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Synthesis of Chiral Pyridines by Cobalt(I)-Catalyzed Cocyclotrimerization of Acetylene with Optically Active Nitriles

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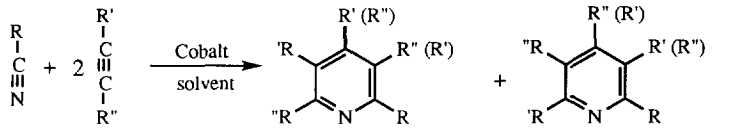
1. Introduction

In recent years chiral ligands of different structures having the pyridine ring as the central building block have been used extensively as valuable auxiliaries in asymmetric synthesis.[1] Synthetic approaches to the regioselective preparation of pyridine derivatives continue unabated.[2] In this context, the cobalt-catalyzed cocyclotrimerization reaction of alkynes with nitriles represents a straightforward method for the construction of the pyridine ring.[3] When substituted alkynes are allowed to react with nitriles in the presence of a cobalt catalyst, a mixture of regioisomeric substituted pyridines is obtained, making this reaction useless for synthetic purposes (Scheme 1). However, when acetylene is used as the alkyne component (Scheme 1, R'=R"=H) only 2-substituted pyridines are obtained.

Scheme 1



The first preparation of an optically active pyridine by this catalytic one-step synthesis was presented in 1975 by Botteghi *et al* . who, as part of a study aimed at the preparation of the three regioisomeric *sec*-butylpyridines, applied the technique to an optically active nitrile.[4] Thus *sec*-butyl cyanide on cyclization with acetylene above 8 atm. at 140 °C with (π-cyclopentadienyl)cobalt 1,5-cyclooctadiene as catalyst afforded the corresponding optically active 2-*sec*-butylpyridine in over 90 % yield and 96 % enantiomeric excess. The most interesting feature of this pyridine is the presence of a stereogenic centre attached to the heterocyclic ring. The cobalt(I)-catalyzed cocyclotrimerization of acetylene with chiral nitriles is the only method so far available for the selective

synthesis of optically active 2-substituted pyridines with a stereogenic centre bonded to the 2-position of the heterocyclic ring. Moreover, the application of this methodology to chiral functionalized cyano compounds leads to the preparation of functionalized 2-substituted pyridines.

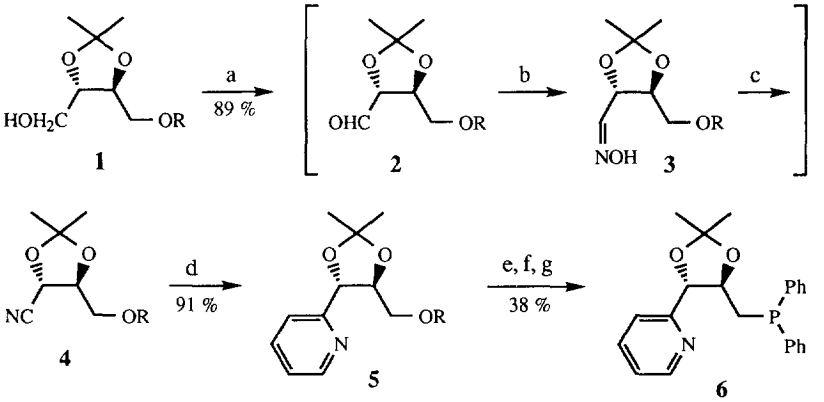
It should be pointed out that, although a number of cobalt catalysts are effective in the cyclization of acetylene with nitriles, (π-cyclopentadienyl)cobalt 1,5-cyclooctadiene [CpCo(COD)] was the only one used in the synthesis of optically active pyridines. This stems from the consideration that a comparative study on the catalytic activity of various cobalt catalysts revealed that CpCo(COD) was the most effective catalyst with respect to both the conversion of the starting nitrile and the turnover number (measured as number of mols of pyridine per mol of cobalt and hours).[5]

This account has the purpose of reporting the syntheses of those chiral pyridine derivatives in which the key step is the formation of the pyridine ring by CpCo(COD) catalyzed cocyclotrimerization of acetylene with chiral cyano derivatives. It is hoped that this report will result in a broader use of this methodology.

2. 2-Alkylpyridines

Seversal synthetic methods are described in the literature for obtaining 2-alkylsubstituted pyridines with a stereogenic carbon atom adjacent to the heterocyclic ring: a) optical resolution of racemic compounds through fractional crystallization of diastereomeric pyridinium salts of homochiral acids such as tartaric acid and its derivatives;[6] b) separation of enantiomers by chiral preparative HPLC;[7] c) chromatographic separation of diastereomeric carbamates obtained by reaction of a lithium derivative of an alkylpyridine with (-)-menthyl chloroformate followed by reduction with AlH_3;[8] d) asymmetric cross-coupling reactions between racemic Grignard reagents and halopyridines catalyzed by Ni(II)-complexes with optically active chelating diphosphines, such as (R)-1,2-bis(diphenylphosphino)propane;[9] e) cross-coupling reaction between optically active Grignard reagents and halopyridines catalyzed by Ni(II)-complexes with (R)-1,2-bis(diphenylphosphino)ethane.[10]

Scheme 2



R = *t*-$BuPh_2Si$ -

a: $(COCl)_2$, DMSO, Et_3N,-78 °C; b: $NH_2OH{\cdot}HCl$, 10% K_2CO_3; c: N,N'-carbonyldiimidazo d: CpCo(COD), acetylene, toluene, 120 °C, 14 atm, 24h; e: Bu_4NF, THF; f: TsCl, Et_3N, DMPA, CH_2Cl_2; g: Ph_3P, Na/K,dioxane.

The most convenient synthetic route to optically active 2-alkylpyridines consists of the cobalt(I)-catalyzed cocyclotrimerization of acetylene with chiral nitriles which are easily available in high enantiomeric excess from

a variety of substrates.[11] Scheme 2 shows the preparation of PYDIPHOS (**6**) as a representative example of a synthesis in which the key step is the construction of the heterocyclic ring by this method.[12] The synthesis of PYDIPHOS (**6**), the first representative member of enantiomerically pure pyridylphosphines, starts from the monoprotected diol **1**, prepared from diethyl L-(+)-tartrate. Swern oxidation of **1** gave the aldehyde **2**. The crude aldehyde was converted into the nitrile **4** *via* formation of the corresponding oxime followed by dehydration with N,N'-carbonyldiimidazole. Cocyclotrimerization of nitrile **4** with acetylene in the presence of CpCo(COD) at 120 °C and 14 atm afforded the key pyridine intermediate **6** in 91% yield . The hydroxyl group was then deprotected and converted into the corresponding tosylate. Finally, nucleophilic displacement of the tosyl group with a Na/K diphenylphosphide mixture gave PYDIPHOS in 39% overall yield based on **1**.

The cyclization has also been performed on dicyano compounds to give dipyridines. Scheme 3 illustrates the synthesis of (4R,5R)-2,2-dimethyl-4,5-bis(2-pyridyl)-1,3-dioxolane from L-(+)tartaric acid. Reaction of **8** with gaseous ammonia in methanol for 10 days afforded the diamide **9** in fairly quantitative yield. Treatment of **9** with *p*-toluenesulphonyl chloride in pyridine at 100 °C for 5h gave the dinitrile **10** in 95 % yield. Cocyclotrimerization of **10** with acetylene in the presence of CpCo(COD) afforded the dipyridine **12** in 70% yield. To obtain total conversion of the dinitrile **5** the cyclotrimerization was performed at 140 °C for 36h.

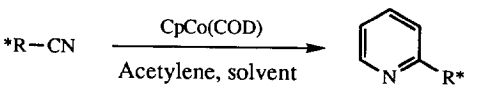
We were also interested in obtaining the monoazaanellation compound of the dicyano compound **10**. The pyridine **11** was obtained by perfoming the reaction of cyclotrimerization at 100 °C for 24h. In these conditions total conversion of the starting material was obtained and the nitrile **11** was recovered in 41% yield with the dipyridine **12** (25 %).[13]

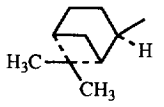
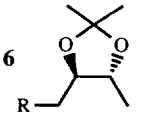
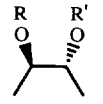
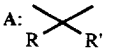
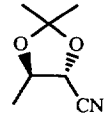
Table 1 summarizes the results obtained in the cocyclotrimerization of acetylene with optically active nitriles using CpCo(COD) as catalyst. Most of the chemical yields are in the range 77-98%. The use of a solvent like toluene increases the yields, especially if no volatile alkylpyridines are produced. In the case of sterically hindered 2,3,3-trimethylbutanenitrile (entry 2), both a reasonable reaction rate and good yield (77%) are achieved by increasing the catalyst-to-substrate molar ratio and the reaction time. The reaction usually runs with negligible racemization of the stereogenic centre present in the substrate, even if the cocyclotrimerization conditions are not so mild and the stereogenic centre is bound to the cyano group. Only when starting with (S)-2-phenylpropanenitrile (entry 3) was the corresponding pyridine found to be significantly racemized. This phenomenon becomes more evident as the reaction time increases (entry 3:B). We cannot give a reasonable explanation of this fact on the basis of the well elucidated mechanism of this catalytic process in which the stereogenic centre is not involved. However, it is possible that in the case of (S)-2-phenylpropanenitrile the mobility of the benzylic hydrogen is further enhanced in the activation step of the nitrile, in which the nitrogen atom of the cyano group is coordinated to the metal.

3. 2,2'- and 2,4'-Bipyridines

Optically active bipyridines have been successfully employed as chiral ligands for enantioselective catalysis.[21-23] Among the bipyridines, those with a C_2-symmetry axis have displayed the best stereoselectivity in asymmetrial processes.[5,7,8,22] However, interesting results have also been obtained with unsymmetric ones.[18] These unsymmetric binuclear pyridine derivatives can be synthesized by the cobalt catalyzed cocyclotrimerization of acetylene with chiral cyanopyridines. These compounds can be obtained by cyanation of pyridine N-oxides.[23] Regiospecific introduction of a cyano group into the 2-position of a pyridine is obtained by treatment of its N-oxide derivative with trimethylsilylcarbonitrile and dimethylcarbamyl chloride, whereas

TABLE 1 - Cocyclotrimerization reaction of chiral alkyl nitrilles and acetylene catalyzed by (π-cyclopentadienyl)cobalt 1,5-cyclooctadiene [CpCo(COD)]

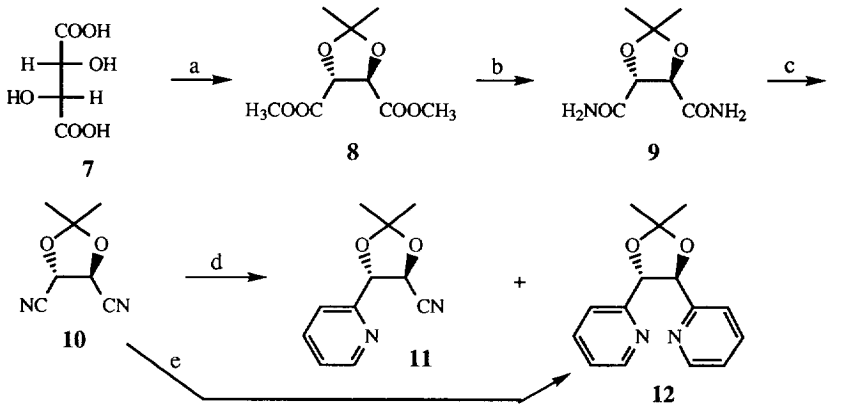


Nitrile				Reaction conditions					2-Alkylpyridine			
entry	R*	$[\alpha]_D^{25}$ (A)	% e.e. (conf)	molar ratio substr/catal	Solvent	Temp. (°C)	P.(r.t.) (atm)	Time (h)	Yield (%)	$[\alpha]_D^{25}$ (A)	% e.e.	Ref.
1	C_2H_5-CH(CH$_3$)-	+33.2[a]	85 (S)	32	none	140	8	4	95	+31.9[a]	80	4
		+30.3[a]	84 (S)	27	none	140	10	10	85	+23.7[a]	59	17
		+31.8[a]	88 (S)	37	none	140	15	5	77	+31.3[a]	78	15
		+1.7[g]	26 (S)	32	none	140	14	12	20	+9.2[h]	25	17
2	t-C_4H_9-CH(CH$_3$)-	+2.3[g]	35 (S)	17	toluene	160	10	7	50	+11.5[h]	32	17
		-5.8[g]	89 (R)	18	toluene	140	15	22	77	-31.8[h]	89	20
3	C_6H_5-CH(CH$_3$)-	-8.4[a]	65 (S)	28	toluene	140	14	20	95	+43.1[c]	60	17
		-9.5[a]	72 (S)	26	toluene	140	10	60	85	+29.4[c]	41	16
4	t-C_4H_9-CH(CH$_3$)-CH_2-	-10.3[c]	30 (R)	40	toluene	140	10	70	65	-16.8[a]	30	17
5		-7.1[d]	98 (1S,2S)	17	toluene	100	12	20	53	-17.9[d]	98	18
6		A: -3.6[c]	98 (R,R)	21	toluene	120	14	24	94	-2.6[e]	98	12
		B: -16.8[c]	98 (R,R)	27	toluene	120	14	24	82	-2.2[e]	98	19
	R= **A**: t-$BuPh_2Si$; **B**: C_6H_5-CH_2											
7		A: -165[f]	98 (R,R)	13	toluene	140	14	36	72	-88.2[f]	98	14
		B: +98.9[f]	98 (R,R)	13	toluene	120	14	36	70	+153.0[f]	98	14
	 **B**: R=R'=C_6H_5-CH_2											
8		-165[f]	98 (R,R)	13	toluene	100	14	24	72	-38.1[c]	98	14

A: determined in solution of = a: neat; b: ethanol; c: cyclohexane; d: benzene; e: chloroform; f: methanol; g: n-pentane; h: ethanol

regioselective cyanation with potassium cyanide of the N-oxidemethylsulphate salt of a pyridine affords a mixture of 2- and 4-cyanopyridine in 67/33 % ratio, respectively.[15] The components of this mixture can be easily separated by acid-basic elaboration.[18]

Scheme 3



a: $(CH_3)_2C(OCH_3)_2$, TsOH; b: NH_3, CH_3OH, 10d; c: TsCl, Py, 100 °C, 5h; d: CpCo(COD), acetylene, toluene, 100 °C, 14 atm, 24h; e: CpCo(COD), acetylene, toluene, 140 °C, 14 atm, 36h.

Scheme 4 reports the synthesis of a new bipyridine-phosphine derivative in which the two key steps are the regiospecific cyanation of the pyridine **13** and the azaanellation reaction of cyanopyridine **14**.[19]

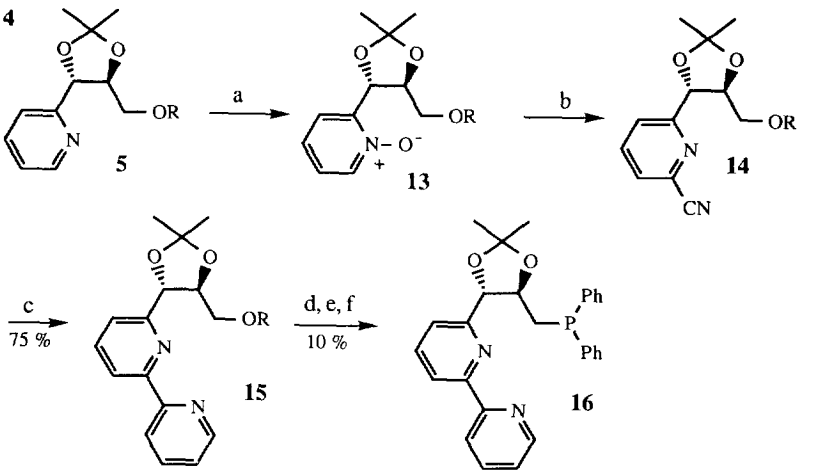
Recently, we focused our attention on chiral 2,2':6,6'-terpyridine, a new class of ligands for asymmetric catalysis.[24] We were interested in preparing terpyridines with a chiral substituent on the central pyridine ring.[25] The strategy was based on the monoazaanellation of 2,6-dicyanopyridines obtained by regiospecific reiterative introduction of two cyano groups into the 2,6-positions of substituted pyridines. We selected the 3-methylpyridine (**17**) as the prototype to develop the basic methodology from (Scheme 5).

Treatment of 3-methylpyridine 1-oxide (**18**) with trimethylsilylcarbonitrile and dimethylcarbamyl chloride gave a 9:1 mixture of 2-cyano-5-methylpyridine (**19**) and 2-cyano-3-methylpyridine (**20**) in 95% yield. The mixture of **19** and **20** was converted into the corresponding mixture of N-oxides by oxidation with 30% H_2O_2 in AcOH at 80 °C for 72h. By treatment with an equimolar amount of dimethyl sulphate at 80 °C for 24h, the crude mixture of N-oxides (**21** and **22**) gave the corresponding N-methoxymethylsulphate salts which were dissolved in water and added dropwise (0 °C) to an aqueous solution containing an excess of potassium cyanide. The dinitrile **23** was obtained in 79% yield based on the mixture of **19** and **20**. Cocyclotrimerization of **23** with acetylene and CpCo(COD) as catalytic precursor at 100 °C and 13 atm for 48 hours afforded a 48/52 mixture of the bipyridines **24** and **25** in 70 % yield (65% conversion).

To gain the desired terpyridine **23** a variety of conditions (e.g. varying temperature, solvent and reaction time) were explored, but all the attempts were unsuccessful. For example, when the reaction was performed at 150 °C for 48 h, compound **23** was recovered in 55 % yield (60% conversion). The reaction carried out in N,N-dimethylformamide at 110 °C for 24 h, allowed complete reaction of the substrate but also in this case bipyridines **24** and **25** were obtained only in low yield (37%). The outcome of the reaction could be

rationalized by considering the formation of the 2,2':6',2"-terpyridine (**26**) whose concentration increases as the concentration of 6-cyano-2,2'-bipyridine rises. Although low, the amount of formed 2,2':6',2"-terpyridine is enough to bind cobalt and give an inactive catalytic species. To confirm this hypothesis, we tried the cyclotrimerization of **23** in the presence of 2,2':6',2"-terpyridine. After 48 h at 100 °C the starting material was recovered unchanged.

Scheme 4



R = *t*-$BuPh_2Si$ -

a: MCPA, $CHCl_3$, 24h; b: $(CH_3)_3SiCN$, $(CH_3)_2NCOCl$, CH_2Cl_2, r.t., 6d; c: CpCo(COD), acetylene, toluene, 140 °C, 14 atm, 24h; d: Bu_4NF, THF; e: TsCl, Et_3N, DMPA, CH_2Cl_2; f: Ph_3P, Na/K, dioxane;

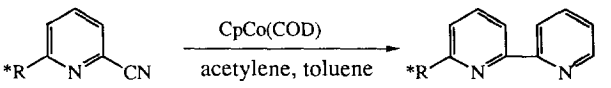
We also attempted to prepare the bis-bipyridine **30** by cobalt catalyzed cocyclotrimerization of acetylene with the bis-cyanopyridine **28**, obtained from the (4R,5R)-2,2-dimethyl-3,4-bis(2-pyridyl)-1,3-dioxolane **12** by oxidation with 3-chloroperbenzoic acid followed by regiospecific cyanation with trimethylchlorosilane and dimethylcarbamylchloride[26] (Scheme 6). Although drastic conditions of cocyclotrimerization (140 °C) were used, only low conversion of the starting material was obtained with the compound of monoazaanellation. Also in this case the outcome of the reaction can be rationalized by considering the formation of a tricordinate adduct between the compound **30** and the cobalt to give an inactive catalytic species.

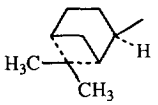
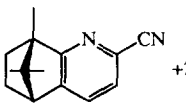
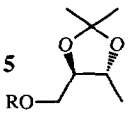
Table 2 reports the results obtained in the cocyclotrimerization of acetylene with optically active cyanopyridines using (π-cyclopentadienyl)cobalt 1,5-cyclooctadiene [CyCo(COD)]. Most of the chemical yields are in the range 70-95%. The only solvent used is toluene and the molar ratio substrate/catalyst is in the range of 17-32.

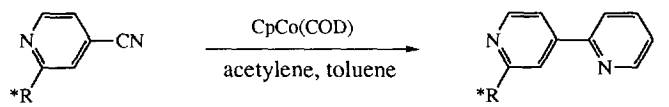
4. 2-(1-Hydroxyalkyl)pyridines

Optically active pyridyl alcohols have recently attracted attention because of their utility as chiral ligands in metal complexes for stereoselective catalysis.[28,29] Chiral 2-(1-hydroxyalkyl)pyridines have been prepared in three ways: a) asymmetric reduction of the corresponding ketones by diisopinocampheylborane chloride (DIP-Cl);[22] b) catalytic biotransformations;[30] c) resolution of racemic alcohols.[28]

TABLE 2 - Cocyclotrimerization reaction of chiral cyanopyridines and acetylene catalyzed by (π-cyclopentadieny)cobalt 1,5-cyclooctadiene [CpCo(COD)]



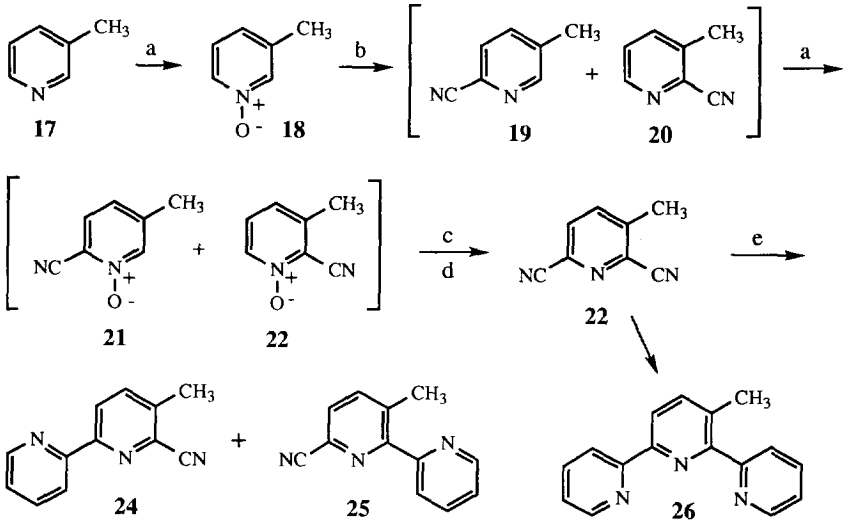
2-Cyanopyridine				Reaction conditions				2,2'-Bipyridine			
entry	R*	$[\alpha]_D^{25}$ (A)	% e.e. (conf)	molar ratio substr/catal	Temp. (°C)	P (r.t.) (atm)	Time (h)	Yield (%)	$[\alpha]_D^{25}$ (A)	% e.e.	Ref.
1	C_2H_5 - CH - CH_3	+29.5[a]	78 (S)	32	120	13	20	83	+25.9[a]	76	15
		—	64 (S)	27	120	13	20	80	+21.4[a]	63	15
2	C_6H_5 - CH - CH_3	—	— (S)[d]	18	100	12	24	80	+61.9[a]	41	16
		—	— (S)[e]						+133.8[a]	89	18
3		-3.38[b]	95 (1S,2S)	17	100	12	24	70	+25.4	95	18
4		+25.3[a]	97 (5R,8S)	17	130	10	10	69	-26.6[a]	99	27
5	 A: t-$BuPh_2Si$- B: C_6H_5-CH_2-	A: +5.0[c]	>95 (R,R)	20	120	14	24	94	-2.6[c]	>95	19
		B: -16.8[c]	>95 (R,R)	19	120	14	24	82	-2.2[c]	>95	19



4-Cyanopyridine				Reaction conditions				2,4'-Bipyridine			
entry	R*	$[\alpha]_D^{25}$ (A)	% e.e (conf)	molar ratio substr/catal	Temp. (°C)	P.max (atm)	Time (h)	Yield (%)	$[\alpha]_D^{25}$ (A)	% e.e.	Ref.
6	C_2H_5 - CH - CH_3	+26.2[a]	78 (S)	32	120	13	20	80			15
			64(S)	32	120	13	20	80	+14.6[a]	64	15

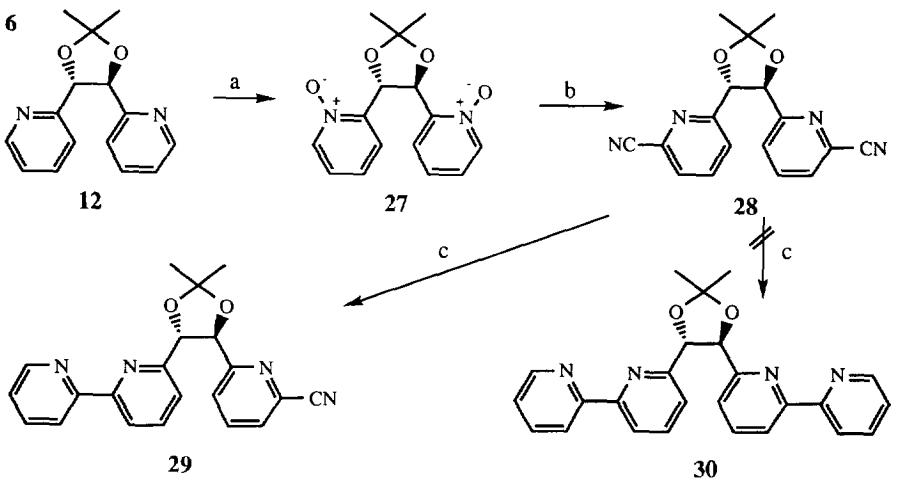
A: determined in solution of = a: cyclohexane; b: benzene; c: chloroform. d: the op of the (S)-2(1-methylbenzyl)pyridine used as starting point for the synthesis of (S)-2-cyano-6(1-methylbenzyl)pyridine was 41%. e: the op of the (+)-(S)-2-phenylpropanoic acid {$[\alpha]^{22}_D$ +90.3 (c, 3.2 cyclohexane)} used for the synthesis of (S)-2-cyano-6(1-methylbenzyl)pyridine was 98.8 %.

Scheme 5



a: CH_3COOH, H_2O_2, 80 °C, 72 h; b: $(CH_3)_3SiCN$, $(CH_3)_2NCOCl$, CH_2Cl_2,48 h; c: $(CH_3O)_2SO_2$, 80 °C, 24 h; then KCN/H_2O, 0 °C, 24 h; d: CpCo(COD), acetylene, toluene, 100 °C, 48 h.

Scheme 6

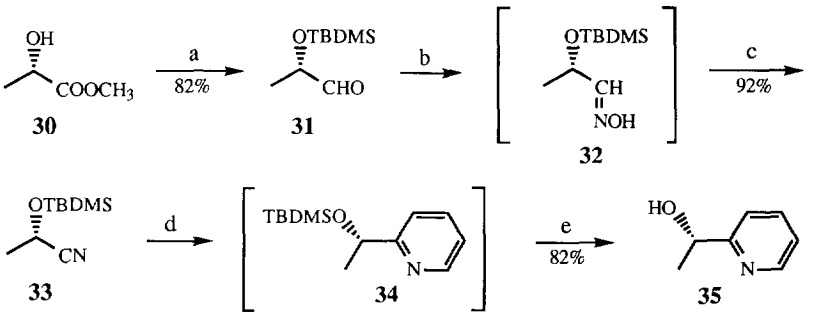


a: MCPA (4 equiv.), $CHCl_3$, 2d; b: $(CH_3)_2NCOCl$, $(CH_3)_3SiCN$, CH_2Cl_2,r.t., 6d; c: CpCo(COD), acetylene, toluene, 140 °C, 14 atm, 48h.

However, these synthetic approaches are not always successful. For instance several of our attempts to prepare the optically active 2-(1-hydroxyethyl)pyridine by reduction of the 2-acetylpyridine with DIP-Cl failed. We demonstrated that cobalt(I)-catalyzed cocyclotrimerization of chiral O-protected α-hydroxynitriles with acetylene affords a convenient method for the preparation of 2-(1-hydroxyalkyl)pyridines with high enantiomeric

excess.[31] This procedure is extremely straightforward since enantiomerically pure cyanohydrins are readily available by the catalytic asymmetric addition of hydrogen cyanide to carbonyl compounds.[32] The basic methodology was developed on the commercial (S)-2-hydroxypropanoic acid methyl ester (**1**) (Scheme 7). The aldehyde **31** was converted into the nitrile **33** *via* the formation of the corresponding oxime followed by dehydration with N,N'-carbonyldiimidazole. Cobalt catalyzed cocyclotrimerization of nitrile **33** with acetylene afforded the unisolated pyridine **34** which by treatment with 10 % hydrochloric acid gave the hydroxy pyridine **35** in 60 % overall yield based on **30** and 100 % enantiomeric excess.

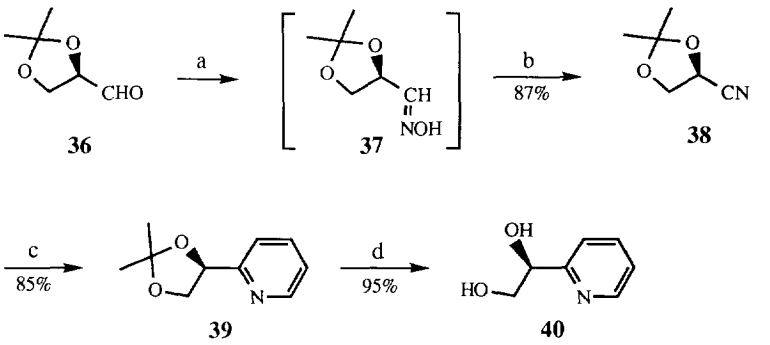
Scheme 7



a: literature; b: NH_2OH HCl,10% K_2CO_3, MeOH; c: N,N'-carbonyldiimidazole, CH_2Cl_2 2h, r.t.; d: CpCo(COD), acetylene, toluene, 120 °C, 14 atm.; e: 10 % HCl

This procedure was extended[31] to the preparation of hydroxy pyridines containing other functional groups. 2,3-O-(Isopropylidene)-D-glyceraldehyde (**36**), easily obtained from D-mannitol, was converted following the above procedure into the pyridine **39** in 85 % yield. Removal of the acetonide group afforded the 2-(1,2-dihydroxyethyl)pyridine **40** in 81 % overall yield (based on **36**) and 98 % enantiomeric excess (Scheme 8).

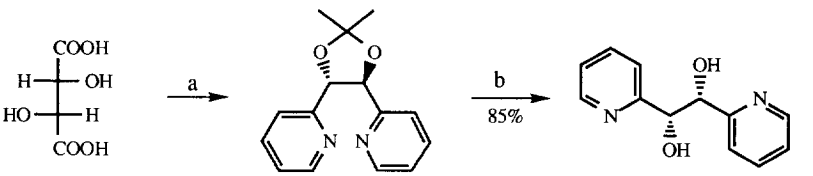
Scheme 8



a: NH_2OH HCl,10% K_2CO_3, MeOH; b: N,N'-carbonyldiimidazole, CH_2Cl_2, 2h, r.t.; c: CpCo(COD), acetylene, toluene, 120 °C, 14 atm.; d: 6 % HCl;

(1R,2R)-1,2-Bis(2-pyridyl)-1,2-ethanediol (**41**) was also prepared from the dipyridine **12** which was obtained from L-(+)tartaric acid according to Scheme 3.[14] Deprotection of the acetonide group by aqueous H_2SO_4 in refluxed EtOH for 4h gave the glycol **41** in 85 % yield (Scheme 9).[29]

Scheme 9



7 **12** **41**

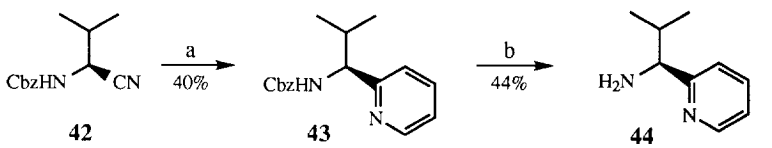
a: see Scheme 3; b: H_2SO_4 (0.1 M), EtOH, reflux, 4h.

5. 2-(1-Aminoalkyl)pyridines

In recent years, chiral ligands containing two nitrogen atoms, such as 1,2-diamine derivatives,[33] 2,2'-bipyridines[21,22] and 1,10-phenanthrolines,[21] have been used extensively in enantioselective reactions. In this context chiral aminopyridines have been found very effective ligands in the enantioselective addition of diethylzinc to aldehydes giving enantiolection up to 100 %.[34] Chiral aminopyridines have been prepared in three main ways: a) catalytic reduction of chiral 2-pyridyl imines derived from (R)-phenylglycinol, followed by oxidative cleavage;[35] b) alkylation of imines derived from 2-hydroxypinan-3-one and 2-aminomethylpyridine, followed by removal of the chiral auxiliary;[36] c) resolution of racemic amines.[37]

We have prepared optically active aminopyridines containing a stereogenic centre bonded to the heterocycle and adjacent to the heteroatom. Naturally occurring amino acids were used as suitable starting materials. At first, we undertook the synthesis of (S)-2-(2-amino-3-methyl)pyridine **44** (Scheme 10).[38] Thus, cocyclotrimerization of (S)-2-(benzyloxycarbonyl)amino-3-methylbutanenitrile (**42**) prepared from L-valine (99% ee) with acetylene (14 atm) in the presence of CpCo(COD) (3.2 mol %) at 110 °C for 22h gave the pyridine **43** in moderate yield (40%). Deprotection of this derivative, conducted under reflux in 6N hydrochloric acid solution, gave **44** (44% yield) having only 15% ee. A tentative explanation of the stereochemical outcome of the reaction has been ascribed to the presence of a hydrogen atom still bound to the amide nitrogen atom, which should have permitted the racemization under the severe (110 °C, 72 hours) conditions of the azaanellation. A decrease in the cyclotrimerization temperature of about 30 °C resulted in a slight increase (20 %) in the stereoselectivity of the process, in addition, however, to a strong decrease in the conversion (12% after 110 hours at 78 °C).

Scheme 10



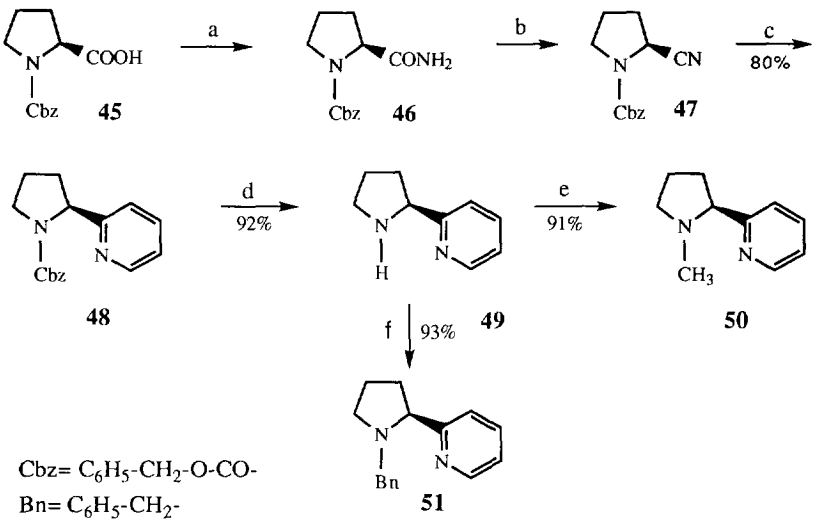
42 **43** **44**

Cbz= C_6H_5-CH_2-O-CO-

a: CpCo(COD) (3.2 mol %), toluene, acetylene, 14 atm, 110 °C, 22h; b: 6N HCl reflux, 1h.

In order to confirm this hypothesis we undertook the synthesis of 2-[(2S)-2-pyrrolidiny]pyridine from L-proline (**49**) (Scheme 11).[39] Cocyclotrimerization of the nitrile **47** with acetylene in the presence of CpCo(COD) (3.2 mol %) at 110 °C for 22 hours gave the pyridine **48** in good yield (82 %). Deprotection of **48** afforded the aminopyridine **49** in 92 % yield. The ee of this compound resulted as 96 % which is very close to that of L-proline (98 %) used as starting material.

Scheme 11



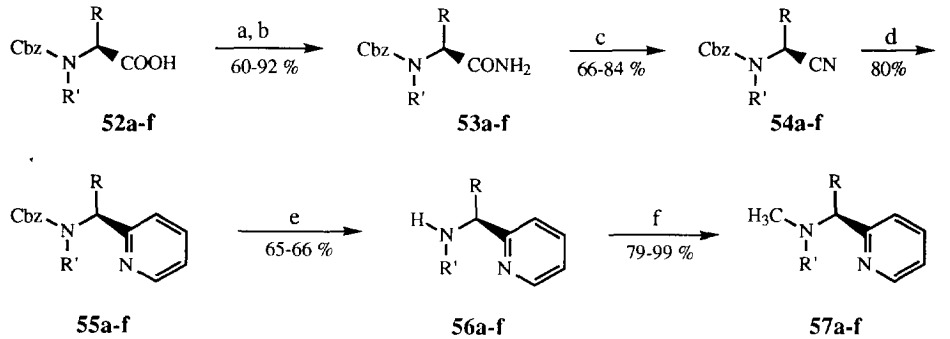
a: EtO_2CCl, 4-methylmorpholine, THF, -12 °C, 10 min; and then NH_3, 25 %, r.t.,12h; b: Ts/Py, 100 °C, 3-16h; c: CpCo(COD) (3.2 mol %), toluene, acetylene, 14 atm, 110 °C, 22h; d: 6N HCl, reflux, 1h; e: $HCHO/HCO_2H$, reflux, 12h; f: BnCl, DMF, Na_2CO_3, NaI, reflux, 2h.

This procedure was extended to the synthesis of N-methyl and N,N-dimethyl 2-(1-aminoalkyl)pyridines **57a-f** (Scheme 12).[38] In this case the reaction of cyclotrimerization occurred in only 4 % of racemization.
An example of non-N-alkylated 2-(1-aminoalkyl)pyridines has been reported (Scheme 13).[38] In this case the nitrogen atom of the L-leucine (98 % ee) was protected by the phthaloyl group giving an amino acid derivative without hydrogen atoms on the nitrogen atom. Cocyclotrimerization of nitrile **60** carried out at 110 °C for 72 hours gave the pyridine **61** in moderate yield (54 %). After removal of the phthaloyl group the aminopyridine **62** was recovered in 90 % ee. An 8 % of racemization has been observed in the overall process.

Recently, two new β-amino alcohols, namely (R)-2-amino-2-(2'-pyridyl)ethanol (**68a**) and (1R,2R)-1-amino-1-(2'-pyridyl)propan-2-olo (**68b**) were prepared starting from L-serine and L-threonine, respectively (Scheme 14).[40] The synthesis involved the simultaneous protection of the hydroxy and amino groups by formation of the 2,2-dimethyl-1,3-oxazolidine ring. Cocyclotrimerization of nitriles **66a-b** was performed at 160 °C for 3-6 days. The critical role of temperature in this process was noteworthy. In fact, up to 150 °C no appreciable reaction was observed, while at 160 °C the reaction took place, though with moderate conversion owing to the

degradation of the catalyst. By increasing the amount of the catalyst no improvement both in conversion and yield was obtained. No loss of enantiomeric purity in the overall process was observed.

Scheme 12

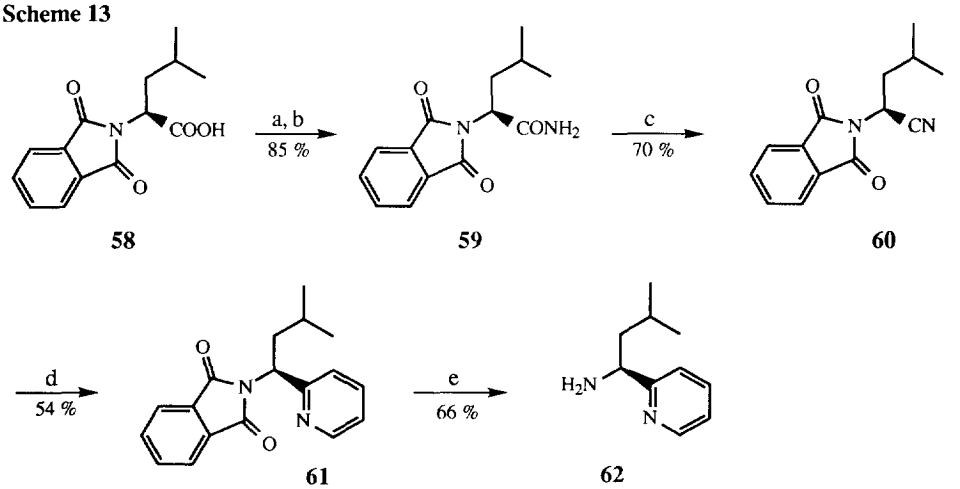


	a	b	c	d	e	f
R	*i*-Pr	Me	*i*-Pr	*i*-Bu	*s*-Bu	Bu
R'	H	Me	Me	Me	Me	Me

Cbz= C_6H_5-CH_2-O-CO-

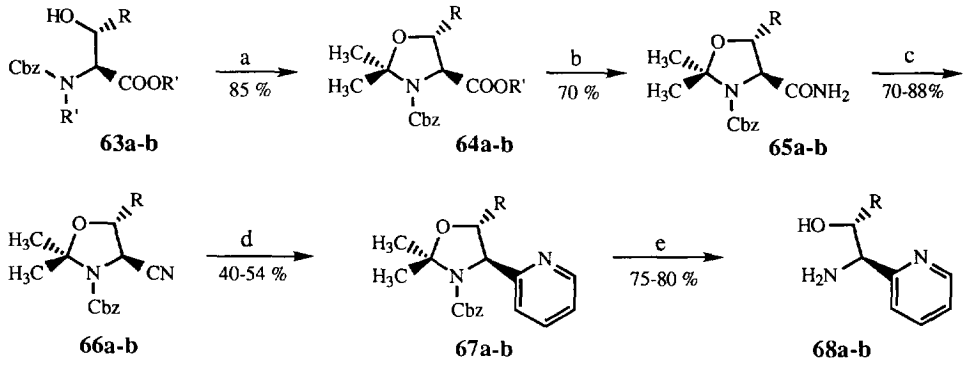
a: EtO_2CCl, 4-methylmorpholine, THF, -12 °C, 10 min; b: NH_3, 25 %, r.t.,12h; c: Ts/Py, 100 °C, 3-16h; d: CpCo(COD) (3.2 mol %), toluene, acetylene, 14 atm; e: 6N HCl reflux, 1h; f: HCHO/ HCO_2H, reflux.

Scheme 13



a: EtO_2CCl, 4-methylmorpholine, THF, -12 °C, 10 min; b: NH_3 (25 %), r.t.,12h; c: Ts/Py, 100 °C, 16h; d: CpCo(COD) (3.2 mol %), toluene, acetylene, 14 atm; e: NH_2NH_2, H_2O, MeOH, r.t., 12 h.

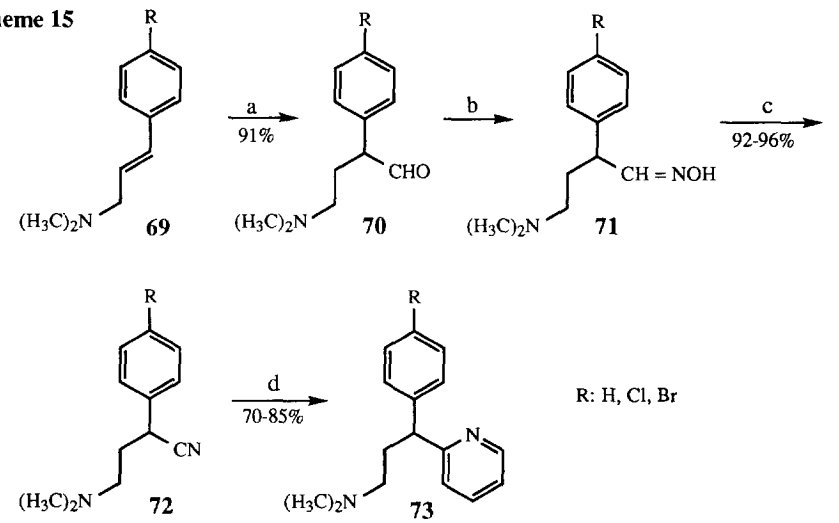
Scheme 14



a: R = H, R' = CH_3 **b**: R = CH_3, R' = H Cbz= C_6H_5-CH_2-O-CO-

a: $Me_2C(OMe)_2$, BF_3 Et_2O, 24h; b: for a NH_3/MeOH, 3 days, r.t.; for b $ClCO_2Et$, THF, TEA, -20 °C, 30 min. then NH_3, -20 °C to r.t., 20h; c: *p*-TsCl, pyridine, 80 °C, 1h; d: CpCo(COD) (3 mol %), toluene, acetylene, 12-14 atm, 160 °C, 3-6 days; e: 4N HCl, 24h, 100 °C.

Scheme 15



a: CO, H_2, $HRh(CO)(PPh_3)_3$, 80 °C; b: NH_2OH, H_2O/MeOH, r.t., 24h; c: CS_2, CH_2Cl_2, *n*-$Bu_4N^+HSO_4^-$, NaOH; d: acetylene, CpCo(COD), 140 °C, 36 h.

Recently, we undertook the synthesis of pheniramines,[41] which are among the most important antihistaminic agents. Our approach was based on the highly regioselective hydroformylation catalyzed by rhodium carbonyl

phosphine complexes of N-cinnamylamine derivatives **69** (Scheme 14). The aldehydes obtained were converted into the corresponding nitriles using CS_2 as the dehydrating agent of the intermediate aldoximes **71**. Cocyclotrimerization of nitriles **72** carried out at 140 °C for 36 hours in the presence of CpCo(COD) gave the pyridine **73** in good yield (85%). The overall yields were around 70%. Asymmetric hydroformylation of **69** to obtain the chiral aldehydes **70** is currently under investigation in our laboratory.

6. Experimental details

Synthesis of pyridines: general procedure

(π–Cyclopentadienyl)cobalt 1,5-cyclooctadiene[a] was placed in an autoclave which was then closed and air evacuated (0.1 mm). A solution of the nitrile[a,b] in the degassed[c] solvent[d] was introduced by suction into the autoclave. The reaction vessel was pressurized with acetylene[e] and then rocked and heated.[f] After acetylene was no longer absorbed,[g] the autoclave was cooled and the residual gas released[h]. The mixture was filtered, the solvent evaporated and the pyridine isolated by the usual methods depending on its physical properties.[i,l]

a- A molar ratio substrated/catalyst of about 20 is satisfactory to ensure a reasonable reaction rate.

b- Pure nitriles should be used. Particular care should be taken to eliminate any trace of acidity.

c- A degassed solution of the nitrile in the solvent is obtained by bubbling nitrogen or argon into the solution for a few minutes.

d- Toluene is the solvent of choice. When the nitrile is only slightly soluble in toluene, N,N-dimethylformamide can be used.

e- The autoclave is pressurized at 10-17 atm of acetylene at room temperature. Because of the high solubilitry of acetylene in toluene, to pressurize the autoclave it is advisable to proceed as follows: connect the autoclave to the source of acetylene and shake the autoclave; close the gas-tap and shake the autoclave. If after shaking the autoclave the gas pressure lowers, repeat this operation. When an autoclave of 0.2 l containing a solution of the nitrile in toluene (70-100 ml) saturated with acetylene at 12-14 atm at r.t. is heated at 120-140 °C, the internal pressure rises to 35-40 atm. This fact is not a problem since this reaction has been carried out with a maximum pressure of acetylene of 60 atm (pressure during the reaction). Apparently the nitrile triple bond is able to prevent the decomposition of acelytene in a manner similar to acetone.

f- Temperatures ranging from 80 to 140 °C were used with toluene as solvent. With N,N-dimethylformamide it is advisable not to exceed 100 °C to avoid decomposition of the solvent.

g- Reaction times are reported in Table 1 and 2.

h- This operation should carried out cautiously because of the residual acetylene dissolved into the solvent. It is opportune to operate as follows: open the gas-tap, cautiously release the acetylene and then close the gas-tap; shake the autoclave and release the gas. Before opening the autoclave this operation should be repeated until no gas is released.

i- Pure pyridines are obtained by simple acid-base elaboration if no functional group sensitive to this treatment is present.

l- Yields are shown in Tables 1 and 2.

(π-Cyclopentadienyl)cobalt-1,5-cyclooctadiene [CpCo(COD)]

Cyclopentadiene (7.35 g, 111.35 mmol) and 1,5-cyclooctadiene (29.2 g, 270.3 mmol) were added to a 1.0 M solution of triethylaluminium in hexane (400 ml). The mixture was vigorously stirred under argon at 0/-10 °C and cobalt(III)acetylacetonate (38.5 g, 108.1 mmol) was added in small portions (over about 2 h). A vigorous gas evolution occurred. After the addition of the cobalt salt, the mixture was allowed to warm up to room temperature over 2 h and was then filtered through a glass frit and the filtrate cooled to -50 °C. The orange-brown product crystallized out in 10 h. The supernatant liquid was removed, and the crystals washed with pentane (2 x 50 ml) at -50 °C and dried under vacuum to give CpCo(COD) (19.2 g, 77 % yield).

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