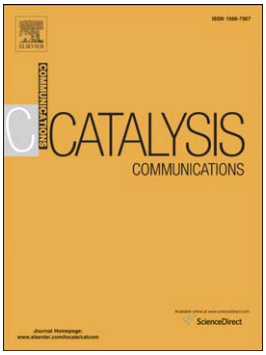

Hydrogenation of α-enaminoketones with cobalt phosphine-modified catalysts

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Hydrogenation of α-enaminoketones with cobalt phosphine-modified catalysts[1]

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[1]Dedicated to the memory of Professor Leopoldo Garcia-Colin S.

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Abstract

The synthesis of α-enamines and hydrogenation of these compounds were studied using cobalt-modified complexes. Cobalt complexes were characterized by ^{1}H, ^{13}C and ^{31}P NMR, elemental analysis and IR spectroscopy. Furthermore, the molecular structures of complexes **C1-C2** and **C4-C5** have been determined by single-crystal X-ray diffraction. All cobalt complexes investigated were active catalysts for the hydrogenation reaction. The best catalytic activity was obtained with an ortho-substituent in the phosphine ligand. Noteworthy, the reduction was chemoselective over the double bond.

Keywords: Dicobalt octacarbonyl, enamines, homogeneous catalysis, hydrogenation, aminoketones.

1. Introduction

Interest in the chemistry of $Co_2(CO)_8$ continues to grow due to its potential applications in catalysis.[1-7] The main thrust of research in the chemistry of cobalt-modified complex has been on carbonylation[8] and Pauson-Khand reactions(PKR), since the hydroformylation of olefins to yield aldehydes and alcohols is one of the largest-scale industrial homogeneous catalytic processes.[9] Additionally, dicobalt octacarbonyl complexes show catalytic activity towards polymerization,[10] copolymerization,[11] (PKR) through heterogeneous catalysis,[12] and *N-tert*-butyl-*trans*-α-ethoxycarbonyl-β-phenyl-β-lactam (TBL) synthesis.[13] Recently, we have reported new features of a cobalt-modified complex in the asymmetric hydrogenation of imines[14] and one-pot synthesis of secondary amides,[15] under H_2/CO and H_2 pressure, respectively. In this study, we found that $HCo(CO)_{4-n}L_n$ (n= 1,2) can be formed *in situ* as an active species from $Co_2(CO)_8$ and ligand (L) under H_2/CO pressure. According to recent works, the hydride species

can also be involved in the reaction of hydrogenation of enamines carbon-carbon double bonds. In the last several years, different metal catalysts have been employed for this reaction. Among the various catalytic systems so far (Ru, Ir, Pd, Rh)[16] have been applied to hydrogenation of enamines. In contrast, there has been no report on the hydrogenation of α-enamines with cobalt-modified catalysts. In the same context, there are few reports where α-enamines were used. Lau employed a copper complex for allylic amination of ketones,[17] Tamariz *et. al* have worked with non-symmetric α-ketones obtaining in the reaction mixture α-imino and α-enamino ketones, although they worked only with iminoketones as precursors of dienes on Diels-Alder reaction.[18] On the other hand, Klosin used α-enamines from 1,2-cyclohexane-diones to obtain unsymmetrical imino-enamine ligands.[19] Likewise, Zhang et. al recently worked in asymmetric hydrogenation of α-enamines interesting approach to amphetamines. Herein, we wish to report the synthesis of several new α-aminoketones by the cobalt-modified-catalyzed chemoselective hydrogenation of α-enaminoketones in the presence of H_2/CO.

2. Experimental

2.1 General

All reactions and manipulations were carried out under nitrogen atmosphere using Schlenk-type techniques. Column chromatography was performed on silica (70-230 mesh). The ^{1}H, ^{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. 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.

2.2 Typical procedure for synthesis of α-enaminoketones

A mixture of 5mmol of α-diketone and 5 mmol of aniline derivative in 10 mL of dried methylene chloride was stirred overnight in the presence of 2 mol % of $Mg(ClO_4)_2$ and 2g of $MgSO_4$ as drying agent. The organic solution was filtered and concentrated to give pure α-enaminoketone through silica gel flash chromatography (hexane/ethyl acetate).

2.3 Synthesis of complexes C_1-C_6

Under a N_2 atmosphere, phosphine ligand (2 mmol) **(L)** was added to a stirred solution of $Co_2(CO)_8$ (1 mmol) in tetrahydrofuran or toluene (10mL). The reaction mixture was stirred for 1 hour under CO bubbling at 50°C. The organic solvent was evaporated under reduced pressure. The resulting solid was washed several times with diethyl ether and pentane, finally dried under vacuum to give the desired complex.

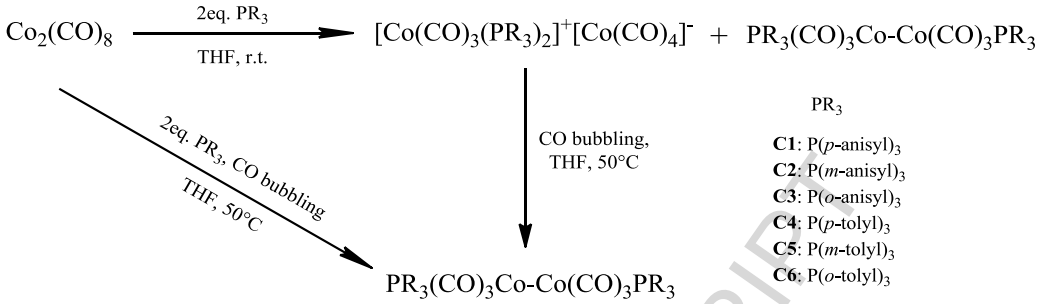
2.4 Procedure for hydrogenation of α-enaminoketones

To a solution of complex **C1-C6** (2 mol %) in THF (5mL) was added a solution of enamine (100mg) in THF (5mL) under N_2 atmosphere, and the mixture was stirred for 15 min. The solution was transferred to a 45 mL stainless steel Parr reactor under N_2 atmosphere. The reaction vessel was pressurized with H_2 and CO (1/3 ratio), then the reactor was immersed in an oil bath at 120°C during 30 hours. At the end of this time, the reactor was cooled and the gas mixture was liberated. The solution was concentrated and the product was purified by chromatography column on silica with hexane/ethyl acetate as eluent.

3. Results and discussion

3.1 Characterization of C1-C6 and crystal structure of C1, C2, C4 and C5 complexes

Different dimers were characterized by IR, elemental analysis, ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy and X-ray crystallography. Cobalt carbonyl dimers **C1-C6** of the type $[LCo(CO)_3]_2$ can be synthesized from $Co_2(CO)_8$ and phosphine ligand (L) in THF under CO bubbling at 50°C for 1h. However, in absence of CO, the mixture of dimer and $[CoL_2(CO)_3]^+[Co(CO)_4]^-$ salt are formed in few minutes(scheme 1), when this mixture is treated with CO bubbling at 50°C only the dimer was obtained, the named compounds were identified by comparison with similar cobalt salts.[20-21] When we used PPh_3 as ligand no CO bubbling is necessary.[22] However, using more basic phosphines the use of CO atmosphere is necessary in order to obtain the dimers as is previously reported by Klingler et al.[23] All cobalt phosphine salt derivatives shown bands at 1992 and 1868 cm^{-1}, in contrast the dimers showed a very strong single band at 1936 cm^{-1}(See Table S1 in the supporting information).



Scheme 1.

The ^{1}H and ^{13}C NMR spectra of different dimers show only small variations between the chemical shifts of the free and bonding ligands, furthermore in ^{13}C spectra shows a broad single signal resonance at δ 196 ppm(average), which could be assigned to the $(CO)_{terminal}$ groups. The ^{31}P spectra showed only one broad singlet for all complexes. The molecular structure of **C1**, **C2** and **C4**, **C5** complexes are shown in Figs.1-4. Crystallographic data are summarized in Table S2 (See supporting information), while select bond lengths (Å) and angles (°) are given in Table S3 and Table S4 (See supporting information). Several attempts to obtain suitable crystals of complexes **C3** and **C6** were unfruitful.

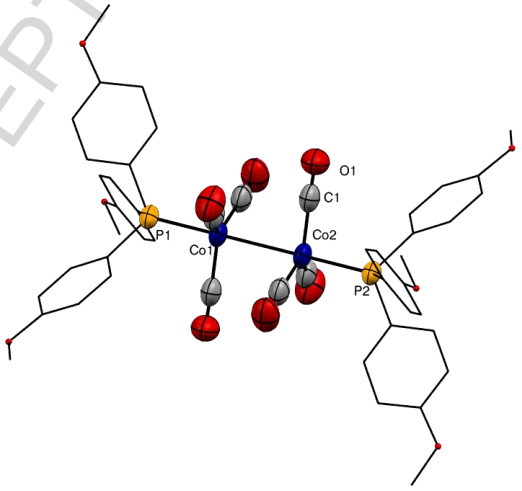


Figure 1. Molecular structure of $[Co_2(CO)_6\{P(p\text{-}MeO\text{-}C_6H_4)_3\}_2]$ **C1**. Hydrogen atoms were omitted for clarity.[24]

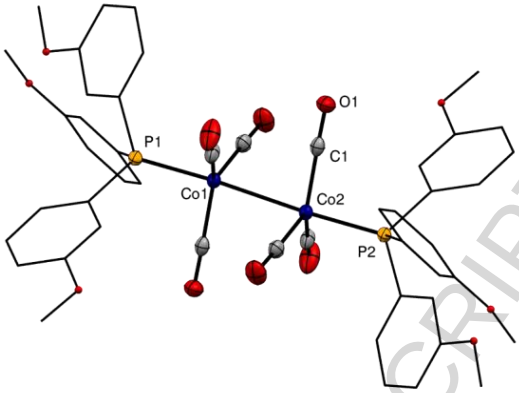


Figure 2. Molecular structure of $[Co_2(CO)_6\{P(m\text{-}MeO\text{-}C_6H_4)_3\}_2]$ **C2**. Hydrogen atoms were omitted for clarity.[24]

Crystals of **C1-C2** and **C4-C5** suitable for X-ray structure determination were grown by layering a saturated dichloromethane solution of complexes with diethyl ether. Complexes **C1**, **C4,** and **C2**, **C5** crystallize in hexagonal and triclinic systems, with space groups R-3 and P-1 respectively. The molecular diagrams of **C1**, **C2** and **C4**, **C5**, display dinuclear arrangement of trigonal $[Co(L)(CO)_3]$ units, in which the two phosphine ligand are observed in *anti*-position with respect to the Co−Co bond. Furthermore, the molecular structure shows that all carbonyl groups are terminal, and this conformation is associated with these types of molecules.[25] Cone angles were calculated according to the Tolman model[26] but using the real Co−P bond distance in all cases. The effective cone angles of molecular **C1**, **C2**, **C4** and **C5** were calculated as 145°, 148°, 145° and 148, respectively.

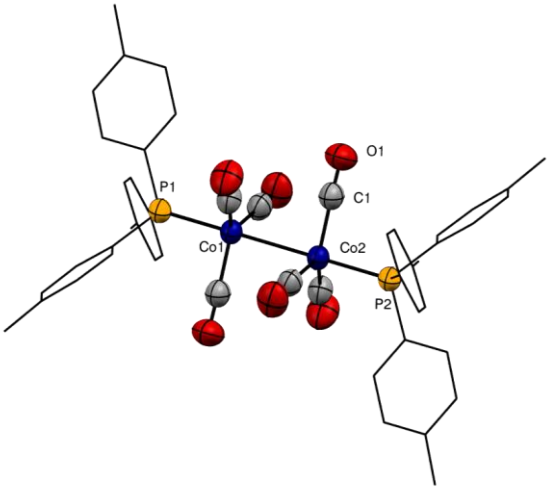


Figure 3. Molecular structure of $[Co_2(CO)_6\{P(p\text{-}Me\text{-}C_6H_4)_3\}_2]$ **C4.** Hydrogen atoms were omitted for clarity.[24]

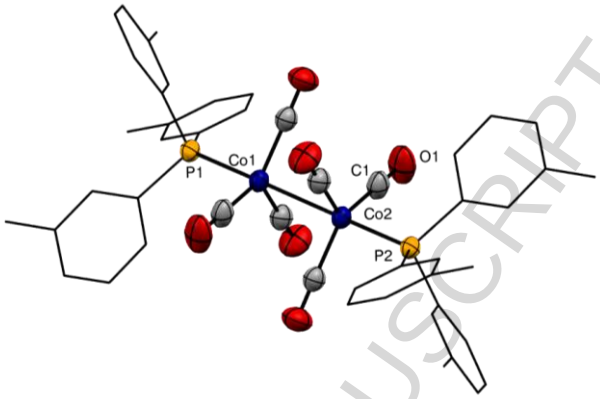


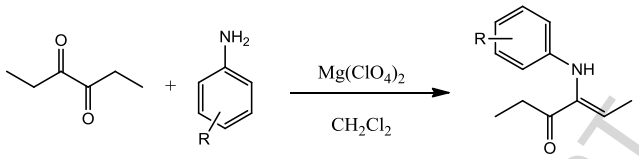
Figure 4. Molecular structure of $[Co_2(CO)_6\{P(m\text{-}Me\text{-}C_6H_4)_3\}_2]$ **C5.** Hydrogen atoms were omitted for clarity.[24]

For molecules **C1** and **C4,** the P−Co−Co angle is 180(°), unlike **C2** and **C5**, where angles are 175.22(2)(°) and 178.59(2)(°) giving a slight deviation from linearity. Furthermore, the distortion due to the ligand is also manifested in the angles of P−Co−CO, 94.13(°), 93.99(°, average), 94.31(°) and 94.99 (°, average), respectively (See Table S3 and S4). Co−Co bond distances in **C1**, **C4** and **C5** were found to be 2.883(1) Å, 2.671(13) Å and 2.671(5) Å, while that for **C2** was found to be smaller, 2.649(5) Å. The same trend was found for Co−P bond lengths in **C1** (2.197(1) Å), **C4** (2.193(14) Å), and **C5** (2.196(6) Å), which were longer than **C2** (2.185(6) Å). This could be attributed to the bulkiness of the methoxy group; this observation is consistent with that reported for similar cobalt complexes.[27] With these complexes in hand, we examine their efficiency in hydrogenation reaction of α-enamines.

3.2 Catalytic activities of cobalt carbonyl dimers(C1-C6) in hydrogenation of α-enaminoketones

Initially, we have prepared new α-enamino ketones by the reaction of α-diketones with aniline derivatives; the general procedure for preparation of enamines (**1a-7a**) was as follows. A mixture of amine derivative (2 mmol), the corresponding α-diketone (2 mmol), $Mg(ClO_4)_2$ (2 %mmol) in CH_2Cl_2 was stirred overnight (Table 1). At the end of the reaction the product was purified by chromatography column.

Table 1. Synthesis of α-enaminoketones using $Mg(ClO_4)_2$.



Entry	R_3	Compound	Yield %[a]
1	H	**1a**	86
2	*p*-MeO	**2a**	88
3	*p*-Me	**3a**	84
4	*p*-Cl	**4a**	83
5	*p*-F	**5a**	82
6	*m*-Me	**6a**	83
7	*m*-Cl	**7a**	80

[a]Isolated product.

All compounds described were characterized by various physicochemical methods. In MS-EI an *m/z* molecular ion peak was observed for all compounds, followed by a peak with a loss of the $[M^+\text{-}COC_nH_{n+2}]$ group. Analysis of these compounds by infrared spectroscopy reveals a strong band at 1668 cm^{-1}, due to the presence of the carbonyl group and vibrations corresponding to the N-H group at 3363 cm^{-1}. All compounds were characterized by ^1H, ^{13}C, DEPT 135, HETCOR, HMBC, COSY and NOESY experiments, where we found solely the Z isomer(See Figures S1 and S2 in the supporting information). The ^1H-NMR spectra analysis of the products supported this stereo structure, where the proton of N-H group appeared in the region of 5.97-6.12 ppm.[28]

Next, with the α-enaminoketones in hand, we examined hydrogenation for these compounds with different cobalt complexes synthesized under various conditions. We started our study with **1a** as standard substrate to optimize the reaction conditions, the results are summarized in Table 2. When the initial hydrogenation experiment was carried out under 12 hours reaction, it was found low conversion (entry 1). However, when it was worked upon prolonged reaction time the conversion is better (entries 2 and 3). When the reaction was carried out in the absence of the ligand, the product was obtained in low yield (entry 4). Moreover, no catalytic activity was found when it was worked-up with triarylphosphite, alkyl and tricyclohexyl phosphine ligands (entries 5-7). The same results were found when working only with hydrogen gas pressure (entries 9 and 10). The reactivity was lower when triphenylantimony ligand was used (Entry 8).

Table 2. Hydrogenation of α-enaminoketones under various conditions.[a]

Entry	$Co_2(CO)_8$	Ligand	H_2/CO[f]	Conversion %[b]
1[c]	2	$P(C_6H_5)_3$	1:3	34
2[d]	2	$P(C_6H_5)_3$	1:3	61
3[e]	2	$P(C_6H_5)_3$	1:3	83
4	2	-	1:3	30
5	2	$P(O\text{-}C_6H_5)_3$	1:3	0
6	2	$P(C_6H_{11})_3$	1:3	0
7	2	$P(C_2H_5)_3$	1:3	0
8	2	$Sb(C_6H_5)_3$	1:3	15
9	2	$Sb(C_6H_5)_3$	1:0	0
10	2	$P(o\text{-}CH_3C_6H_4)_3$, **C6**	1:0	0
11	2	$P(p\text{-}CH_3C_6H_4)_3$, **C4**	1:3	43
12	2	$P(m\text{-}CH_3C_6H_4)_3$, **C5**	1:3	70
13	2	$P(o\text{-}CH_3C_6H_4)_3$, **C6**	1:3	90
14	2	$P(p\text{-}FC_6H_4)_3$	1:3	32

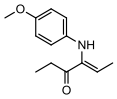
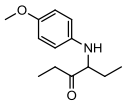
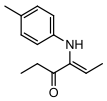
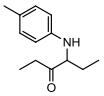
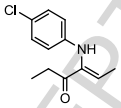
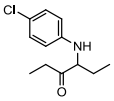
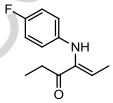
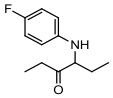
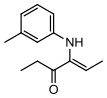
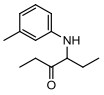
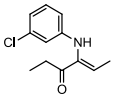
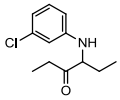
[a]Reaction conditions: 100mg of α-enamine **1a**, 2mol% of complex and dry THF (10mL) as solvent, time reaction 30h and 450psi (H_2/CO) and 120 °C. [b]Conversion determined by GC-MS. [c]12h. [d]24h. [e]30h.[f]This H_2/CO (1:3) is the best ratio previously found by our group.[14]

On the other hand, we investigated the substituent effect on the aromatic ring in the phosphine. An interesting effect was observed using methyl group in different positions on the aromatic ring. Gratifyingly, we found that the *o*-methyl substituted catalyst significantly improved the yield (entries 11-13). In contrast, the reactivity was low when the electron-donating methyl group was replaced by an electron-withdrawing fluoro group (entry 14).

With the optimized conditions obtained, we tested the previously synthesized (**C1-C6)** complexes in the hydrogenation reaction of α-enamines. Results are presented in Table 3. All reactions were carried out in tretrahydrofuran under 450psi (H_2/CO, 1:3 ratio) pressure with a catalyst loading of 2 mol%. Thus, we investigated the difference in the catalytic activity between the cobalt complexes in the hydrogenation reaction of enamines. It is interesting to note that all cobalt-modified complexes were active in the reduction reaction. Nevertheless, the conversion is strongly dependent on the substituent in the phosphine ligand; accordingly, we found that the general reactivity order for *methyl* substituted ligand in the catalytic promoters was

ortho>meta>para, where the *ortho* substituent gave the best yield, this behavior is evident for all results in table 3. In the *methoxy* cases no good correlation was found.

Table 3. Hydrogenation of α-enamines with different cobalt complexes.[a]

Entry	α-enamine	Complex	Product	Conv[b]/Yield[c] %
1	 **1a**	C1 C3	 **1b**	41 40/35
2	 **2a**	C1 C2 C3 C4 C5 C6	 **2b**	65 49 58 61/56 60/50 62/56
3	 **3a**	C1 C2 C3 C4 C5 C6	 **3b**	95/92 60 90/87 80/77 85/84 99/96
4	 **4a**	C1 C2 C3 C4 C5 C6	 **4b**	40 60 80 40 93 93/90
5	 **5a**	C1 C2 C3 C4 C5 C6	 **5b**	80 50 85/82 80 85 87/85
6	 **6a**	C1 C2 C3 C4 C5 C6	 **6b**	40 60/57 45 40 50 95/93
7	 **7a**	C1 C2 C3 C4 C5 C6	 **7b**	54 40 99/95 35 45 99/97

[a]Reaction conditions: 100mg of α-enamine, 2mol% of complex and dry THF (10mL) as solvent, time reaction 30h and 450psi (H_2/CO) and 120 °C. [b]Conversion determined by GC-MS. [c]Isolated product.

When working with **C1** and **C3** complexes, the expected product **1b** was found in a low yield (entry 1, table 3. vs entries 11-13, table 2). Additionally, the presence of *p*-MeO group on the substrate **2a**, resulted in low yields (entry 2, table 3). This last behavior could be attributed to steric effect of the substituent in the substrate, also the involvement of non-bonding electrons on *p*-MeO group promotes electronic delocalization to form an iminic group conjugated with C=C bond. Consequently, a retardatory effect on hydrogenation rate must be observed. In contrast, when the reaction was carried out with **3a** and the six complexes (**C1**-**C6**), gave excellent yields among the six (entry 3). We also examined the reaction with electron-withdrawing groups. *p*-Cl and *p*-F substituted on the substrate afforded the corresponding products **4b** and **5b** with good yields (entries 4 and 5). Whereas *m*-Cl and *m*-Me substrates **6a** and **7a** gave the expected products **6b** and **7b** in low yields (entries 6 and 7). However, complexes with substituents in *ortho*-position showed the best results (entry 6, **C6**, 95% and entry 7, **C3** and **C6**, 99%). Noteworthy, the reduction was chemoselective over double bond. This is an advantage, because the carbonyl group can be used for additional functionalization or transformation.[29] In order to evaluate the source of chemoselectivity in this process, we have focused our attention in enaminic nitrogen on substrate, the lone pair on nitrogen should be coordinated to cobalt ion, approximating and activating C=C bond more than C=O bond. Additionally, at our experience with this kind of substrates we have never found carbonyl reduction using $HCo(CO)_3L$ species.

4. Conclusion

In summary, we have developed a methodology for the hydrogenation of α-enaminoketones to corresponding α-aminoketone compounds with good conversion using cobalt complexes. Likewise, we have found that all complexes were active in the hydrogenation reaction, obtained the best result when we used *ortho*-methyl-substituted ligand. This catalytic system is straightforward and easy to prepare. The use of this complex in the catalytic asymmetric hydrogenation is being currently under investigation in our laboratory. Studies conducting to elucidate the mechanism of this reaction are in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

Notes and references

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Graphical Abstract

Hydrogenation of α-enaminoketones with cobalt phosphine-modified catalysts[1]

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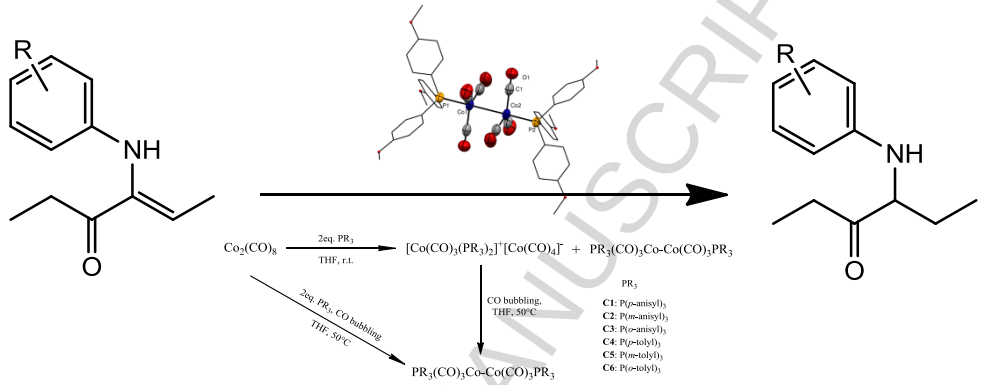

Research Highlights

The first example of catalytic hydrogenation of α-enamino-ketones with $L(CO)_3Co\text{-}Co(CO)_3L$.

Good yields of secondary α-amine-ketones were obtained.

Completely chemo selective reaction.

Ortho-substituted phosphines gave the best results.