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Cobalt-Catalyzed Enantioselective Hydrogenation of Trisubstituted Carbocyclic Olefins: An Access to Chiral Cyclic Amides

Soumyadeep Chakrabortty, Katharina Konieczny, Felix J. de Zwart, Eduard. O. Bobylev, Eszter Baráth, Sergey Tin, Bernd H. Müller, Joost N. H. Reek, Bas de Bruin, and Johannes G. de Vries*

In memory of Professor Paul C. J. Kamer

Abstract: The enantioselective hydrogenation of cyclic enamides has been achieved using an earth-abundant cobalt-bisphosphine catalyst. Using CoCl₂/(S,S)-Ph-BPE, several trisubstituted carbocyclic enamides were reduced with high activity and excellent enantioselectivity (up to 99 %) to the corresponding saturated amides. The methodology can be extended to the synthesis of chiral amines by base hydrolysis of the hydrogenation products. Preliminary mechanistic investigations reveal the presence of a high spin cobalt (II) species in the catalytic cycle. We propose that the hydrogenation of the carbon-carbon double bond proceeds via a sigma-bond-metathesis pathway.

Introduction

Enantioselective hydrogenation has emerged as one of the most atom-economic strategies for the synthesis of enantiopure saturated motifs from their prochiral precursors.[1] Many important pharmaceuticals and agrochemicals are produced on large scale via asymmetric hydrogenation.[2] The catalytic performance is strongly influenced by the presence of coordinating groups in the substrate and the catalyst-substrate interactions which guide the chirality transfer to the product. Enantiopure carbocyclic motifs such as chiral cyclic alkanes, amines, amides, ethers, esters etc. are commonly found in important pharmaceuticals and numerous bioactive molecules.[3] Among the various synthetic methods for the preparation of such molecules, enantioselective hydrogenation of the cyclic substrates bearing their corresponding unsaturated double bonds (C=C, C=C, C=O) is one of the most desired and environmentally benign strategies. The catalytic activity and stereo-selectivity are also highly influenced by the ligands employed in the reaction. Chiral phosphines have performed the best thus far in asymmetric hydrogenation of functionalized and minimally functionalized cyclic alkenes.[3] Mixed donor P,N ligands developed by Pfaltz’s group,[26] Andersson’s group[28] and Diéguez’s group[4] have also been successful, delivering a high degree of enantioselectivity for several types of olefins.[5]

Enantio-induction in asymmetric hydrogenation of some prochiral olefins such as the cyclic trisubstituted alkenes with amide functionalities is still a challenging task, especially the β-derivative (i.e., 2-substituted derivatives). The asymmetric hydrogenation of this class of olefins is highly desirable, as their corresponding chiral amine derivatives such as the prostanoid (TP) antagonist),[9] Indatraline (antidepressive agent)[9] have therapeutic properties (Figure 1, top). Very often, the chiral amide synthesis relies on the use of transition metal catalysis (Figure 1, middle); although still very few catalysts are known to deliver excellent ee’s in the reduction of this particular class of cyclic olefins. For example, N-(2,4-dihydropyridine-2-yl) acetamide was hydrogenated using Ru-BINAP as catalyst affording 90–95 % ee.[11] Zhang and co-workers reported the Rh/PennPhos catalyst for asymmetric hydrogenation of cyclic enamides where excellent enantiomeric purity was observed in the case of several α-enamides up to > 99 %, and up to 71 % ee in the case of β-derivatives.[14] Three years later, the same group also observed similar selectivities using Rh/α-Ph-hexa-MeO-BIPHEP as catalyst for the hydrogenation of α-enamides.[15] Minnaard, de Vries, Feringa and co-workers reported the use of a Rh/phosphoramidite catalytic system,
achieving up to 94 % enantioselectivity.\[16\] Reek, de Vries and co-workers also achieved 94 % ee with a supramolecular Rh-catalyst.\[17\] Riera, Verdaguer and co-workers utilized the MaxPHOS ligand for the Ir-catalyzed asymmetric hydrogenation of several cyclic enamides, where 99 % ee was achieved at a relatively low partial pressure of hydrogen (H\(_2\)).\[18\] Pàmies, Diéguez and co-workers applied their P,N (phosphite-oxazoline) ligand family for the Ir- and Rh-catalyzed hydrogenation of several classes of olefins resulting in excellent enantioselectivities.\[19\] Use of a novel C2-symmetric P-chirogenic bisphosphine WingPhos developed by Tang and co-workers also resulted in excellent ee.\[20\]

Using the C2-symmetric P-chirogenic bisphosphine WingPhos developed by Tang and co-workers also resulted in excellent ee.\[20\] However, most of these methods depend on the use of precious metals such as rhodium, ruthenium and iridium (as described in Figure 1, bottom) for their remarkable activity and robustness. The high costs and volatile prices of the late transition metals have made researchers think about alternatives. The replacement of precious metals by earth abundant first-row transition metals has become an active area of research since the last decades.\[21\] 3d-Metals possess different chemical properties compared to their 4d or 5d congeners due to smaller d-orbital splitting. Very often this makes the 3d-transition metal catalysts to operate via different mechanisms, as well as results in different deactivation pathways of these compared to noble metal catalysts. Especially in asymmetric hydrogenation 3d metals can offer advantages, such as novel reactivity, altered selectivity, different mechanism, or reduced catalyst cost. Therefore, a de novo strategy has to be followed by the chemists for the transition of precious metals to the first-row transition metals.

Figure 1. Selected examples of drugs containing a cyclic chiral amine-scaffold (top); Schematic representation for the synthesis of chiral amide via asymmetric hydrogenation (middle); State of the art of chiral catalysts for enantioselective hydrogenation of cyclic enamides (bottom).
Although cobalt catalysts have been used frequently in homogeneous hydrogenation reactions,[23] since the pioneering work by Yoshimura in 1973 on enantioselective olefin hydrogenation by the bis(dimethylglyoximato)cobalt(II)-quinine complex,[24] not much progress has been made in this direction of research until 40 years later Chirik and co-workers discovered via high throughput screening that bis-(iminopyridine-Co)[3] and bisphosphine-Co[5] are sufficiently active for the hydrogenation of unprotected and functionalized olefins delivering excellent enantioselectivities.[24] Since then, enantioselective hydrogenation of C=C bonds using 1st row transition-metals (such as cobalt and nickel) has become an active area of research, especially in the last seven years.[25,26] Following our long-standing interest in transition metal catalyzed asymmetric hydrogenation, herein, we report the cobalt catalyzed enantioselective hydrogenation of carbocyclic enamides. Employing CoCl$_2$ in combination with a commercially available chiral bisphosphate as ligand, excellent yields and enantioselectivities have been achieved. Hydrolysis of the resulting chiral amides resulted in the cyclic chiral amines with high optical purities which are of high interest for the preparation of active pharmaceuticals. Additional experiments, including electron paramagnetic resonance (EPR) spectroscopy and Mass spectrometry, have been carried out to shed light on the mechanistic cycle.

**Results and Discussion**

_**Reaction Development, Optimization, and Scope**_

We started our initial screening with the hydrogenation of $N$-(3,4-dihydropyridin-2-yl)acetamide (1a) using different cobalt precursors in combination with the air stable P-chiral bisphosphine ligands (R,R)-QuinoxP* (L1) and (S,S)-Ph-BPE (L5) (Table 1). Cobalt tetrafluoroborate hexahydrate [Co(BF$_4$)$_2$·6H$_2$O] was inactive in the hydrogenation of 1a using (R,R)-QuinoxP* (L1) as ligand (Table 1, entry 1), whereas >99% conversion was achieved using (S,S)-Ph-BPE (L5) as ligand (entry 2, Table 1). Moderate enantioselectivity was observed (e.r. 71:29) in the presence of this metal precursor. Cobalt acetyacetonate [Co(acac)$_2$] and dicyclobutylcarbonyl [Co(CO)$_2$] were found to be completely inert for this transformation, using (R,R)-QuinoxP* (L1) and (S,S)-Ph-BPE (L5) in MeOH (Table 1, entries 5–8). [Co(stearate)$_2$](S,S)-Ph-BPE (L5) was active in MeOH delivering moderate enantioselectivity (e.r. 72:28) with full conversion, although [Co(stearate)$_2$](R,R) QuinoxP* (L1) failed to catalyze the reaction. Anhydrous cobalt (II) chloride with (S,S)-Ph-BPE afforded full conversion of the starting material to the desired product with a promising ee of 88%.

The solvent effect on the reactivity and enantioselectivity was also thoroughly examined. Following the lead of the high activity of CoCl$_2$(S,S)-Ph-BPE in polar protic medium, several alcoholic solvents were screened. The results are outlined in the Supporting Information (Table S1). [Co-BF$_4$]$_2$6H$_2$O/(S,S)-Ph-BPE (L5) did not yield the desired product in iso-propanol (i-PrOH) and trifluoroethanol (TFE), whereas full conversion was achieved in tert-butanol (t-BuOH) with up to 88% of ee. [Co(acac)$_2$](S,S)-Ph-BPE (L5) also resulted in no conversion in different alcoholic solvents (Table S1, Supporting Information). Surprisingly, CoCl$_2$(S,S)-Ph-BPE (L5) was found to be active only in methanol (MeOH), while use of other protic solvents resulted in sluggish reactions. On the other hand, [Co(stearate)$_2$](S,S)-Ph-BPE (L5) was fairly active in most of the screened solvents. Full conversion was achieved in methanol (MeOH), ethanol (EtOH) and isopropanol (i-PrOH) with up to 78% of enantioselectivity (Supporting Information, Table S1). Excellent ee (up to 90%) was observed in tert-butanol (t-BuOH) and trifluoroethanol (TFE) at the cost of >50% conversion of the starting enamide (Table S1, Supporting Information). The effect of the ligand in the asymmetric hydrogenation was also

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**Table 1**: Evaluation of different Co-precursors in the asymmetric hydrogenation of enamides 1a using BPE and QuinoxP* as chiral ligands.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Co]</th>
<th>Ligand</th>
<th>Conversion of 1a [%]</th>
<th>Enantiomeric ratio (e.r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Co(BF$_4$)$_2$·6H$_2$O</td>
<td>(R,R)-QuinoxP*</td>
<td>&gt;99</td>
<td>71:29</td>
</tr>
<tr>
<td>2</td>
<td>(S,S-BPE)</td>
<td>&gt;99</td>
<td>71:29</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CoCl$_2$</td>
<td>(R,R)-QuinoxP*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>(S,S-BPE)</td>
<td>&gt;99</td>
<td>94:6</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Co(acac)$_2$</td>
<td>(R,R)-QuinoxP*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>(S,S-BPE)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Co(CO)$_2$</td>
<td>(R,R)-QuinoxP*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>(S,S-BPE)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Co(stearate)$_2$</td>
<td>(R,R)-QuinoxP*</td>
<td>&gt;99</td>
<td>72:28</td>
</tr>
<tr>
<td>10</td>
<td>(S,S-BPE)</td>
<td>&gt;99</td>
<td>72:28</td>
<td></td>
</tr>
</tbody>
</table>

[a] Reaction conditions: [Co] (5 mol%), Ligand (5 mol%), solvent = MeOH, H$_2$ (60 bar), temperature = 60 °C, reaction time = 16 h. Conversion was determined by GC using internal standard (dodecane), GC-MS and NMR analysis. Enantiomeric ratio was determined by chiral HPLC (see Supporting Information for the HPLC method).
studied using several bidentate phosphines (Figure 2). Axially chiral (R) or (S)-BINAP (L2 and L3) failed to catalyze the reaction using CoCl₂ as metal precursor in methanol. The catalyst based on (R,R)-Chiraphos (L4) was also found to be inactive. The use of (S,S)-Me-DuPhos (L7) and (R)-Xyl-Garphos (L10) resulted in very low conversions of the cyclic enamide 1a. The complexes based on (S)-Phanephos (L8) and L9 also failed to catalyze the hydrogenation of 1a. The reactivity of the CoCl₂/(S,S)-Ph-BPE catalyst was decreased upon lowering the temperature below 60°C. However, the enantioselectivity remained almost the same even at lower temperatures, up to 90%. The hydrogenation of 1a at 30°C provided <5 % conversion using 60 bar of H₂ pressure (Figure S54, see Supporting Information). In order to check the catalytic activity, several other catalysts based on noble metals and 1st row transition metals have also been employed for the asymmetric hydrogenation of 1a using (S,S)-Ph-BPE as ligand (Supporting Information, Table S2). Typical iridium precursors used for olefin hydrogenation results was evaluated. The presence of a methoxy substituent on the fused benzene ring was well tolerated by the catalyst and led to no deleterious effects on yield or enantioselectivity. Enamide 1b (5-OMe) was hydrogenated in 90% enantiomeric excess to 2b, a potential precursor in the synthesis of Rotigotine (Figure 1, top). Increased enantiomeric excess could be obtained by increasing the steric bulk of the amide group in the 5-OMe enamides. For instance, the enamides 2j (tert-butyl), 2k (ethyl), 2l (di-Pr), and 2m (cyclohexyl) were near-quantitatively hydrogenated with enantioselectivities up to 98 %. The benzamide was hydrogenated to 2n (82 % ee). The other regioisomers of 1i, namely 1o (6-OMe), 1q (7-OMe) and 1x (8-OMe) were hydrogenated with similar enantioselectivity (up to 91 %). A similar trend was also noticed with the other methoxy derivatives such as 2p (6-OMe, tert-butyl), 2r (7-OMe, ethyl), 2s (7-OMe, i-Pr), 2t (7-OMe, tert-butyl), 2u (7-OMe, cyclohexyl), 2v (7-OMe, phenyl), where up to >99 % ee was achieved. The enamide 2w with a long alkyl chain, derived from the corresponding stearic acid derivative was also hydrogenated with excellent yield and 88 % ee. A β-cyclic enamide with an electron-withdrawing group (bromine, Br) at the 6-position of the fused benzene ring was hydrogenated in excellent yield and with 84 % ee. Additionally, we have also investigated the hydrogenation of e-enamides employing the same catalytic conditions. The enamides 1z (from α-tetralone), 1aa (from 4-chromanone), 1ab (from thiochroman-4-one), 1ac (6-OMe), 1ad (5,7-dimethyl) and 1ae (7-bromo) were hydro-

Figure 2. Ligand screening in the asymmetric hydrogenation of 1a, reaction conditions: [Co] (5 mol%), Ligand (5 mol%), solvent = MeOH, H₂ (60 bar), temperature = 60 °C, reaction time = 16 h. Conversion was determined by GC and NMR analysis.
Scheme 1. Substrate evaluation using the Co/BPE catalyst. Reaction conditions: [CoCl₂] (5 mol%), (S,S-Ph-BPE) (5 mol%), solvent = MeOH, H₂ (60 bar), temperature = 60 °C, reaction time = 18–20 h. Conversion was determined by GC using internal standard (dodecane), GC-MS and NMR analysis. Enantiomeric ratio was determined by chiral HPLC (see Supporting Information for the HPLC method).
generated in excellent yields and enantioselectivities up to 99%. The seven-membered enamide 1af (from 1-Benzosuberone) was also hydrogenated with 86% ee and 97% yield.

However, the similar trisubstituted cyclic enamide (3-benzoylaminocoumarins) carrying an additional oxo functionality at the 2-position (substrate 1ag) could not be hydrogenated under the optimized reaction conditions. Hydrogenation of cyclohexane-based tetra-substituted olefins was also examined using the Co/BPE catalyst. Unfortunately, this catalyst failed to convert the cyclohexane derived tetrasubstituted enamides (Scheme 1: N-(2-benzylecylclex-1-en-1-yl)acetamide, 1ah and N-(3,4,5,6-tetrahydro-1,1'-biphenyl)-2-yl)acetamide, 1ai), which belong to the most challenging class of substrates in the asymmetric hydrogenation of olefins. These findings indirectly suggests that the specific mode of substrate-coordination or substrate-binding in the active catalyst is also an important factor in the Co-catalyzed asymmetric hydrogenation.[27]

Mechanistic Studies

Whereas the mechanisms of Rh- and Ir-catalyzed asymmetric hydrogenations have been studied extensively, investigation of the mechanism of cobalt-catalyzed hydrogenation is much more problematic because of its unclear oxidation state(s) in hydrogenation reactions. Aside from this, the other factor that makes cobalt catalysis puzzling is the spin state(s) in hydrogenation reactions. Aside from this, the spin state(s) in hydrogenation reactions. Aside from this, the spin state(s) in hydrogenation reactions. Aside from this, the spin state(s) in hydrogenation reactions. Aside from this, the spin state(s) in hydrogenation reactions. Aside from this, the spin state(s) in hydrogenation reactions. Aside from this, the spin state(s) in hydrogenation reactions. Aside from this, the spin state(s) in hydrogenation reactions. Aside from this, the spin state(s) in hydrogenation reactions.
These findings with substrates 1o, 1z and 1aa clearly show that cyclic enamide (both α- and β- isomers) hydrogenation is an isomerization (imide-enamide tautomerization) free asymmetric direct hydrogenation (ADH) process with molecular hydrogen (H₂). Next, we conducted several EPR experiments mimicking the catalytic conditions using 1a as model substrate to get an insight about the catalytically active species (abbreviated as cs, as described in the proposed mechanism). First, we performed an EPR measurement of a mixture where the CoCl₂, BPE and substrate is dissolved in MeOH and heated up to 60°C. The EPR spectra (Figure S75, see Supporting Information for further details) shows the presence of high spin (S = 3/2) Co(II) species. Next, we conducted a high pressure EPR measurement using 10 bar of H₂ (pressure limit of the tube: 13 bar) where a similar signal was observed corresponding to Co(II), S = 3/2 (Figure S76 and S77, see Supporting Information). In the following experiment, the sample was prepared following the standard catalytic conditions in a high-pressure autoclave and then subjected to EPR measurement after 6 h (as we observed ≈ 20% conversion of the starting material using 1a, which confirmed the formation of the active catalyst in the reaction mixture) to identify the involved species (Figure 3b). Absence of any low spin (S = 1/2) Co(II) or zero valent Co (S = 1/2) species strongly suggests the involvement of Co(III) as an active metal centre in the hydrogenation activity of the cyclic enamides (Figure S78, see Supporting Information for the detailed protocol).
followed). We assume that after formation of the cobalt monohydride $\text{cs1}$ migratory insertion of the alkene occurs. Then the hydrogen complex $\text{cs2}$ forms which undergoes a sigma bond metathesis pathway through a redox neutral catalytic cycle (Scheme 2). Related to this, Hopmann and co-workers have lately proposed a non-redox reaction pathway for Co/bisphosphine catalyzed selective allylic and homoallylic alcohol hydrogenations.[27] A similar mechanism was also proposed for the Co-catalyzed asymmetric hydrogenation of unsaturated carboxylic acids by Zhang and co-workers.[26c] To support this observation further, an additional experiment using triethylamine ($\text{Et}_3\text{N}$) was performed. It is expected that the chloride abstraction from the Co-precursor is much easier in the presence of additional base under reductive conditions, which could potentially form a Co$^0$ species that can undergo oxidative addition of dihydrogen. Following this idea, we measured the EPR of the reaction mixture with $\text{Et}_3\text{N}$, where it shows indeed the presence of a Co$^0$ species ($S = 1/2$) (Figure S79, see Supporting Information for the detailed protocol followed). However, the catalytic activity was not the same, as >60% conversion was achieved using $\text{1a}$ as model substrate using 60 bar of H$_2$ pressure in MeOH with a decrease in enantioselectivity (40% ee). The diminished activity and selectivity of the cobalt catalyst suggests the involvement of a different mechanism (Supporting Information, Figure S82) for the enantio-induction compared to our standard catalytic conditions. Furthermore, several mass spectrometric measurements were carried out using the model substrate $\text{1a}$ using the optimized catalytic conditions with the aim of identifying the possible involved species in the catalytic cycle. After 2 h of reaction without addition of hydrogen the sample was analyzed with mass spectrometry. Two species were observed that could potentially be involved in the catalytic cycle: (a) m/z 600.13 which is ligand bound cobalt chloride; (b) m/z 787.23 which is ligand- and substrate-bound cobalt chloride; have been detected (Fig 3c).

Based on our experimental findings, the EPR and mass experiments and the literature precedence,[26c, 27] we propose the following mechanism for the Co/bisphosphine catalyzed asymmetric hydrogenation of enamides via a redox neutral catalytic cycle (Scheme 2). In the first step, the catalyst-substrate complex $\text{cs0}$ reacts with hydrogen to form the mono-hydride complex $\text{cs1}$. This could occur through reaction of hydrogen with the cationic monochloro-complex, followed by loss of a proton. The binding of the amide group presumably adds to the stability of this intermediary cationic complex. Alternatively, this conversion could proceed via direct metathesis of $\text{cs0}$ with hydrogen.[30] Next, migratory insertion of the alkene leads to cobalt-alkyl complex $\text{cs2}$. This complex reacts with hydrogen to from $\text{cs3}$. Sigma-bond metathesis of $\text{cs3}$ leads to formation of the mono-hydride complex $\text{cs4}$ to which the product remains bound via the amide bond. Exchange of product for substrate to form $\text{cs1}$ closes the catalytic cycle. It is not clear at what stage of the catalytic cycle the substrate inhibition occurs. Possible candidates are $\text{cs1}$, where binding of a second substrate molecule via its amide oxygen atom could displace the alkene binding of the first substrate molecule, as well as $\text{cs2}$ where an additional substrate molecule could bind via its amide bond and thus inhibit hydrogen bonding. For the product inhibition there are even more possibilities. The most obvious one is $\text{cs4}$ where the product needs to dissociate and the substrate needs to bind either via a dissociative or an associative
mechanism. But similar inhibition on cs1 and cs2 by binding via the amide oxygen is equally possible.

**Gram Scale Synthesis and Application**

The hydrogenation of 1a and 1z was performed on gram scale (6.0 mmol) with high yield and a high degree of enantioselectivity, as documented in the scalability protocol (See Supporting Information for details). Compound 2a and 2z were synthesized in both enantiomeric (R and S) forms using the S,S- and R,R-Ph-BPE ligand (Scheme 3a and b).

This synthetic protocol was also extended to the synthesis of the chiral primary amines from their corresponding chiral amides. 1,2,3,4-Tetrahydroanaphalen-1-amine 3z was synthesized with full retention of configuration in both enantiomeric forms by hydrolysis of amide 2z under basic conditions (Scheme 3b).

**Conclusion**

In summary, we have developed a highly efficient Co-catalyzed enantioselective hydrogenation of tri-substituted carbocyclic enamides, a challenging class of substrates with regard to enantio-induction. Excellent enantioselectivity (up to > 99 %) and yield have been achieved using Co<sup>II</sup>-BPE as hydrogenation catalyst for a range of cyclic enamides derived from the corresponding α- and β-tetralones. Experimental evidence based on mass spectrometry, EPR and isotope labelling indicate the possible involvement of a high spin Co<sup>II</sup> species in the catalytic cycle, and we propose that hydrogenation proceeds via a sigma-bond metathesis pathway to produce the chiral amides. This methodology, based on the use of a commercially available chiral bisphosphine ligand (Ph-BPE), for the production of chiral amides from their endocyclic prochiral enamides via the asymmetric hydrogenation strategy, expands the possibilities for the use of earth-abundant transition metals in asymmetric catalysis.
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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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