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Concise synthesis of Azilect via cobalt-catalyzed enantioselective hydrogenation in a bio-based solvent†

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An asymmetric synthesis of rasagiline (Azilect), an anti Parkinson's therapeutic, was developed employing an earth-abundant metal catalyst in a bio-based solvent. The asymmetric hydrogenation of the indane-derived enamined was performed using [Co(OTf)2]/(S,S)-BPE as the precatalyst as the key step for enantioselection. The effect on enantio-induction in structurally different indenyl acetamides was also examined. Rasagiline was synthesized in 70% overall yield and 98% ee. Based on the experimental results, including isotope labelling and EPR studies, we propose the involvement of a redox active Co(0)/Co(II) cycle in the asymmetric hydrogenation pathway.

Introduction

Chiral amines cover a wide range of small molecule pharmaceuticals, agrochemicals and many other industrially relevant fine chemicals.1,2 Chiral primary and secondary amines have been used as building blocks for asymmetric synthesis, preparation of natural products, chiral auxiliary or as resolving agents. Resolution via crystallization of diastereomeric salts is still used regularly for their preparation in enantiopure form. A number of catalytic methods have widely been established and investigated in the last decades using transition metal stereo-selective catalysis as the key tool covering a range of structural diversity.3 The used methods comprise asymmetric allylic amination,4 hydroamination of alkenes,5–8 reductive amination of ketones9–13 and addition of alkyl/aryl nucleophiles to imines.14,15 Nevertheless, enantioselective reduction of N-containing unsaturated compounds, such as asymmetric hydrogenation (AH)16 of imines,17 enamines18 or enamides,19 is considered to be atom economic, efficient, and more sustainable. Various transition metals in combination with chiral phosphines have shown excellent chemo, regio and enantioselectivity in asymmetric direct hydrogenation (ADH) processes.20 As a result, many large scale processes21 involving asymmetric hydrogenation as the key step, such as the synthesis of an intermediate for DMP 777 (human leukocyte elastase inhibitor) (Bristol-Myers Squibb process),22 the synthesis of the unnatural β-aryl-α-amino acid for the preparation of dual CCK1/CCK2 receptor antagonist (Johnson & Johnson process),23 production of Aliskirin intermediate (DSM process),24 preparation of a chiral allylic acylamine intermediate (Takeda process) for the drug rozerem or ramelton (treatment for insomnia),25 and certainly more have been developed during last two decades. In most cases, the 4d or 5d metals such as rhodium, ruthenium or iridium have prevailed over others because of remarkable robustness and activity.26,27 However, the high cost, fluctuating prizes and the limited supply of precious metals,28–31 has inspired researchers to seek an alternative to the precious metal catalysis.32 Due to their abundance and much lower cost, use of first-row transition metals is quite attractive for use in catalysis, although challenges exist with the usage of 3d metals due to their lower electronegativity, smaller d-orbitals, and the propensity towards one electron chemistry. After the discovery of cobalt catalyzed asymmetric hydrogenation of functionalized olefins33 via high throughput screening, first row transition metals34 in asymmetric hydrogenation35 have become an attractive and important area of research, especially Co-catalyzed enantioselective olefin hydrogenation. The use of readily available cobalt precursors and enantiopure ligands have generated highly active catalysts for the synthesis of levetiracetam,36 hydrogenation of N-functionalized amines,37 α,β-unsaturated carboxylic
acids, functionalized alkenes, enynes, azole derived tri-substituted alkene, and other unsaturated compounds. A handful of Rh-based homogeneous catalysts are known for the preparation of chiral N(-indan-1-yl)-acetamide (1b) or, 1-indanamine (1c). Construction of such chiral N-building blocks is essential for the preparation of active pharmaceuticals, such as rasagiline (anti Parkinson’s therapeutic), ladostigil (treatment for neurodegenerative disorders), indatraline (antidepressive agent) or Aficamten (CK-274, ph. II candidate for cardiomyopathy). Initial developments for the synthesis of rasagiline (or chiral amino-indane derivatives) were mainly based on the use of classical resolution (Fig. 1b), where 50% loss of yield was the major drawback. A gram-scale chemoenzymatic dynamic kinetic resolution method and a biocatalytic (imine reductases) method have also been reported recently, producing rasagiline in moderate yield but with high enantioselectivity.

Encouraged by our previous results on cobalt-catalyzed olefin hydrogenation, we envisioned that the corresponding cyclic enamide (Fig. 1c) could serve as substrate for the synthesis of indane-amide derived active pharmaceuticals via asymmetric hydrogenation.

Herein, we report the asymmetric synthesis of (R)-rasagiline (Azilect: treatment of Parkinson’s disease) via enantioselective hydrogenation of indanone-derived trisubstituted enamide as the key step (Fig. 1, bottom). Using cobalt trflate [Co(OTf)₂] as precursor and commercial bisphosphines as ligand, excellent yields and enantioselectivities could be obtained in the preparation of the indane-amide, which was further hydrolysed to the corresponding amine. Propargylation of the enantioenriched amine resulted in the desired product (rasagiline). Additional investigations involving control experiments, isotope labelling and EPR studies were performed to investigate the mechanism of the asymmetric hydrogenation step.

Results and discussion

We started our investigation using [Co(stearate)₂] as metal precursor and commercial chiral bisphosphines (S,S)-PhBPE and (R,R)-QuinoxP* as ligands (Table S1†). [Co(stearate)₂]/(R,R)-QuinoxP* was found to be completely inactive in polar protic solvents (entry 5–8, Table S1†) for the hydrogenation of N-(1H-inden-3-yl)-acetamide (1a) using 60 bar of H₂ pressure at 60 °C, although full conversion was achieved in iso-propanol albeit with poor enantioselectivity using (S,S)-PhBPE as ligand (entry 2, Table S1†). The enantiomeric ratio was increased (50%) upon changing the solvent to tert-butanol at 75% conversion of 1a. Altering the [Co] source to CoCl₂ also resulted in 40% ee (entry 1, Table S2†) at 70% conversion. Catalysts based on the bidentate phosphines (S,S)-MeDuPhos and (R,R)-QuinoxP* with CoCl₂ did not catalyze the hydrogenation in different alcoholic solvents (entry 5–12, Table S2†). Several 1st row-metal based precursors were also examined (Table S3†). Most of them were inactive in the hydrogenation except the catalyst generated by NiCl₂/(S,S)-PhBPE which resulted in 70% conversion with 40% ee. To our delight, both the reactivity and enantioselectivity were increased upon addition of additives. Use of CoCl₂/(S,S)-PhBPE resulted in full conversion with 80% ee in MeOH (entry 1, Table S4†) using 50 mol% Zn as an additive. A similar ee was also observed in TFE although conversion was low. Use of CoCl₂/(S,S)-MeDuPhos resulted in poor activity and selectivity (entry 3 and 4, Table S4†).

The effect of the counter anion in the hydrogenation was also thoroughly investigated using different Co(n) precursors (Fig. 2). Use of [Co(acac)₃] and [Co(oxalate)₂] resulted in up to 82% ee although poor conversions were obtained (Fig. 2). Other dihalides (F, Br, I), the stearate and the BF₄ salt of [Co]+ resulted in up to >99% conversion and up to 85% ee (Fig. 2). The [Co(OTf)₂]/(S,S)-PhBPE was found to be the best precatalyst in MeOH which produced N-(2,3-dihydro-1H-inden-1-yl)-acetamide (1b) in 88% ee.

The effect of different bidentate commercial chiral phosphines was also studied using these optimized conditions (Table 1). The catalysts based on Co(OTf)₂ and axially chiral (S)-BINAP, P-chiral QuinoxP* and BenzP* failed to catalyze the hydrogenation at 50 °C and 50 bar of H₂ pressure (Table 1, entry 6–8). Although use of (S)-Xyl-GarPhos and JosiPhos resulted in up to 99% conversion the ee remained low at 50% (Table 1, entry 1 and 2).

The complex based on (R,S)-DuanPhos catalyzed the hydrogenation to 60% conversion and 64% ee (Table 1,
entry 5). The effect of the substituents (alkyl/aryl) of the cyclic phospholane (BPE ligand class) was also investigated in the Co-catalyzed hydrogenation of 1a. The catalyst (in situ) prepared by using the \((R,R)\)-iPrBPE resulted in only 80% conversion and 76% ee (Table 1, entry 4), whereas use of \((S,S)\)-PhBPE resulted in full conversion with 88% ee (entry 3, Table S5). Thus, the \((S,S)\)-PhBPE was chosen for further optimizations.

Next, the influence of the solvent on the reactivity and enantioselectivity was thoroughly investigated using [Co(OTf)_2]/\((S,S)\)-PhBPE. The hydrogenation was completely arrested in heptane at 50 °C (Fig. 3). Other protic solvents such as tert-BuOH, tert-AmyloH, 1-BuOH, iso-ProOH and EtOH were also found to be quite useful in the hydrogenation of 1a resulting in up to 84% ee and full conversion (Fig. 3).

To our delight, full conversion with 88% ee was obtained upon use of [Co(OTf)_2]/\((S,S)\)-PhBPE when bio-based solvent 2-Me-THF was used. Lowering the temperature to 40 °C did not affect the reactivity in 2-MeTHF, although a slight decrease in conversion was noticed in MeOH (Tables S5 and S6†). This result prompted us to check the impact of temperature and H2 pressure in the hydrogenation of 1a in both MeOH and 2-MeTHF as solvent. Table S7 (ESI) shows the detailed results. The hydrogenation of 1a can be performed at even 5 bar of H2 pressure using [Co(OTf)_2]/\((S,S)\)-PhBPE in 2-MeTHF at 50 °C without affecting the ee (88%). The formation of 1b was arrested in MeOH at room temperature, whereas 90% conversion was observed in 2-MeTHF. Hence 2-MeTHF was chosen for the investigation of the further scope.

The catalytic activity was also verified using the presynthesized \(\left(\{(S,S)\text{-PhBPE}\}\text{Co(OTf)}_2\right)\) complex (Fig. 4). The \(N\)-(1-indan-1-yl)acetamide (1b) was obtained in 96% yield and 90% ee.

Very often, the alkyl or aryl substituent on the nitrogen atom of the enamide is a key factor affecting the enantioselectivity. It has been reported that the enantioselectivity dropped from 92% to 7% upon changing the phenyl group to iso-propyl along with a reduced conversion using Rh/SYNPHOS catalyst using \(N\)-(1-benzylpiperidin-3-yl)-enamides as substrates.66 On the other hand, the ee could be improved with 56% upon changing the Me substituent (40% ee) to \(-\text{PhBPE in 2-MeTHF. A modest increase (3%) in conversion was observed in}\) 2-MeTHF. Hence 2-MeTHF was chosen for the investigation of the further scope.

Hence, we examined the amide substituent effect in the enantioselective hydrogenation of the enamides with two additional enamide derivatives (Fig. 5) employing the [Co(OTf)_2]/\((S,S)\)-PhBPE in 2-MeTHF. A modest increase (3%) in ee was observed upon changing the group to Ph (Fig. 5, substrate 3a). The extent of stereoselection can also be influenced by varying the substituents at the aromatic ring of the substrate.68 In order to check the effect on the enantioselectivity, we synthesized and hydrogenated four different 1-indanone derived substituted (6-methoxy, 7-methoxy) and halogen (6-Br, 6-F) containing enamides in the hydrogenation reaction (Fig. 5). The conversion of the hydrogenation was not affected using the 5-methoxy (4a) and 6-methoxy (5a) derivatives as substrate, where up to 90% ee was found. No dehydrofluorination was observed with 6a (80% ee). The 6-bromo derivative (7a), which is one of the key intermediates for the synthesis of Aficamten (phase II
candidate) was hydrogenated but the enantioselectivity was disappointing (60% ee).

Next, we synthesized rasagiline via Co-catalyzed asymmetric hydrogenation of 1a (Fig. 6). N-(Indan-1-yl)-acetamide was synthesized using Co/[(S.S)-PhBPE in 96% isolated yield and 88% ee (>99% ee via recrystallization, 89% yield). Then (R)-1-indanamine (1c) was synthesized via base-catalyzed hydrolysis of the amide in 89% yield without affecting the ee. Finally, rasagiline was produced via N-propargylation of 1c in acetonitrile with 81% yield and 98% ee.

It has already been observed that Zn can also reduce Co(II) to Co(I) and thus a Co(I)/Co(III) cycle has also been proposed for the cobalt-catalysed asymmetric hydrogenation facilitated by the presence of ZnCl2.44 Considering this fact, we have synthesized different Co(I)-precatalysts and employed them under the optimized conditions to elucidate the hydrogenation pathway. Low conversion and ee’s were observed using Co(I)-1, Co(I)-2 and Co(I)-3 as precatalysts (Fig. 7) as compared to the Co(II)/Zn method (optimized conditions). However, the enantioselectivity was improved to 89% in the presence of Zn (50 mol%) which also resulted in full conversion of 1a (Fig. 7) using Co(I)-3 as precatalyst. These results indicate that the stereo-determining step (SDS) is not same for the Co(II)/Co(i) as for the Co(i)/Co(II) cycle and as a result, ruled out the possibility of a Co(II)/ Co(i) cycle under these conditions. Similarly, very low conversion (30%) and ee (40%) have been observed using 5 mol% [Co(OTf)2]/[(S,S)-PhBPE under Zn-free condition (entry 13, Table S7†). These results exclude the possibility of a “non-redox” Co(u) cycle and strongly support a “redox” active catalytic pathway in the hydrogenation of 1a under the optimized conditions.

Next, we used CW X-Band EPR spectroscopy at low temperature (9 K) to gain insight into the possibly involved Co-species. We investigated the in situ mixed [Co(OTf)2]/[(S.S)-PhBPE precatalyst system, which was reduced with zinc under a H2 (10 bar) atmosphere. After depressurizing and freeze-quenching the precatalyst mixture, the EPR spectrum showed features that indicate the presence of a Co(u) complex (g_eff = 4.3, see
Fig. 8i, black trace). Thereafter, a sample of the catalytic mixture was prepared using standard conditions and depressurizing the reaction after two hours to 1 bar of H₂, before freeze-quenching the sample (Fig. 8i, red trace). This provided a spectrum which could be fitted to two species: a high-spin Co(II) complex (\(S = \frac{3}{2}\), \(g = 2.35\), \(D = 0.77\) cm\(^{-1}\), \(E/D < 0.01\)) and a low-spin Co(0) complex (\(S = \frac{1}{2}\), \(g_\parallel = 2.32\), \(g_\perp = 1.99\)).

Based on the experimental evidence and the EPR studies, we postulate that cobalt (II) is reduced first to a cobalt(0) species (Fig. 8ii) via two electron reduction by Zn. This hypothesis was confirmed by performing the reduction of the precatalyst with zinc and substrate in the absence of hydrogen, which provided a more intense signal for the low-spin Co(0) species [Fig. 8i, blue trace]. Therefore, we propose that the reaction is initiated by reduction of the Co(u) precatalyst to a Co(0)-species (Fig. 8ii, Co-2). Thereafter, the Co(0) species coordinates with the substrate followed by the formation of a \(\sigma\)-complex (Co-3) with H₂ that undergoes oxidative hydride transfer to form Co(u) complex Co-4, which rapidly undergoes reductive elimination back to Co(0) releasing the amide product.

To investigate the hydrogenation pathway further, isotope labelling experiments have been performed. The bis-deuterated product (1b-\(d_2\)) was obtained employing [Co(OTf)\(_2\)]/(S,S)-PhBPE as precatalyst in 2-MeTHF using 15 bar of D₂ (Fig. 8iii). No N-acyl imine deuterated product has been noticed as observed by NMR analysis (\(\text{H}^{13}\)C, and C-D coupling, Fig. 8iii). Hence, the hydrogenation of 1a is the isomerization (enamide–imide) free asymmetric C≡C hydrogenation with molecular hydrogen (Fig. S45, ESI†).

Conclusions

Excellent enantioslectivity and yield have been achieved in the cobalt-catalyzed asymmetric hydrogenation of tri-
substituted cyclic indanone derived enamides, a challenging class of substrates with respect to enantio-induction. The hydrogenation can be easily effected by in situ mixing of [Co(OTf)2]/(S,S)-PhBPE or by using [(S,S)-PhBPE-Co(OTf)2] as precatalyst without affecting the activity and enantioselectivity. The catalyst needs activation by zinc. The isotope labelling experiment showed that the double bond of the indanone-derived enamide is directly reduced by the N-acylimine. Experimental evidence based on EPR spectroscopy suggests the Zn promoted reduction of Co(II) to Co(0) as the first step in the mechanism. The Co(0) complex undergoes oxidative hydride transfer to the olefin via a redox active Co(0)/Co(II) cycle.

Abbreviations

AH Asymmetric hydrogenation
EPR Electron paramagnetic resonance
CW Continuous wave

Author contributions

Conceptualization: SC, JGdV; reaction optimization and experimental: SC, EB; EPR experiments: FJdZ, DDS, JNHR, BdB; writing – original draft: SC, FJdZ, DDS; writing – review & editing: SC, FJdZ, DDS, EB, JNHR, BdB, JGdV.

Conflicts of interest

There are no conflicts to declare.

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