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Tetrahedron: *Asymmetry*

Asymmetric cyclocarbonylation of 1,6-enynes with cobalt catalysts

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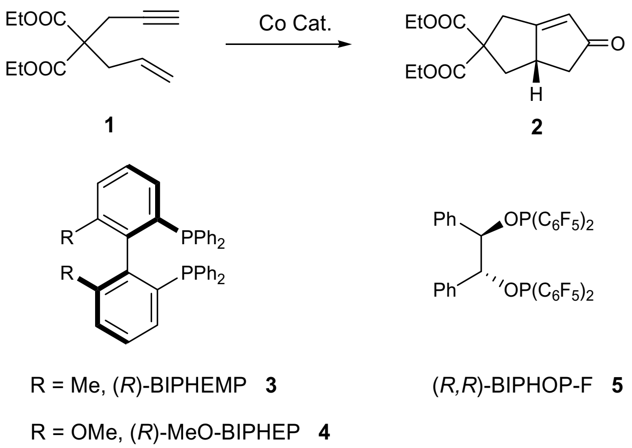
Abstract—Octacarbonyldicobalt or cobalt(II) salts in the presence of a reducing agent and when modified with (*R*)-(6,6′-dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine) (MeO-BIPHEP) are active and highly enantioselective (ee up to 91.5%) catalyst precursors for the cyclocarbonylation of enynes such as 4,4-bis(carboethoxy)hex-6-en-1-yne. The reactivity of both catalytic systems towards cyclocarbonylation increases when the carbon monoxide pressure is increased. However, the enantioselectivity of the systems decreases, but increases again as the ligand-to-cobalt molar ratio increases.

1. Introduction

Following the discovery of the [2+2+1] cycloaddition of an alkyne, an alkene and CO, promoted by octacarbonyldicobalt as the stoichiometric reagent (Pauson-Khand reaction), successful attempts were made to perform the reaction catalytically.[1] Furthermore, in addition to research aimed at developing efficient catalysts using other metals, more accessible sources of the cobalt catalyst were investigated to replace the very labile $Co_2(CO)_8$.[2] Among others, cobalt dibromide in the presence of zinc as a reducing agent was useful, even though its concentration was rather high (0.4 equiv).[3] Presumably the Co(I) or Co(II) precursors are reduced in situ by carbon monoxide.[4] In other reactions, however, Co(I) species are often mentioned to be formed during reduction, starting from Co(II) or Co(III) sources.[5–8] Another reason why this cyclocarbonylation reaction is interesting is the possibility to efficiently steer the process with high enantioselectivity.[2] In particular, when BINAP-type ligands were used, high asymmetric inductions were obtained.[9–11] In view of our interest in asymmetric carbonylation reactions, we have investigated the enantioselective cyclocarbonylation of 4,4-bis(carboethoxy)hex-6-en-1-yne **1** (Fig. 1) using either cobalt(0) or cobalt(II) catalysts precursors in the presence of a reducing agent, both modified with [(*R*)-(6,6′-dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine)] **4** in order to identify similarities or differences between these systems.[12]



1

2

R = Me, (*R*)-BIPHEMP **3**

R = OMe, (*R*)-MeO-BIPHEP **4**

(*R,R*)-BIPHOP-F **5**

Figure 1. Asymmetric carbonylation of **1** using cobalt catalysts modified with chiral bidentate ligands.

2. Results and discussion

A few experiments were performed to identify an appropriate ligand for this catalysis (Table 1) using dimethoxyethane as the solvent and octacarbonyldicobalt as the cobalt source. BIPHOP-F ligand **5** showed low catalytic activity and no enantioselectivity (entry 1).

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Table 1. Reaction of **1** in DME catalyzed by $Co_2(CO)_6(P^\wedge P)$ (5 mol%)

Entry	P^P:Co	Ligand	P^a (bar)	T (°C)	Time (h)	Conversion (%)	Yield **2** (%)	Ee (%)
1	1:2	(*R*,*R*)-BIPHOP-F	1	90	65	85	14	0
2	1:2	(*R*)-BIPHEMP	1.8	110	2.8	99	90	60.8
3	1:2	(*R*)-MeO-BIPHEP	1.8	110	2.3	93	66	87.7
4	1:3	(*R*)-MeO-BIPHEP	1.8	110	3.0	99	85	56.3
5	1:1	(*R*)-MeO-BIPHEP	1.8	110	4.5	99	89	89.4
6	3:2	(*R*)-MeO-BIPHEP	1.8	110	4.5	99	86	91.5
7	1:2	(*R*)-MeO-BIPHEP	4.2	110	2.2	100	92	58.7
8	1:1	(*R*)-MeO-BIPHEP	4.2	110	5.0	95	86	78.4
9	1:2	(*R*)-MeO-BIPHEP	4.2	90	97	97	90	59.3
10	1:2	(*R*)-MeO-BIPHEP	1.0	110	3.5	95	65	88.1
11	1:2	(*R*)-MeO-BIPHEP	6.0	110	2.9	100	94	22.0
12[b]	1:3	(*R*)-MeO-BIPHEP	4.2	110	2.7	100	94	10.6
13[b]	1:2	(*R*)-MeO-BIPHEP	4.2	110	3.1	99	95	29.7
14[b]	1:1	(*R*)-MeO-BIPHEP	4.2	110	4.0	99	92	60.1
15[b]	3:2	(*R*)-MeO-BIPHEP	4.2	110	4.5	98	92	73.6

[a] Absolute pressure measured at room temperature.

[b] Reaction were carried out in THF.

Even though the atropisomeric ligand MeO-BIPHEP **4** was somewhat less selective than the atropisomeric BIPHEMP **3** (a competitive noncarbonylative cyclization takes place), it showed a much higher enantioselectivity (entry 2 vs entry 3). Therefore, the following experiments were done using ligand **4**. A high enantioselectivity (87.7% ee) was obtained using a ligand-to-cobalt molar ratio of 1:2. Lower ratios (1:3) resulted in a lower enantioselectivity (56.3% ee). By increasing the ratio to 1:1 and to 1.5:1 the enantioselectivity slightly increased to reach 91.5% ee (entry 6), but the catalytic activity decreased somewhat. A similar behaviour was observed when tetrahydrofuran was substituted for dimethoxyethane as the solvent; however, the enantioselectivity in the former solvent was much lower. The aforementioned increase in enantioselectivity at ratios higher than unity is in contrast to that observed using BINAP as the ligand, for which the optimum ratio of ligand-to-metal for high enantioselectivity was 1:2.[9] Similar behaviour was observed when bidentate phosphites were used as the ligand; in this case, however, excess ligand caused a strong decrease in catalytic activity.[13] The influence of a higher ligand concentration (molar ratios 1:2 and 1:1) on the enantioselectivity is more pronounced at a higher carbon monoxide pressure; at 4.2 bar the ee value increased from 58.7% to 78.4% (entries 7 and 8). Reducing the reaction temperature by 20 °C caused a considerable decrease in the catalytic activity but only a slight increase in the enantioselectivity (entries 7 and 9). An increase in the carbon monoxide pressure (entries 3, 7, 10 and 11) resulted in a higher yield of the cyclocarbonylation product but had a strong negative effect on the enantioselectivity, with the ee being as low as 22.0% at 6 bar pressure.

Table 2 shows the results with $CoCl_2$[(*R*)-MeO-BIPHEP, or a complex formed in situ from the cobalt salt and the diphosphine, as the catalyst precursor in the presence of a reducing agent in tetrahydrofuran. In general, the reactivity of this catalytic system at the same metal concentration was considerably lower than that of the octacarbonyldicobalt catalyst precursor. There was no catalytic activity when $NaBH_4$ was used as the reducing agent. In contrast, $LiAlH_4$ is an efficient system, but the enantioselectivity of the reaction was also lower (39.6% vs 78.4% ee) than that of the cobalt carbonyl system. When zinc was used as the reducing agent, an induction time of about 2 h was usually observed. However, the system led to a higher catalytic activity and enantioselectivity (60.3% ee). Furthermore, the influence of the temperature (90 vs 110 °C) on the enantioselectivity was very small (61.6% ee at 90 °C). Whereas an under stoichiometric amount of the ligand with respect to the

Table 2. Reaction of **1** in THF catalyzed by $CoCl_2$((*R*)-MeO-BIPHEP) (10 mol%) and reducing agent

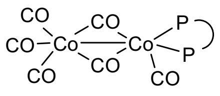
Entry	P^P:Co	Red. agent	P^a (bar)	T (°C)	Time (h)	Conversion (%)	Yield **2** (%)	Ee (%)
1	1:1	$LiAlH_4$	4.2	110	47	33	28	39.6
2	1:1	$NaBH_4$	4.2	110	48	5	0	0
3	1:1	Zn	4.2	110	21	98	83	60.3
4	1:2	Zn	4.2	110	19	100	94	8.5
5	3:4	Zn	4.2	110	31	99	91	41.0
6	3:2	Zn	4.2	110	25	99	86	62.3
7	1:1	Zn	4.2	90	42	83	79	61.6
8	1:1	Zn	1	110	68	44	34	72.6
9	1:1	Zn	1.8	110	42	96	76	82.3
10	1:1	Zn	6.0	110	18.5	99	91	37.5

[a] Absolute pressure measured at room temperature.

cobalt salt led to lower enantioselectivities, an excess amount (e.g., at 1.5 molar ratio) increases the optical yield only slightly. An increase in the carbon monoxide pressure, from 1.8 to 6.0 bar, led to higher catalytic activity but a decrease in the enantioselectivity. It should be noted that the enantioselectivity at 1 bar is lower than that at 1.8 bar; the reaction under these conditions is, however, rather slow.

3. Conclusions

Figure 2 shows the results obtained with tetrahydrofuran as the solvent in both catalytic systems at various ligand-to-metal ratios at a carbon monoxide pressure of 4.2 bar. The similar behaviour of the catalytic systems suggests that similar species may be involved in the catalysis, independent of the catalyst precursor. The nature of the cobalt species, which are modified by the bidentate ligands and are responsible for the carbonylative cyclization reaction of enynes when octacarbonyldicobalt is the catalyst precursor, is still a matter of speculation. Binuclear complexes are generally favoured; in these complexes the ligand can either chelate a single metal atom **6**[11] or bridge the two metal atoms **7**.[9,13,14] Working with $Co_2(CO)_8$ and a high ligand-to-metal ratio of one, mononuclear species **8** are known to form and may be catalytically active, too.[15] On the basis of the contrasting effect of a higher ligand-to-metal molar ratio and of the carbon monoxide pressure on the enantioselectivity of the reaction, different species with different ligand-to-cobalt ratios may be active simultaneously during the catalysis.



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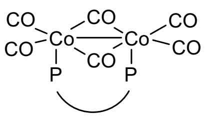

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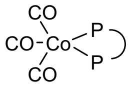

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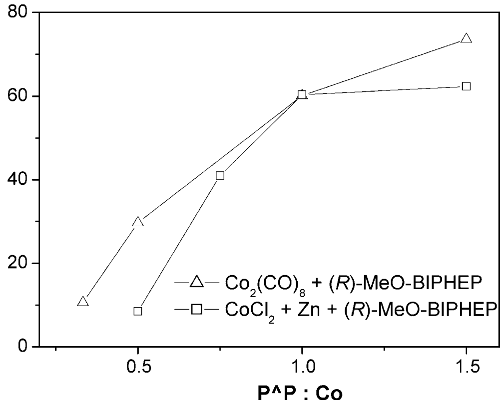

Figure 2. Influence of the ligand-to-cobalt molecular ratio on the enantioselectivity of the carbonylation cyclization of **1**. Reaction conditions: THF (solvent), 110 °C, 4.2 bar CO.

4. Experimental

4.1. General

All reactions were carried out under an inert atmosphere (argon). Flash chromatography was performed on Fluka Silica gel 60 (230–400 mesh). All the yields are isolated yields. The enantiomeric excess of the products was determined by GC (Hewlett Packard 5890 instrument equipped with a Supelco BETADEX-120 column). (*R*)-MeO-BIPHEP and (*R*)-BIPHEMP were kindly given by Hoffmann-La Roche AG, Basel, Switzerland and were used without further purification. (*R*,*R*)-BIPHOP-F was prepared according to the procedure in the literature.[16,17] Characterization of cyclocarbonylation product **2** is in agreement with earlier publications.[4,18]

4.2. General procedure for the catalytic asymmetric Pauson-Khand reaction with $Co_2(CO)_8$/P^P catalytic system

A dry 50 mL Schlenk tube was equipped with a magnetic stirrer bar with a flexible Teflon tube connected to a 60 mL stainless steel autoclave through a septum. $Co_2(CO)_8$ (10.1 mg, 0.03 mmol) and (*R*)-MeO-BIPHEP (17.2 mg, 0.03 mmol) were added to the Schlenk tube and stirred in 12 mL of DME in a CO atmosphere for 15 min at room temperature. Substrate **1** (150 mg, 0.63 mmol) was added with a syringe and the reaction solution was sucked into the pre-evacuated autoclave and washed with 4 mL of DME. After adjusting the carbon monoxide pressure at room temperature the autoclave was heated to 110 °C. Switching on the mechanical stirrer, the reaction started after 15 min. The course of the reaction was followed by gas chromatography and stopped after the given time. The crude product was purified by means of flash chromatography.

4.3. General procedure for the catalytic asymmetric Pauson-Khand reaction with $CoCl_2$(P^P)/Zn catalytic system

$CoCl_2$[(*R*)-MeO-BIPHEP] (41.0 mg, 0.06 mmol) was placed in a dry 50 mL Schlenk tube equipped with a magnetic stirrer bar and a flexible Teflon tube connected through a septum to a 60 mL stainless steel autoclave containing zinc metal (4.2 mg, 0.06 mmol). THF (12 mL) was added to the Schlenk tube and the mixture was stirred at room temperature for 15 min. The rest of the procedure was the same as that described in Section 4.2.

4.4. (*R*)-(6,6′-Dimethoxy-2,2′-diyl)bis(diphenylphosphine)-dichlorocobalt[19,20]

Anhydrous cobalt chloride (0.134 g, 1.03 mmol) was mixed with (*R*)-MeO-BIPHEP (0.6 g, 1.03 mmol) in a 100 mL round-bottomed flask in acetone (40 mL) at room temperature. After 48 h of stirring a green precipitation was formed. After filtration and washing with hexane (2 × 5 mL) the desired product was obtained as a green powder (0.654 g, 0.92 mmol, 89%). Suitable crystals for structure determination were obtained by recrystallization from CH_2Cl_2/hexane. Anal. Calcd for $C_{38}H_{32}Cl_2O_2P_2Co$ (712.46): C, 62.81; H, 4.68. Found: C, 62.81; H, 4.66.

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