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Cobalt-catalyzed hydrogenation of β-enamino esters using an internal mixture of bidentate and monodentate ligands

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ABSTRACT

Different β-amino esters have been obtained in good yields by means of octacarbonyldicobalt-catalyzed hydrogenation of β-enamine esters in the presence of mixture of a bidentate phosphine chiral (*R*-BINAP) and a monodentate phosphine achiral (PPh_3). Likewise, a non-symmetric Co/BINAP/PPh_3 complex was isolated. This new compound was used in the hydrogenation reaction under different conditions and the results suggest that this heterocombination could be responsible for improving enantiomeric excess in the reduction products.

Introduction

$Co_2(CO)_8$-catalyzed reactions have played key roles for the synthesis of useful organic compounds in both academia and industry. In general, the principal application of dicobalt octacarbonyl is in carbonylation reactions, however; this complex has been effective in different reactions such as 1,3-oxazinan-4-ones synthesis [1], cyclodimerization of 1,4-dilithio-1,3-butadienes [2], hydrosilylation of amides [3]. This ability in the activation of small molecules reveals the potential application of $Co_2(CO)_8$ in different catalytic reactions. On the other hand, enamines represent an important class of compounds due to their occurrence in natural products [4]. Likewise, these compounds have received significant attention in organic synthesis due to their versatility as intermediates in the synthesis of heterocycles with a variety of biological activities, such as anticonvulsant [5], anti-inflammatory [6] and anticancer compounds [7]. Therefore, several protocols are available for the synthesis of enamines. The most common method is a reaction between β-keto esters or β-dicarbonyl compounds and aniline in the presence of aromatic solvents by azeotropic removal of water. However, this method has been displaced by the use of Lewis acids [8,9], because they are easy to handle, inexpensive and relatively stable to air and moisture. On the other hand, chiral amino esters are important compounds that can be used as building blocks for the synthesis of β-peptides and β-lactams [10,11] as well as other classes of compounds with biological and pharmacological activity [12,13]; because of this, the interest in β-amino esters has continued to grow. In this context, β-enamino esters are convenient precursors in the synthesis of chiral β-amino esters by asymmetric hydrogenation. In this case, a number of transition metal catalytic systems have been developed wherein focus of the studies has been on Rh, Ir and Ru [14–16]. Zhang and co-workers first reported the rhodium-catalyzed asymmetric hydrogenation of *N*-aryl β-enamino esters with good to excellent enantioselectivities [17]. They also extended this strategy to the asymmetric hydrogenation of unprotected enamino esters catalyzed using iridium complexes [18]; the first report of this reaction was made by the Merck and Solvias groups [19]. Likewise, few iridium complexes have been used in the asymmetric hydrogenation of *N*-aryl β-enamines. For example, Renaud et al. found that [IrCl(COD)] complex was active in this reaction with good yields. However, when they worked with chiral ligands (phosphoramidite ligands) in the same reaction no chiral induction was found [20]. More recently, Vries et al. working with $[Ir(COD)_2]BArF$ complexes in the

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presence of a mixture of chiral and achiral monodentate ligands obtained good yields and good enantioselectivities [21]. In the case of ruthenium, there are a few reports of the hydrogenation of *N*-aryl β-enamino esters; the first example was reported by Moroi et al. at Takasato [22]. In 2010, Hebbache et al. reported the hydrogenation of *N*-benzyl β-enamino esters using different ruthenium complexes under acidic conditions [20]. Despite these examples, there have been few reports on the hydrogenation of this type of compound, especially using cobalt as a catalytic precursor. It is noteworthy that we recently used a cobalt-modified complex for the hydrogenation of imines and α-enamino ketones, obtaining good results [23,24]. Here, we aim to extend this methodology to the hydrogenation of *N*-aryl β-enamino esters using $Co_2(CO)_8$ and a mix of ligands consisting of chiral bidentate phosphine and achiral monodentate phosphine.

Experimental section

General

All reactions and manipulations were carried out under nitrogen atmosphere using Schlenk-type techniques. Column chromatography was performed on silica (70–230 and 230–400 mesh). The ^1H, ^{13}C NMR spectra were recorded on a Bruker-Advance 300 spectrometer in $CDCl_3$ as solvent at 25 °C. Mass spectra were obtained using a JEOL JMS-SX102A instrument. Elemental analyses for compounds were obtained on an Elementary Analyzer CE-440. IR spectra were recorded on a Nicolet FTIR magna 750 spectrophotometer. Optical rotations were measured on a Perkin–Elmer 343 spectropolarimeter. HPLC analyses were performed on a Hewlett Packard 1100 system with UV-DAD. Separations were achieved on a Diacel Chiracel OD-H and OD columns. X-ray determination was collected on a Bruker SMART APEX CCD area diffractometer by the ω-scan method. All chemicals and solvents were used as received unless otherwise stated. Tetrahydrofuran (Na, benzophenone), hexane (Na, benzophenone), and methylene chloride (P_2O_5) were distilled under nitrogen prior to use.

Table 1
Crystal data and structure refinement for **II**.

II·THF	
Empirical formula	$C_{68}H_{49}Co_2O_5P_3$
Formula weight (g mol^{-1})	1160.84
Temperature	298(2) K
Crystal color	Brown
Crystal system	Triclinic
Space group	*P*-1
Crystal size (mm)	0.451 × 0.251 × 0.056
a (Å)	11.1513(4)
b (Å)	13.7071(5)
c (Å)	20.2515(8)
α (°)	105.384(2)
β (°)	90.599(3)
γ (°)	103.826(2)
V (Å^3)	2889.06(19)
Z	2
D_{cal} (mg/cm^3)	1.334
μ (mm^{-1})	0.780
2*θ* (°)	2.084–25.38
Reflections collected	24,647
Independent reflections	10,524
R_{int}	0.0486
*R*1 [$I > 2\sigma(I)$]	0.0619
wR_2 [all data]	0.1952
Goodness-of-fit	1.011
Max./min. Δ*ρ* (e Å^{-3})	0.810 and −0.490

Crystallography

Crystallographic and experimental details of crystal structure determination are listed in Table 1. Single crystal for X-ray diffraction was obtained by slow diffusion of pentane into a THF solution of **II**. Single crystal was mounted on a glass fiber at room temperature. The crystal was then placed on a Bruker SMART APEX CCD diffractometer, equipped with Mo Kα radiation. Systematic absence and intensity statistic were used in space group determinations. The structure was determined using direct methods [25]. Anisotropic structure refinement was achieved using full-matrix, least-squares techniques on all non-hydrogen atoms. All hydrogen atoms were placed in idealized positions, based on hybridization, with isotropic thermal parameter fixed at 1.2 times the value of the attached atom. Structure solution and refinement was performed using SHELXTL v 6.10 [26].

General procedure for synthesis of β-enamino esters

A mixture of the β-dicarbonyl compound (2 mmol), the amine (2 mmol) and $CoCl_2$ (1 mol%) was stirred at room temperature for 12 h. The crude reaction mixture was passed through a pad of Na_2SO_4. Subsequently, the solvent was evaporated under reduced pressure to provide the crude product. Further purification was carried out by silica gel flash chromatography with hexane-ethyl acetate (8:2) to afford pure β-enamino esters with excellent yields.

General procedure for hydrogenation reaction of β-enamino esters

The hydrogenation was performed on a 4712 model Parr reactor. In a Schlenk tube under nitrogen atmosphere, corresponding β-enamino ester (100 mg, 0.037 mmol) was added to a solution of $Co_2(CO)_8$ (1 mol%), (*R*)-BINAP (2 mol%) and PPh_3 (2 mol %) in THF (10 mL), the reaction mixture was stirred for 10 min. Then, the solution was transferred to a 45 mL steel Parr vessel previously purged with vacuum-nitrogen. The reaction vessel was pressurized at 450 psi with a H_2/CO mixture in a 1/3 ratio. The reactor was placed in a preheated oil bath at 120° with magnetic stirring for 36 h. At the end of the reaction time, the reactor was cooled and the gases were liberated. The solution was concentrated under reduced pressure and resulting product was purified by chromatography column using hexane and ethyl acetate as eluents.

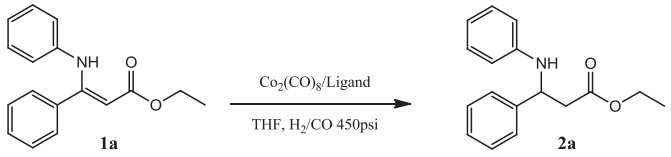
Mercury drop experiment

Following the above described procedure for hydrogenation reaction; four drops of elemental Hg were added. After 36 h, the solution was filtered and purified by column chromatography on silica gel.

Results and discussion

Initial hydrogenation experiments were performed at 450 psi of H_2/CO pressure and 120 °C, using 1 mol% of catalyst with Co/L* = 1/2 prepared *in situ*. Enamine **1a** was chosen as model substrate; the results are summarized in Table 2. First, different times and temperatures were probed to obtain β-amino ester **2a**. We observed that the [$Co_2(CO)_8$/*rac*-BINAP] catalytic system exhibited higher reactivity at 120 °C with 3 h of time reaction (entries 1, 2, 3 and 4). In contrast, if the reaction temperature was less than 120 °C the catalytic activity decreased (entries 5 and 6). Furthermore, the catalytic efficiency of the cobalt complexes in

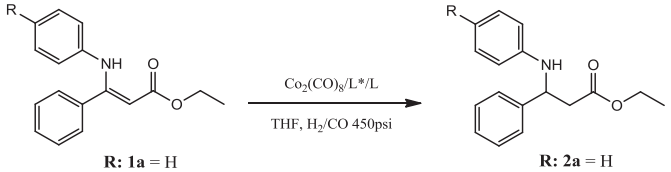
Table 2
Hydrogenation of **1a** β-enamino esters under various conditions.[a]



Entry	Temperature (°C)	Time (h)	Ligand	Yield (%)[b]	ee (%)[c]
1	120	24	*rac*-BINAP	90	*rac*
2	120	15	*rac*-BINAP	89	*rac*
3	120	7	*rac*-BINAP	90	*rac*
4	120	3	*rac*-BINAP	89	*rac*
5	100	7	*rac*-BINAP	0	–
6	25	24	*rac*-BINAP	0	–
7	120	7	(*R*)-BINAP	91	*rac*
8	120	7	(*R*)-Tol-BINAP	92	*rac*
9	120	7	(*R*)-H_8-BINAP	95	*rac*
10	120	7	(*R*,*R*)-DIOP	71	*rac*
11	120	7	(*R*,*R*)-Me-DuPHOS	81	*rac*
12	120	7	(*R*)-PROPHOS	84	*rac*

[a] Reaction conditions: 0.37 mmol of **1a** enamine, 1 mol% $Co_2(CO)_8$ (0.0037 mmol), (0.0075 mmol) ligand, 10 mL THF, H_2/CO (1:3, 450 psi), 120 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis with Daicel chiralcel OD-H and OD columns.

Table 3
Asymmetric hydrogenation of β-enamines using $Co_2(CO)_8$ with mixed ligands.[a]



Entry	Co/L*/L	Product	Yield (%)[b]	ee (%)[c]
1	1/1/1	**2a**	75	0
2	1/1/2	**2a**	51	0
3	1/1/3	**2a**	43	12
4	1/2/1	**2a**	75	2
5	1/3/1	**2a**	81	1
6	1/2/2	**2a**	37	20
7	1/3/3	**2a**	41	4
8	1/1/1	**2b**	70	0
9	1/2/1	**2b**	71	8
10	1/2/2	**2b**	22	37
11[d]	1/2/2	**2a**	85	20
12[e]	1/2/2	**2a**	91	21
13[f]	1/2/2	**2a**	91	22
14[g]	1/2/2	**2a**	92	21
15	1/2/2	**2a**	89	20

[a] Reaction conditions: 0.37 mmol of **1a** or **1b** enamine, 1 mol% of $Co_2(CO)_8$ (0.0037 mmol), ligands: L* = (*R*)-BINAP (0.0075 mmol) and L = PPh_3 (0.0075 mmol), 10 mL THF, H_2/CO (1:3, 450 psi), 120 °C, 7 h.
[b] Isolated yield.
[c] Determined by HPLC analysis with Daicel chiralcel OD-H and OD columns.
[d] 24 h.
[e] 30 h.
[f] 36 h.
[g] 48 h.

the asymmetric hydrogenation reaction of β-enamines was evaluated; for this purpose the racemic ligand was changed to (*R*)-BINAP. In this case, product **2a** was obtained as a racemic mixture (entry 7). To improve the enantiomeric excess, different chiral phosphorus ligands such as (*R*)-Tol-BINAP, (*R*)-H_8-BINAP, (*R*,*R*)-DIOP, (*R*,*R*)-Me-DuPHOS and (*R*)-PROPHOS were probed; unfortunately, all cases gave racemic mixtures (entries 8–12). Similar results were found by Enthaler et al. for the hydrogenation of β-dehydroamino acid catalyzed by iridium complexes with (*R*,*R*)-DIOP, (*S*)-BINAP and (*S*,*S*)-Me-DuPHOS [27].

In order to improve the enantiomeric excesses, we decided to use a mixture of chiral and achiral ligands. This idea has been developed by Reetz [28,29] and Feringa [30,31] for more than a decade. They also demonstrated that it is possible to increase enantioselectivity and reactivity by using mixtures of chiral monodentate ligands [32]. In this context, they have postulated that the corresponding heterocombination generated from a mixture of ligands coordinated to a metal center is more selective than the corresponding homocombination [32]. Therefore, for our initial experiments we decided to work with a mixture of (*R*)-BINAP and PPh_3. The monodentate ligand was selected based on excellent results reported in the literature on asymmetric hydrogenation reactions of carbon–carbon double bonds [21,31,33]. Initially, the $Co_2(CO)_8$/(*R*)-BINAP ratio was kept constant at 1:1 and only the PPh_3 ratio was varied. The results are presented in Table 3. When we increased the quantity of monodentate ligand, a decrease in the reaction yields was found and no chiral induction was observed in products **2a**–**b** (entries 1, 2 and 8). The reaction with ratio Co/L*/L (1:1:3) gave a moderate yield and slightly increased the enantioselectivity (entry 3). Then, we investigated the effect of increasing the BINAP ratio. No chiral induction was observed when the bidentate ligand was increased to ratios of 1:2:1 or 1:3:1. A similar result was obtained to that with 1:3:3 (entries 4, 5, 9 and 7). Interestingly, the Co/L*/L (1:2:2) combination increased the enantiomeric excess from 12% to 22% and 8% to 37% for products **2a** and **2b**, respectively (entries 6 and 10). These results may suggest that the 1:2:2 ratio is essential for asymmetric induction, showing that the heterocombination between $Co_2(CO)_8$, (*R*)-BINAP and PPh_3 could be responsible for the increase in enantioselectivity. On the other hand, the yield of the reaction increased to up to 91% when the reaction was carried out for 36 h (entries 11–14). In order to test the homogeneity of the catalytic system a mercury drop experiment was done (See Supplementary material). The result showed no inhibition of the process and no significant differences in yield was observed, this result is consistent with a homogeneous process (entry 15).

The effect of the different monodentate ligands in the asymmetric hydrogenation reaction was also investigated; the results are shown in Table 4. These experiments were performed using a Co/L*/L ratio of 1:2:2 at 450 psi and 120 °C in tetrahydrofuran for 36 h.

When the reaction was carried out in the presence of the **L1** ligand the expected product **2a** was isolated with a yield of 72%; however, this reaction yield was lower compared to when the

Table 4
The effect of different achiral monodentate ligands on the hydrogenation reaction of **1a**.[a]

Entry	Achiral ligand	Yield (%)[b]	ee (%)[c]
1	$P(p\text{-}CH_3C_6H_4)_3$ **L1**	72	0
2	$P(o\text{-}CH_3C_6H_4)_3$ **L2**	46	0
3	$P(C_6H_{11})_3$ **L3**	24	0
4	$P(OC_6H_4)_3$ **L4**	81	0
5	$Sb(C_6H_4)_3$ **L5**	83	1

[a] Reaction conditions: 0.37 mmol of **1a** enamine, 1 mol% of $Co_2(CO)_8$ (0.0037 mmol), ligands: (*R*)-BINAP (0.0075 mmol) and L = achiral ligand (0.0075 mmol), 10 mL THF, H_2/CO (1:3, 450 psi), 120 °C, 36 h.
[b] Isolated yield.
[c] Determined by HPLC analysis with Daicel chiralcel OD-H column.

Table 5
Hydrogenation of enamine **1a** with various chiral bidentate phosphines.[a]

Entry	Chiral ligand	Yield (%)[b]	ee (%)[c]
1	(*R*)-Tol-BINAP	76	1
2	(*R*)-H_8-BINAP	73	2
3	(*R*,*R*)-DIOP	70	2
4	(*R*,*R*)-Me-DuPHOS	72	3
5	(*R*)-PROPHOS	74	1

[a] Reaction conditions: 0.37 mmol of **1a** enamine, 1 mol% of $Co_2(CO)_8$ (0.0037 mmol), ligands: Chiral ligand (L*) (0.0075 mmol) and PPh_3 (L) (0.0075 mmol), 10 mL THF, H_2/CO (1:3, 450 psi), 120 °C, 36 h.
[b] Isolated yield.
[c] Determined by HPLC analysis with Daicel chiralcel OD-H column.

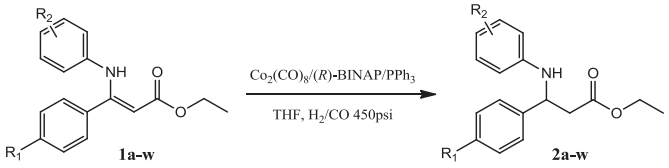
PPh_3 ligand was used (entry 1, Table 4 vs. entry 13, Table 3). Changing the substituent position on the ligand resulted in a poor yield (entry 2). This behavior could be associated with a steric effect in the heterocombination generated with **L2** and (*R*)-BINAP (entry 3), making it impossible to form a mixed ligand species; a similar result was obtained with ligand **L3** (entry 4). In contrast, good yields were obtained with triphenylphosphite **L4** and triphenylstibine **L5** as ligands. Unfortunately, all previous heterocombinations did not improve the enantioselectivity of the reaction. In addition, we explored the use of five different chiral bidentate phosphine ligands (L*) in combination with triphenylphosphine (L) in the hydrogenation of **1a**. The reaction was carried out with a Co/L*/L ratio of 1:2:2 in tetrahydrofuran under 450 psi (H_2/CO) pressure and 120 °C for 36 h. The results are summarized in Table 5. Regrettably, low enantioselectivity was obtained using the different bidentate ligands. Even so, the catalytic systems showed a decrease in catalytic activity (entries 1–5).

In summary, the best results were obtained using $Co_2(CO)_8$/(*R*)-BINAP/PPh_3 (1:2:2) under 450 psi of pressure with 1 mol% of catalyst loading in tetrahydrofuran for 36 h. Using this optimized catalytic system, we explored the scope of the hydrogenation reaction using various *N*-aryl β-enamino esters; the results are summarized in Table 6. In general, good yields were obtained (up to 93%). The results revealed that the substitution on the aromatic ring of the substrate has no effect on the reaction yield. Similarly, the hydrogenation reaction tolerated both electron-donating and electron-withdrawing groups on the substrate, whereas enantiomeric excesses were affected for the substituent position. Thus, in the absence of a substituent on R_2, good yields were obtained with moderate ee% values (entries 1, 13 and 22). However, the existence of a *p*-MeO group on R_2 presented a slight increase in enantioselectivity (entries 2 and 14), while the reaction proceeded with poor enantioselectivity in the presence of *p*-Me (entries 3 and 15).

When the reaction was realized with substrates containing *p*-Cl or *p*-F groups, the desired products resulted but with lower ee% (entries 4–5). In contrast, *p*-MeO and *p*-Me substituents attached to the benzoylacetate moiety in combination with *p*-Cl or *p*-F on the amine moiety gave the best enantioselectivity (entries 16 and 17 and 23). This increase in enantiomeric excess may be attributed to the electronic effects associated with the substituent in position R_1. *meta* Substituents on the amine moiety were also tested; however, low values of ee% were obtained (entries 6 and 7, 18 and 19). Notably, substituents on the *ortho* position of the amine moiety provided the product with an increased ee% value. The small improvement in the ee could be associated with both electronic and steric effects of the substituent at the *ortho* position, although a lower ee% was obtained when the substituent was changed from a *methyl* to an *ethyl* group (entries 8–12, and 20 and 21).

Finally, in order to probe the participation of the heterocombination from cobalt in the hydrogenation reaction, we decided to synthesize a non-symmetrical cobalt complex. First, the addition

Table 6
Asymmetric hydrogenation of β-enamines using Co/(*R*)-BINAP/PPh_3.[a]



Entry	R_1	R_2	Product	Yield (%)[b]	ee (%)[c]
1	H	H	**2a**	93	22
2	H	*p*-MeO	**2b**	85	37
3	H	*p*-Me	**2c**	91	7
4	H	*p*-Cl	**2d**	90	7
5	H	*p*-F	**2e**	89	5
6	H	*m*-Me	**2f**	93	19
7	H	*m*-Cl	**2g**	92	5
8	H	*o*-Me	**2h**	89	19
9	H	*o*-MeO	**2i**	91	38
10	H	*o*-Et	**2j**	88	6
11	H	*o*-Br	**2k**	90	32
12	H	*o*-OH	**2l**	89	26
13	*p*-MeO	H	**2m**	82	18
14	*p*-MeO	*p*-MeO	**2n**	86	20
15	*p*-MeO	*p*-Me	**2o**	89	7
16	*p*-MeO	*p*-Cl	**2p**	84	43
17	*p*-MeO	*p*-F	**2q**	93	21
18	*p*-MeO	*m*-Me	**2r**	87	4
19	*p*-MeO	*m*-Cl	**2s**	80	6
20	*p*-MeO	*o*-Me	**2t**	88	25
21	*p*-MeO	*o*-Et	**2u**	85	15
22	*p*-Me	H	**2v**	82	24
23	*p*-Me	*p*-Cl	**2w**	86	32

[a] Reaction conditions: 0.37 mmol of enamine **1a**–**w**, 1 mol% of $Co_2(CO)_8$ (0.0037 mmol), (*R*)-BINAP (0.0075 mmol) and PPh_3 (0.0075 mmol), ratio = 1/2/2, 10 mL THF, H_2/CO (1:3, 450 psi), 120 °C, 36 h.
[b] Isolated yield.
[c] Determined by HPLC analysis with Daicel chiralcel OD-H and OD columns.

of triphenylphosphine (0.1 mmol) to a solution of $Co_2(CO)_8$ (0.1 mmol) in THF resulted in the $PPh_3Co(CO)_7$ (**I**) complex (Eq. (1)). Then, 0.1 mmol of (*R*)-BINAP was added to a solution of complex **I**, resulting in the expected product (**II**). Compound **II** is a brown powder that is thermally stable at atmospheric pressure but decomposes in solution at 25 °C. Crystals of **II** were grown by layering a saturated tetrahydrofuran solution of **II** with pentene. The ^{31}P NMR spectrum of (**II**) crystals showed three signals at δ 29.2, 28.7, 28.4 ppm corresponding to BINAP and PPh_3. A few minutes later two new signals can be observed (−5.1 ppm PPh_3 and −14.2 ppm BINAP free). This behavior is associated with decoordination of the ligands present in molecule **II**.

$$Co_2(CO)_8 + PPh_3 \xrightarrow[10\ min,\ -CO]{thf,\ r.t.} \underset{\mathbf{I}}{Co_2(CO)_7(PPh_3)} \xrightarrow[3\ h,\ -2CO]{(R)\text{-BINAP}} \underset{\mathbf{II}}{Co_2(CO)_5(PPh_3)(R)\text{-BINAP}} \quad (1)$$

The IR spectrum of **II** showed four absorptions representing CO stretching frequencies at 2046, 2028, 1993 and 1934 cm^{-1}, which could be assigned to $CO_{terminal}$ groups. The molecular structure is shown in Fig. 1. Compound **II** crystallizes in the triclinic space group *P*-1 and displays a dinuclear arrangement in which the phosphine ligands are observed in *anti*-position with respect to the Co–Co bond. This structure reveals two different phosphine ligands and five terminal carbonyls forming a distorted trigonal bipyramidal geometry around the Co atoms. The length of the Co(2)–P(3) = 2.188(17) bond is comparable with different complexes reported in the literature [24]. In addition, the Co(1)–Co(2)–P(3) = 161.796(6)° angle indicates a slight deviation from linearity.

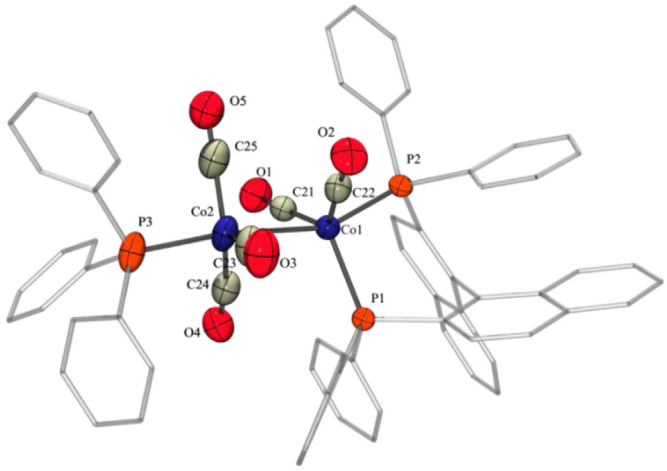
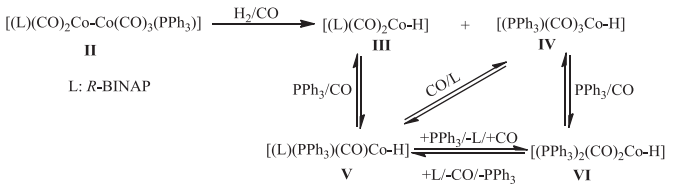


Fig. 1. ORTEP diagram showing the molecular structure of [((*R*)-BINAP)$Co(CO)_2$–$Co(CO)_3(PPh_3)$] (**II**) [35]. Thermal ellipsoids are shown at the 40% probability level, and hydrogen atoms are omitted for clarity. Selected bond distances (Å): Co(1)–P(1), 2.2726(12); Co(1)–P(2), 2.1920(13); Co(2)–P(3), 2.1880(17); Co(1)–Co(2), 2.7170(9); Co(1)–C(21), 1.775(6); Co(1)–C(22), 1.7554(6); Co(1)–C(23), 1.780(7); Co(1)–C(24), 1.752(8); Co(1)–C(25), 1.760(8). Selected bond angles (°): P(1)–Co(1)–P(2), 95.55(5); P(1)–Co(1)–Co(2), 84.79(16); P(2)–Co(1)–Co(2), 156.75(5); P(3)–Co(2)–Co(1), 161.79(6); C(22)–Co(1)–C(21), 127.5(2); C(24)–Co(2)–C(23), 122.3(3); C(24)–Co(2)–C(25), 122.9(3); C(25)–Co(2)–C(23), 113.5(3). Molecule **II** has a residual disorder of 18% in the two phenyl groups at the PPh_3.

Similarly, there is also a deviation from linearity for angle Co(2)–Co(1)–P(2) = 156.75(5); this could be attributed to the bulkiness of the BINAP. The Co–Co bond length was found to be 2.717(9) Å and is similar to other cobalt complexes [23,24,34].

As mentioned before, the asymmetric induction could be associated with heterocombination between $Co_2(CO)_8$, PPh_3 and BINAP. In order to examine this hypothesis, we decided to work with complex **II** in the asymmetric hydrogenation of substrate **1b**. It is worth mentioning that complex **II** in the presence of an extra equiv. of PPh_3 and BINAP may generate different species in equilibrium and it is possible to propose different cobalt hydrides as shown in Eq. (2), since the coordination ability of the ligands may generate both homocombination and heterocombination. The structures of hydrides (III), (IV) and (VI) are suggested based on previously reports in the literature [36–38], we were unable to detect them experimentally but they must exist in the reaction media and only specie (V) can be responsible for the ee observed. We observed that hydride (III) cannot induce ee (*vide supra*) on the reaction product.



(2)

Therefore, the use of different amounts of achiral ligand or chiral ligand can modulate the enantiomeric excess. First, complex **II** was used under the optimized conditions of the hydrogenation reaction. In this reaction we obtained a poor ee (2%) due to the presence of two hydrides (**III** and **IV**) that can be formed from **II** that are competing in the hydrogenation step. A similar effect was observed when hydrogenation of **1b** was carried out with 2 equiv. of PPh_3 and **II**, with only a slight increase in the ee (10%). The best results were obtained (30% ee), when 1 equiv. of PPh_3 and 1 equiv. of (*R*)-BINAP were used in combination with **II**. The possibility of increasing the probability of hydride **V** may be responsible for this increase in enantioselectivity. These results support the proposal that enantiomeric excess is modulated by the heterocombination between cobalt/BINAP/PPh_3.

Conclusion

In summary, we have demonstrated that $Co_2(CO)_8$/(*R*)-BINAP/PPh_3 is a good catalytic system for the hydrogenation of β-enamine esters. The desired amino esters were obtained in good yields but with low enantioselectivities. Finally, a mixture of two different ligands in combination with a new cobalt complex showed that such a heterocombination may improve the enantiomeric excess.

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Appendix A. Supplementary material

CCDC 982740 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Appendix B. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2014.06.028.

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