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Enantioselective Synthesis of Deltacyclenes Using a [CoI$_2$:Zn] Catalytic System

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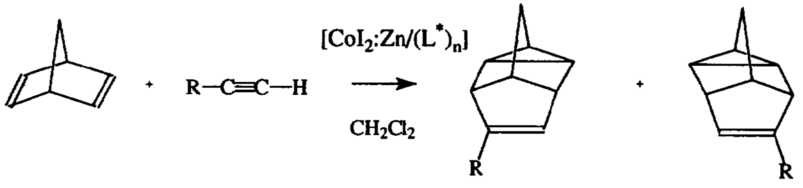
Abstract : The efficient chiral catalyst [CoI$_2$:Zn/(L*)$_n$] readily promotes the homo Diels-Alder reactions between norbornadiene **1** and alkynes **2**, affording tetracyclic compounds called "deltatcyclenes" **3**. In this [2+2+2] cycloadditions, stereochemical control is achieved through the presence of catalytic amount of homochiral mono and bidentate ligands leading to deltacyclenes in high chemical and optical yields.

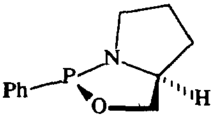
The simplest and shortest approach to the deltacyclenes **3** is the homo Diels-Alder (HDA) cycloaddition [2+2+2] between norbornadiene **1** (NBD) and acetylenic compounds **2**. High enantioselective syntheses of monosubstituted deltacyclenes have been reported by Lautens[1] and Brunner[2,3]. The effective catalyst used by these authors was obtained upon reduction of Co(acac)$_3$ with Et$_2$AlCl in the presence of homochiral ligands. The chelating bisphosphines (*S,S*)-Chiraphos, (*R*)-Prophos and (-)-Norphos were particularly effective while (*R*)-BINAP and (+)-DIOP gave no cycloadduct. It was shown that this catalytic system was very sensitive to several parameters such as the anhydrous character of the cobalt species, the coordinating ability of the solvent and the presence of functional groups on the monosubstituted acetylenes[4,5].

A new catalytic system [CoI$_2$:Zn/(PPh$_3$)$_n$] exhibiting high catalytic activity for the HDA cycloadditions of NBD with various alkynes affording the corresponding deltacyclenes in good to excellent yields,was recently reported[6]. Its activity depends on the nature and the number of ligands coordinated to the cobalt atom. This catalyst is the only effective catalyst for the cycloaddition of internal dialkylalkynes with NBD.



1 **2** **3a** **3b**

We report here a convenient method for the preparation of optically pure deltacyclenes by HDA reaction between NBD and phenylacetylene and 1-hexyne using the efficient system [CoI$_2$:Zn/L*] as catalyst with homochiral organophosphorus ligands easily prepared from amino acids. We have selected mono and bidentate ligands: (2*R*,4*S*)-2-phenyl-1,3,2-oxazaphospholidine **4** synthesized from bis(dimethylamino)phenylphosphine and (*S*)-(+)-prolinol[6], with an asymmetric phosphorus center and AMPP ligands such as (*S*)-(+)-ValNOP **5** and (*S*)-(+)-ProliNOP **6** prepared respectively from (*S*)-Valine and (*S*)-Proline[7].



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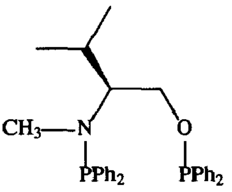

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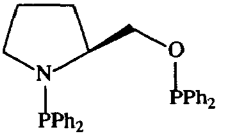

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The effects of the nature of the ligand, the ratio phosphine/cobalt (L^*/Co), the amount of catalyst and the influence of the temperature related to the enantioselectivity of the reaction have been studied. The results are summarized in table 1.

With ligands **4**, **5**, **6** catalytic HDA reactions can be performed. As shown in the table 1, chemical yield and enantioselectivity are closely related to the ratio L^*/Co and the nature of the dienophile. For the phenylacetylene the best results are obtained at 10°C with a ratio L^*/Co=2 for the monodentate ligand **4** (entry 2, e.e.>97%). With a ratio L^*/Co=1 for the bidentate ligands **5** and **6** (entry 9 and 19) the e.e. are 96% and >97% respectively with yields in isolated adducts ranging from 70 to 85% . In the case of 1-hexyne, the best results are obtained with the bidentate ligands at 20°C with a ratio L^*/Co=2, the e.e. are >97% and 94% for the ligands **5** and **6** respectively, chemical yields 80-88% (entries 16 and 22). A mechanistic interpretation of these results (different L^*/Co ratios, optimal temperature), will need further experiments. However a plausible interpretation may be based on the different reactivities between phenylacetylene and 1-hexyne with respect to $[Co^I(L^*)_n]$ complexes, which could play a determining role on the equilibrium between the different active complexes[6].

In order to explain the lack of reactivity of phenyl acetylene when L^*/Co=2 with bidentate ligands (entry 11), and the different rate constants between phenyl and 1-hexyne, we have carried out competitive reactions. The results obtained in the reaction between phenylacetylene (1eq) 1-hexyne (1eq) and NBD (2eq) are summarized in Table 2. With PPh_3 as ligand, the two acetylenic compounds react at the same rate, while with bidentate ligands, 1-hexyne reacts faster than phenylacetylene. This difference is enhanced when the ratio L^*/Co is 2, leading to a competitive factor α=19. These results can be interpreted by the difference in affinity of the two acetylenic compounds for the cobalt.

Furthermore, HDA reactions are not reversible at room temperature. No racemisation of chiral cycloadducts **3a**, R=Ph, R=*n*-Bu is observed when the adducts are stirred in presence of $[CoI_2:Zn/(PPh_3)_2]$ at different temperatures[13]. Futhermore no exchange reactions between cycloadducts **3a**, R=Ph and 1-hexyne or cycloadduct **3a**, R=*n*-Bu and phenylacetylene in presence of the same catalyst could be found.

The chemical yield of the reaction is very sensitive to the amount of catalyst (see entries 8 and 15), but no effects on the enantioselectivity has been noted, contrary to the $[Co(acac)_3/Et_2AlCl]$ catalytic systems[1]. Entries 17-18 reveal that the concentration of $[CoI_2:Zn/\mathbf{5}]$ plays an important role: when the concentration is decreased by a factor 1.5 to 2 the yields increase from 67 to 80%, and a significant change occurs for the enantioselectivity of the reaction, e.e. increasing from 82 to 92%. Decreasing the concentration of each reactants limits also the side reactions, leading to higher yields of deltacyclenes.

Table 1. [2+2+2] Homo Diels-Alder reactions between NBD and alkynes catalysed by cobalt complexes.

Entry	Ligand	**2**, R	L*/Co[a]	Temp [°C]	Rdt [%]	e.e. [%][e]	Abs.Conf.[f]
1	**4**	Ph	1	20	36	61	[R]
2	**4**	Ph	2	10	71	>97	[R]
3	**4**	Ph	2	20	76	85	[R]
4	**4**	Ph	4	20	27	17	[R]
5	**4**	*n*-Bu	1	20	8	-	[S]
6	**4**	*n*-Bu	2	10	96	50	[S]
7	**4**	*n*-Bu	2	20	76	56	[S]
8	**5**	Ph	1[b]	10	32	96	[R]
9	**5**	Ph	1	10	81	96	[R]
10	**5**	Ph	1	20	75	95	[R]
11	**5**	Ph	2	20	15	95	[R]
12	**5**	*n*-Bu	1	10	71	80	[S]
13	**5**	*n*-Bu	1	20	67	82	[S]
14	**5**	*n*-Bu	2	10	84	85	[S]
15	**5**	*n*-Bu	2[b]	20	28	>97	[S]
16	**5**	*n*-Bu	2	20	88	>97	[S]
17	**5**	*n*-Bu	1[c]	20	69	91	[S]
18	**5**	*n*-Bu	1[d]	20	79	92	[S]
19	**6**	Ph	1	10	85	97	[R]
20	**6**	Ph	1	20	76	86	[R]
21	**6**	*n*-Bu	1	10	87	86	[S]
22	**6**	*n*-Bu	2	20	85	94	[S]

[a] Except otherwise noted, each run was performed on 10.9 mmol of NBD, molar ratio NBD/alkyne/Co/Zn = 40/40/1/10, solvent 4 ml of dry CH_2Cl_2. [b] Reaction run with molar ratio NBD/alkyne/Co/Zn = 40/40/0.5/5. [c] 6 ml of solvent was used. [d] 8 ml of solvent was used. [e] The e.e. were determined as follows: racemic and scalemic[9] alkenes **3a**, **3b** were submitted to the hydroboration-oxidation and the resulting alcohols **7a**, **7b** were transformed quantitatively into diastereomeric esters **8a**, **8b** by using the methods described by Mosher[10] and Heumann[11] from optically pure (*R*)-(+)-α-methoxy trifluoromethyl phenyl acetic and (*S*-(o-fluoro phenoxy) lactic acid. The e.e. were determined with ^{19}F NMR for phenyl deltacyclene[12] and with both ^{19}F and ^{1}H NMR for *n*-butyl deltacyclene[13] (recorded respectively at 94 and 400 MHz); d.e. of esters = e.e. of the alkenes **3a**, **3b**. [f] The absolute configuration refers to the stereochemistry of the carbon bearing the oxygen atom in the mentionned-above alcohols of the main enantiomer.

Table 2. Variation of the amount of cycloadducts **3**, R=Ph / **3**, R=*n*-Bu at 20°C.

Entry	Ligand	**3**, R=Ph	**3**, R=*n*-Bu	α
1	2 eq.PPh_3	51	49	≈ 1
2	1 eq. ValNOP	15	85	≈ 6
3	2 eq. ValNOP	5	95	≈19
4	1 eq. ProliNOP	12	88	≈ 6

Each run was performed on 10.9 mmol of NBD, molar ratio NBD/alkyne/Co/Zn = 40/40/1/10, solvent 4 ml of dry CH_2Cl_2

In summary, we have shown that organophosphorus ligands easily prepared from amino acids[7,8] effectively promote the HDA reaction between phenyl acetylene or 1-hexyne and NBD in high optical yields. The results described here establish the active system [CoI$_2$:Zn/(L*)$_n$] as a promising one for the enantioselective synthesis of functional deltacyclenes; experiments are in progress to address these issues.

This work is dedicated to the memory of Pr. Francis Petit.

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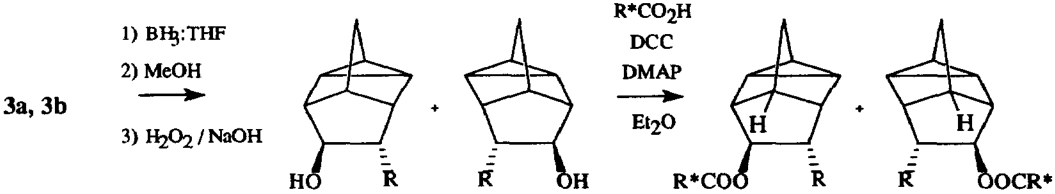
12. The upfield peak, corresponding to the dextrorotatory alkene, was the main signal in the ^{19}F spretrum samples ((*S*)-(o-fluorophenoxy) lactic acid derivates) prepared from ValNOP and ProliNOP.
13. The ratio of the diastereoisomeric esters **8a, 8b** R=*n*-Bu was measured by integration of the labelled H resonance on the ^{1}H spectrum, well resolved at 400 MHz. The main signal, corresponding to the levorotatory alkene, was downfield in the ^{1}H spectra samples ((*R*)-(+)-α-methoxy trifluoromethyl phenyl acetic derivates) prepared from ValNOP et ProliNOP.



7a **7b** **8a** **8b**

14. The ratio of phenyl deltacyclene 3, R=Ph and *n*-butyl deltacyclene R=*n*-Bu was determinated by integration of the two vinylic protons, respectivly at 6.37 and 5.58 ppm, after flash chromatographic purification of the crude mixture.