



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.

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Introduction

$\text{Co}_2(\text{CO})_8$ -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-dithio-1,3-butadienes [2], hydrosilylation of amides [3]. This ability in the activation of small molecules reveals the potential application of $\text{Co}_2(\text{CO})_8$ 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 $[\text{IrCl}(\text{COD})]$ 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 $[\text{Ir}(\text{COD})_2]\text{BARf}$ 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 $\text{Co}_2(\text{CO})_8$ 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.

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 $K\alpha$ 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 $\text{Co}_2(\text{CO})_8$ (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 °C 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 $\text{Co}/\text{L}^* = 1/2$ 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 $[\text{Co}_2(\text{CO})_8/\text{rac-BINAP}]$ 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 1
Crystal data and structure refinement for **II**.

II ·THF	
Empirical formula	$\text{C}_{68}\text{H}_{49}\text{Co}_2\text{O}_5\text{P}_3$
Formula weight (g mol^{-1})	1160.84
Temperature	298(2) K
Crystal color	Brown
Crystal system	Triclinic
Space group	<i>P</i> -1
Crystal size (mm)	$0.451 \times 0.251 \times 0.056$
<i>a</i> (Å)	11.1513(4)
<i>b</i> (Å)	13.7071(5)
<i>c</i> (Å)	20.2515(8)
α (°)	105.384(2)
β (°)	90.599(3)
γ (°)	103.826(2)
<i>V</i> (Å ³)	2889.06(19)
<i>Z</i>	2
<i>D</i> _{cal} (mg/cm^3)	1.334
μ (mm^{-1})	0.780
2θ (°)	2.084–25.38
Reflections collected	24,647
Independent reflections	10,524
<i>R</i> _{int}	0.0486
<i>R</i> 1 [$ I > 2\sigma(I)$]	0.0619
<i>wR</i> ₂ [all data]	0.1952
Goodness-of-fit	1.011
Max./min. $\Delta\rho$ (e Å^{-3})	0.810 and –0.490

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