enantioselective transformations, we studied the [2+2+2] cyclizations of the triynes **1**–**4** in the presence of [CoX_2/Zn or Mn/L] as well as the behavior of the enediyne **5** under such conditions and we present herein our preliminary results.



a) 1. *n*-BuLi, THF, -78°C, $(CH_2O)_n$; 2. CH_3SO_2Cl, 4-DMAP, NEt_3, CH_2Cl_2 ; **6**: 36%; **7** : 46% ; **8** : 48%. b) NaH, $BrCH_2C{\equiv}CSiMe_3$, THF, rt, 55 %. c) 1. NaH, **6** or **7** or **8**, THF, rt; 2. KF, DMSO, rt; **1** : 76%; **2** : 63%; **3** : 83%. d) NaH, THF, **6**, rt, 88%. e) NaH, THF, HMPT, $MsO(CH_2)_4C{\equiv}CH$, 54%

Scheme 1. Preparation of the triynes **1**–**4**

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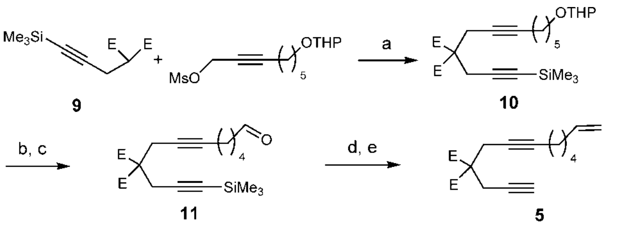
The triynes **1**–**4** were readily prepared as outlined in Scheme 1 from the commercially available 1,5-hexa-, 1,6-hepta-, and 1,7-octadiynes.

Double alkylation of the sodium derivative of dimethyl malonate with silylpropargyl bromide and then with the corresponding mesylates derived from the hepta-2,6-, octa-2,7-, and nona-2,8-diynols provided, after subsequent desilylation, the triynes **1**–**3**. The triyne **4** was obtained by the same procedure with the mesylates of the hepta-2,6-diynol and the hexynol.

Similarly, the enediyne **5** was prepared as described in Scheme 2. The sodium derivative of malonate **9** was alkylated in 95% yield with the mesylate of 8-(tetrahydropyran-2-yloxy)-oct-2-yn-1-ol (generated by the alkylation of the lithium acetylide derived from the tetrahydropyranyl ether of heptynol[13] with paraformaldehyde in 87% yield).

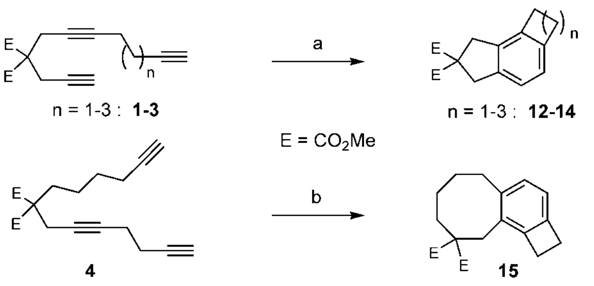


a) NaH, THF, rt, **10** : 95%. b) cat. PTSA, MeOH, 95%. c) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, **11** : 96%. d) *n*-BuLi, Ph_3PCH_3Br, -78°C, THF then rt, 92%. e) KF, DMSO, **5** : quant.

Scheme 2. Preparation of the enediyne **5**

Compound **10** was subsequently deprotected in acidic medium (95%) and oxidized to afford aldehyde **11** in 96% yield. This latter was submitted to a Wittig olefination, followed by desilylation of the triple bond to provide enediyne **5** in 92% yield.

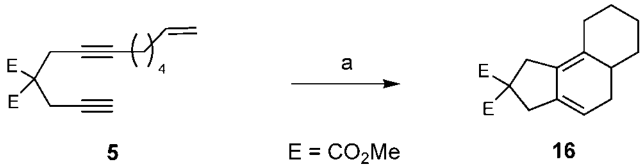
First, triynes **1**–**3** were submitted to the catalytic system 5 mol % CoI_2/50 mol % Mn/10 mol % PPh_3 in dichloromethane at room temperature to provide the corresponding tricyclic compounds **12**–**14** in very high yields (78–86%). Although the reaction proceeds in heterogeneous medium, the stirring speed has no influence on the yield of the reaction. In addition, it was observed that the use of manganese is better that of zinc. Indeed, compound **14** was obtained in 62% when zinc was used as reductive metal while manganese allowed its formation in 83% yield. On the other hand, the cyclization of **4** failed under either of these conditions. However, the corresponding tricyclic compound, **15**, was obtained in presence of 5 mol % of cyclopentadienylcobalt dicarbonyl under irradiation either in refluxing benzene or toluene in 29% and 32% yields, respectively. This last case is quite interesting because the [2+2+2] cyclization led to the 8,6,4 (BCD) taxane ring frame.



a) [5% CoI_2 ; 10% PPh_3 ; 50% Mn], CH_2Cl_2, rt ; **12** : 78%; **13** : 86%; **14** : 83%. b) 5% $CpCo(CO)_2$, toluene, hν, Δ, **15** : 34%

Scheme 3. [2+2+2] Cyclization of the triynes **1**–**4**

When the enediyne **5** was exposed to this catalytic system (5 mol % CoI_2/50 mol % Mn/10 mol % PPh_3), it remained unchanged even after several days. Finally, the tricyclic compound **16** was obtained, after 30 minutes, in 51% yield by using a stoichiometric amount of cobalt diiodide (with the respect to CoI_2/PPh_3/Mn = 1/2/10). Interestingly, the free ligand was directly isolated and no cobalt complexes were observed.



a) CoI_2 (1 equiv.), PPh_3 (2 equiv), Mn (10 equiv), CH_2Cl_2, rt, 51%

Scheme 4. [2+2+2] Cyclization of the enediyne **5**

In order to increase the yield of the reaction, we looked at the effects of the quantity of the cobalt salt, the nature of the solvent, the phosphine, and the cobalt salt as well. The results are summarized in the Table 1.

As can be seen from Table 1, the yield of the cyclization greatly decreased with 0.5 equiv of CoI_2 (entry 2) and surprisingly, after 4 hours the reaction did not progress any further. With 2 equiv of CoI_2 (entry 3), the reaction was fast, but even though it appeared complete by TLC, we could not isolate the cycloadduct. A diphosphine is compatible with the conditions of the reaction (entry 4), indeed in the presence of 1 equiv of diphenylphosphinoethane, the cycloadduct **16** was obtained in 42% yield. Regarding the solvent, the use of THF increases the rate of the reaction, nevertheless the yields are lower than in dichloromethane. Finally, when $CoBr_2$ and $CoCl_2$ are used in dichloromethane, no cyclization occurs (entries 6 and 8). On the other hand, when these reactions were carried out in THF, the formation of the cycloadduct was observed (entries 7 and 9). In almost all cases, although the starting material ap-

Table 1. [2+2+2] Cyclization of the enediyne **5** with the system [CoX_2/Mn/phosphine][a]

Entry	CoX_2 (equiv)	Phosphine (equiv)	Solvent	Time (h)	Yield (%)[b]
1	CoI_2 (1)	PPh_3 (2)	CH_2Cl_2	0.5	51
2	CoI_2 (0.5)	PPh_3 (1)	CH_2Cl_2	4	17
3	CoI_2 (2)	PPh_3 (4)	CH_2Cl_2	0.5	0
4	CoI_2 (1)	dppe (1)	CH_2Cl_2	12	42
5	CoI_2 (1)	PPh_3 (2)	THF	0.1	34
6	$CoBr_2$ (1)	PPh_3 (2)	CH_2Cl_2	24	0
7	$CoBr_2$ (1)	PPh_3 (2)	THF	1	34
8	$CoCl_2$ (1)	PPh_3 (2)	CH_2Cl_2	24	0
9	$CoCl_2$ (1)	PPh_3 (2)	THF	24	19

[a] With respect to CoX_2/Mn/phosphine = 1/10/2.

[b] The reactions are monitored by TLC and, after completion, worked-up.

peared to be totally consumed, the yield of the cyclization remained moderate. The removal of the cycloadduct from the heterogeneous medium seems to be the major problem of the reaction. Indeed, the presence of an excess of manganese probably allows associations with the *gem*-diester. Moreover, the use of one equivalent of cobalt salt appears necessary to drive the reaction to completion, suggesting the formation of a very sensitive complexed form of the tricyclic compound, which could be decomplexed and decomposed during the purification. The exact nature of the catalyst intermediate is not yet known and the cyclization could be promoted either by Co(0) or Co(I) species.

In summary, these preliminary results show that the system CoI_2/Mn/PPh_3 is able to catalyze successfully the intramolecular [2+2+2] cyclizations of triynes at room temperature in very high yields. For the first time, it has been shown that this combination is also efficient for the cyclization of an enediyne in which the olefinic partner is not activated. This system is cheap, easy to handle, and employs phosphines as well as diphosphines. The use of such ligands, associated to the fact that the free dienic compound is directly isolated, bodes well for the success of the catalytic asymmetric version of this reaction. These studies are currently under very active investigations in our laboratories.

Experimental Section

The preparation and spectral data on compounds **1**–**5** and **12**–**16** are available as "Supporting Information" which is available on the ASC website.

Typical Procedure for the Cyclization of 5

In a flask wrapped with aluminium foil, at room temperature, under argon, CoI_2 (163 mg, 0.52 mmol, 1 equiv) was added to a suspension of Mn (286 mg, 5.2 mmol, 10 equiv) and PPh_3 (273 mg, 1.04 mmol, 2 equiv) in CH_2Cl_2 (5 mL) After one hour, a solution of enediyne **5** (0.52 mmol, 1 equiv) in CH_2Cl_2 (3 mL) was added. The reaction was monitored by TLC, and after completion, the reaction mixture was concentrated, filtered over celite, and purified by flash chromatography.

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