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Asymmetric Hydrogenation

Enantioselective Hydrogenation of Tetrasubstituted α,β-Unsaturated Carboxylic Acids Enabled by Cobalt(II) Catalysis: Scope and Mechanistic Insights

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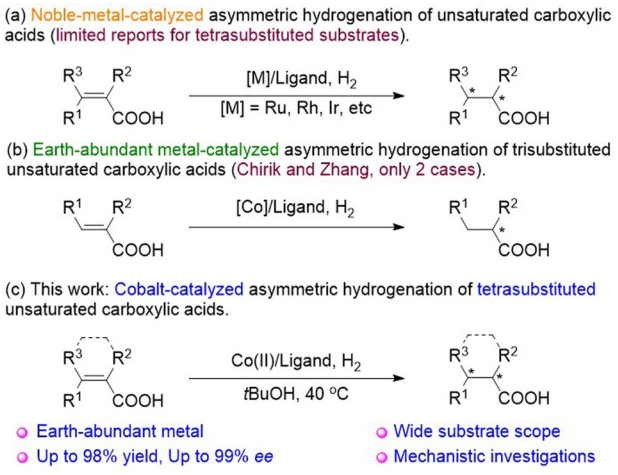
Dedicated to the 10th anniversary of Southern University of Science and Technology

Abstract: *Chiral carboxylic acids are important compounds because of their prevalence in pharmaceuticals, natural products and agrochemicals. Asymmetric hydrogenation of α,β-unsaturated carboxylic acids has been widely recognized as one of the most efficient synthetic approaches to afford such compounds. Although related asymmetric hydrogenation of di- and trisubstituted unsaturated acids with noble metals is well established, asymmetric hydrogenation of challenging tetrasubstituted α,β-unsaturated carboxylic acids is rarely reported. We demonstrate enantioselective hydrogenation of cyclic and acyclic tetrasubstituted α,β-unsaturated carboxylic acids via cobalt(II) catalysis. This protocol showed broad substrate scope and gave chiral carboxylic acids in good yields with excellent enantiocontrol (up to 98% yield and 99% ee). Combined experimental and computational mechanistic studies support a Co^{II} catalytic cycle involving migratory insertion and σ-bond metathesis processes. DFT calculations reveal that enantioselectivity may originate from the steric effect between the phenyl groups of the ligand and the substrate.*

Introduction

Chiral carboxylic acids and their derivatives are important and valuable synthetic intermediates for a wide range of pharmaceuticals,[1] bioactive compounds[2] and natural products.[3] Transition metal-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acids is one of the most direct and efficient protocols for the preparation of chiral carboxylic acids. During the last few decades, the asymmetric hydrogenation of di- and trisubstituted unsaturated acids enabled by some noble metals such as ruthenium,[4] rhodium,[5] and iridium[6] has been successfully and extensively investigated and applied. However, due to their high steric hinderance and low reactivity, limited successes have been achieved for the challenging tetrasubstituted substrates so far,[7] especially for the more challenging cyclic tetrasubstituted ones (Scheme 1a).[8] Notably, the asymmetric hydrogenation of tetrasubstituted α,β-unsaturated carboxylic acids has drawn the attention of many synthetic chemists, due to the wide existence of the resulting products in chiral drugs, natural products and organocatalysis (Figure 1).[9]

Due to their low cost, high abundance in the earth's crust and good biological compatibility, the development of earth-abundant 3d transition metal alternatives to noble-metal catalysts has attracted increasing interest in homogeneous catalytic hydrogenation.[10] Especially, catalysts based on cobalt are highly attractive for asymmetric hydrogenation,[11] and appreciable progress has been made in recent years.[12] Very recently, we and the Chirik group independently reported cobalt-catalyzed enantioselective hydrogenation of α,β-unsaturated carboxylic acids.[12a,b] The catalytic system worked well for both di- and trisubstituted unsaturated acids (Scheme 1b). However, hydrogenation of tetrasubstituted α,β-unsaturated carboxylic acids is still challenging, and to the best of our knowledge, asymmetric hydrogenation of cyclic tetrasubstituted substrates enabled by cobalt or other 3d



Scheme 1. Previous works, and the research reported herein, describing the asymmetric hydrogenation of unsaturated carboxylic acids.

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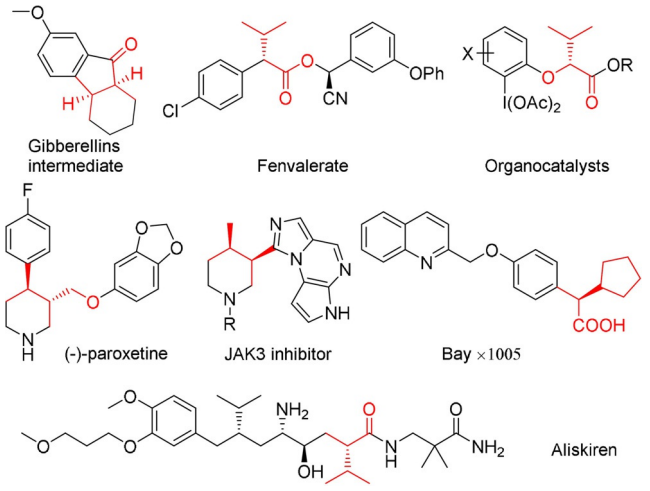


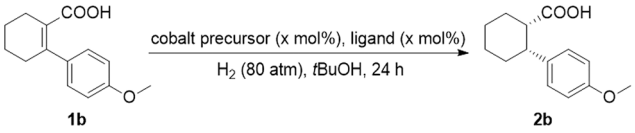
Figure 1. Potential synthetic applications of the asymmetric hydrogenation of tetrasubstituted unsaturated carboxylic acids.

metal catalysis is still underexplored. Herein, we reported a highly efficient and enantioselective Co^{II}-catalyzed hydrogenation of tetrasubstituted α,β-unsaturated carboxylic acids. In particular, the first asymmetric hydrogenation of challenging cyclic tetrasubstituted α,β-unsaturated carboxylic acids via cobalt(II) catalysis (Scheme 1c).

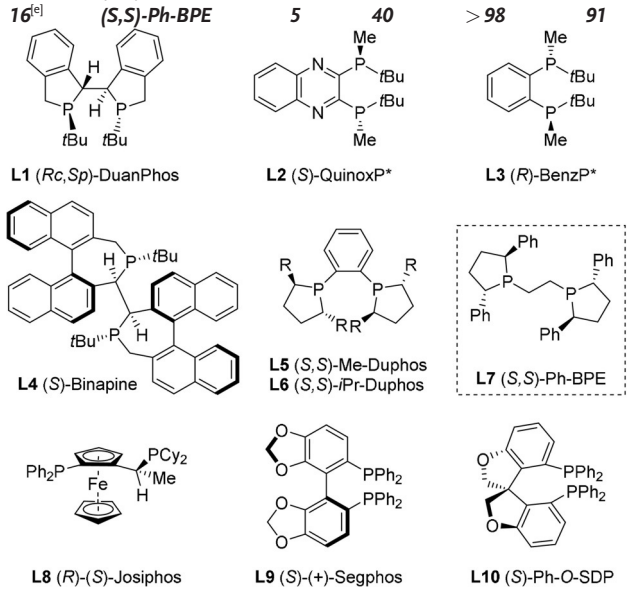
Results and Discussion

Condition optimization. Considering the challenges in asymmetric hydrogenation of cyclic tetrasubstituted α,β-unsaturated carboxylic acids, we initiated our investigation on the asymmetric hydrogenation of the model substrate **1b** by using 10 mol% cobalt(II) catalyst. After screening of various cobalt(II) precursors and solvents, cobalt(II) stearate and *t*BuOH were found to be the best choice, respectively (for details, see the Supporting Information). It should be noted that cobalt precursors played a crucial role in the efficiency and selectivity of current reaction. Furthermore, Zn was not necessary for the activation the Co^{II} precursor in the current reaction (Supporting Information, Table S1). Ligand screening was then investigated and the reactions were conducted under 80 atm H_2 pressure at 50 °C in *t*BuOH, in the presence of 10 mol% of cobalt(II) stearate and 10 mol% of a chiral ligand as the catalyst. Electron-rich diphosphine ligands (R_c,S_p)-DuanPhos[13] and (*S*)-Binapine,[14] which were previously developed by our group, could not give satisfactory results (Table 1, entries 1 and 4). P-chiral diphosphine QuinoxP* and BenzP* gave **2b** in very low conversion and enantioselectivity (entries 2–3). Although moderate to good conversion were obtained by the Me-DuPhos and *i*Pr-DuPhos, the *ee* values were poor (entries 5–6). Notably, the Ph-BPE was found to be the best one, which afforded the desired product **2b** in >98% conversion with 90% *ee* (entry 7). The reaction using (*R*,*S*)-JosiPhos afforded **2b** in 61% conversion with 73% *ee* (entry 8). No desired product was detected when employing (*S*)-SegPhos or (*S*)-Ph-*O*-SDP as the ligand (entries 9–10). To further improve the enantiocontrol, temperature effect was then investigated in the presence of 5 mol% of catalyst. 86% conversion of **2b** was achieved at 35 °C after 48 h (entry 13) and the conversion could increase to 95% after 72 h (entry 15). The *ee* value increased to 92% at rt while the conversion dropped to 62% (entry 14). To our delight, **2b** was obtained in nearly quantitative conversion with 91% *ee* under 80 atm H_2 at 40 °C over 72 h (entry 16).

Table 1: Optimization for Co^{II}-catalyzed asymmetric hydrogenation of tetrasubstituted α,β-unsaturated carboxylic acids.[a]

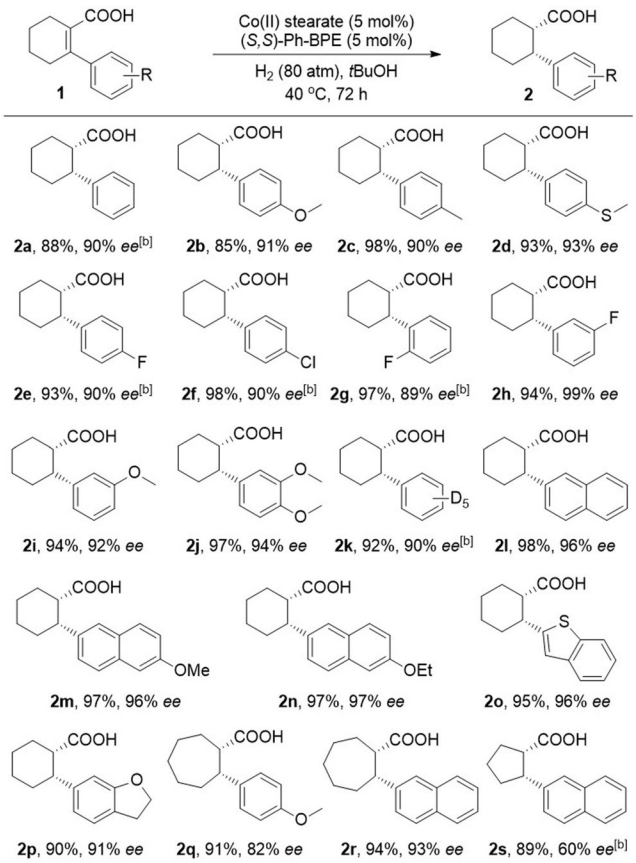


Entry	Ligand	*X* [mol%]	*T* [°C]	Conv. [%][b]	*ee* [%][c]
1	(R_c,S_p)-DuanPhos	10	50	84	3
2	(*S*)-QuinoxP*	10	50	47	12
3	(*R*)-BenzP*	10	50	ND	–
4	(*S*)-Binapine	10	50	77	58
5	(*S*,*S*)-Me-DuPhos	10	50	56	−18
6	(*S*,*S*)-*i*Pr-DuPhos	10	50	95	−44
7	(*S*,*S*)-Ph-BPE	10	50	>98	90
8	(*R*,*S*)-JosiPhos	10	50	61	73
9	(*S*)-SegPhos	10	50	ND	–
10	(*S*)-Ph-*O*-SDP	10	50	ND	–
11	(*S*,*S*)-Ph-BPE	5	50	82	90
12[d]	(*S*,*S*)-Ph-BPE	5	50	>98	90
13[d]	(*S*,*S*)-Ph-BPE	5	35	86	92
14[d]	(*S*,*S*)-Ph-BPE	5	rt	62	92
15[e]	(*S*,*S*)-Ph-BPE	5	35	95	92
16[e]	***(S,S)-Ph-BPE***	***5***	***40***	***>98***	***91***



[a] Reaction conditions: **1** (0.05 mmol), [Co] (10 mol%), (*S*,*S*)-Ph-BPE (10 mol%) in *t*BuOH (0.6 mL) under 80 atm H_2 pressure at 50 °C for 24 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis. [d] 48 h. [e] 72 h.

Substrate scope. With the optimized reaction condition in hand, the substrate scope of cobalt(II)-catalyzed asymmetric hydrogenation was investigated, and the results were summarized in Scheme 2. (The absolute configuration of the products was established by comparison of its optical rotation

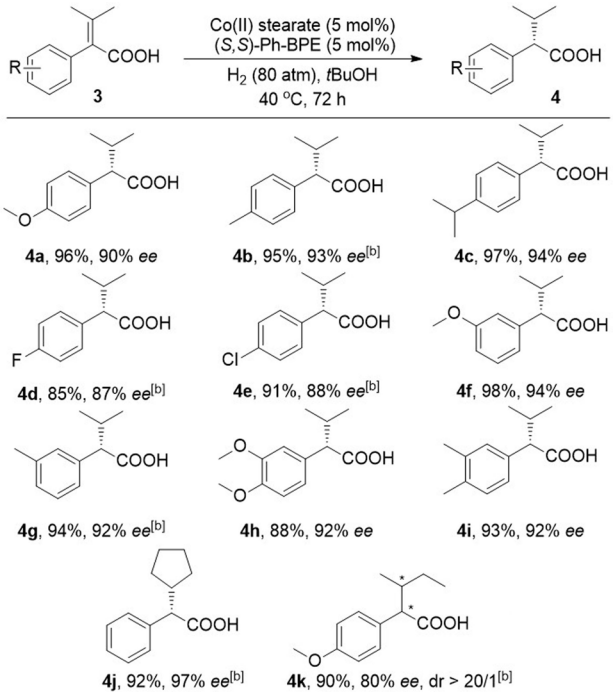


Scheme 2. Cobalt-catalyzed asymmetric hydrogenation of cyclic tetrasubstituted α,β-unsaturated carboxylic acids. [a] Reaction conditions: **1** (0.1 mmol), cobalt(II) stearate (5 mol%), (*S*,*S*)-Ph-BPE (5 mol%) in *t*BuOH (0.6 mL) under 80 atm H_2 pressure at 40°C for 72 h. Yield of isolated products, unless noted otherwise. The *ee* values were determined by HPLC analysis. [b] With 10 mol% of catalyst.

with previous reports.) Most of the reactions proceeded smoothly with 5 mol% of the catalyst under 80 atm H_2 pressure at 40°C, providing the desired products in high isolated yields and enantioselectivities (90–99% *ee*). Substrates bearing both electron-donating and electron-withdrawing groups on the phenyl group were suitable for the reaction to give the hydrogenation products **2a**–**2j** in good to excellent yields and enantioselectivities (85–98% yield, 89–99% *ee*). Furthermore, the phenyl-deuterated substrate **1k** was efficiently hydrogenated to give the desired product **2k** in 92% isolated yield with 90% *ee*. Compared to β-phenyl-substituted unsaturated acids, β-naphthyl-substituted substrates generally exhibited better enantioselectivities to give the desired products **2l**–**2n** (96–97% *ee*). In addition, the method also works efficiently for substrates bearing bicyclic heterocyclic rings, furnishing the chiral acids products **2o** and **2p** in 95% and 90% isolated yield with 96% and 91% *ee*, respectively. The reaction also tolerates substrates bearing seven- or five-membered ring (**1q**–**1s**). **2q** and **2r** were obtained in 91% and 94% yield with 82% and 93% *ee*, respectively. Moreover, **1s** was hydrogenated smoothly to give **2s** in 89% yield with 60% *ee*.

α,β,β-Trisubstituted acrylic acids were also subjected to our [Co]/BPE system due to the corresponding hydrogenation products are key structural component in numerous bioactive molecules.[15] To our delight, the [Co]/BPE system is active for the asymmetric hydrogenation of **3a**, giving **4a** in 96% yield with 90% *ee*. A wide range of acyclic tetrasubstituted α,β-unsaturated carboxylic acids were hydrogenated smoothly to give chiral α-phenyl isopentyl carboxylic acids in good to excellent yields and enantioselectivities (Scheme 3). Substrates with electron-donating (**3a**–**3c**, **3f**, **3g**) or electron-withdrawing group (**3d**, **3e**) on the phenyl group were hydrogenated smoothly to give the desired chiral carboxylic acids in 85–98% yield and 87–94% *ee*. Multi-substituted **3h** and **3i** bearing 3,4-disubstituted methoxy and methyl groups also provided excellent results (92% *ee*, respectively). Exocyclic substrate **3j** was also a suitable substrate for the current reaction, and 93% yield with 97% *ee* was obtained. The substrate **3k** containing two different substituents at the β-position were also synthesized and subjected to the [Co]/BPE system, and **4k** with two contiguous stereocenters was obtained in 90% yield with 80% *ee* and >20/1 dr.

Mechanism study. To elucidate the detailed mechanism of this cobalt(II)-catalyzed asymmetric hydrogenation, a control experiment and a series of deuterium-labelling experiments were conducted, and the results were summarized in Scheme 4. In sharp contrast to the high efficiency exhibited in the hydrogenation of **1b** (85% yield and 91% *ee*), no reaction occurred for the corresponding ester **1b′** under the standard conditions (Scheme 4a). In addition, additives such



Scheme 3. Cobalt-catalyzed asymmetric hydrogenation of acyclic tetrasubstituted α,β-unsaturated carboxylic acids. [a] Reaction conditions: **3** (0.1 mmol), cobalt(II) stearate (5 mol%), (*S*,*S*)-Ph-BPE (5 mol%) in *t*BuOH (0.6 mL) under 80 atm H_2 pressure at 40°C for 72 h. Yield of isolated products, unless noted otherwise. The *ee* values were determined by HPLC analysis. [b] With 10 mol% of catalyst.

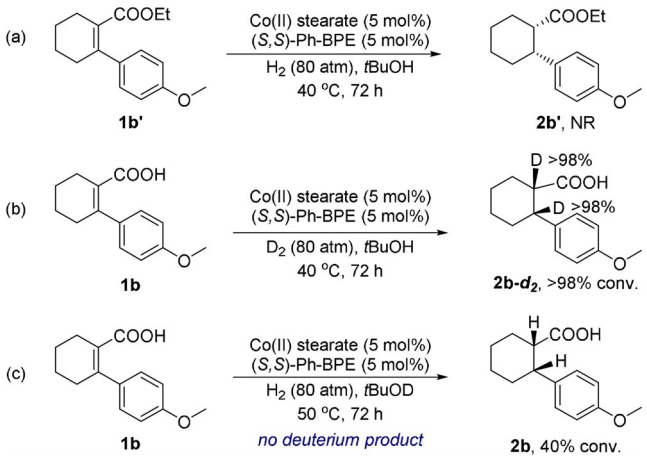
as Zn have no effect on the asymmetric hydrogenation (for details, see the Supporting Information). These results revealed that the carboxyl group was essential in this [Co]/BPE system. It is possibly involved in both the activation of the pre-catalyst and the control of activity and enantioselectivity.

In the presence of D_2, **1b** was hydrogenated smoothly to give deuterated product **2b-*d*$_2$** in >98% conversion (Scheme 4b). Furthermore, no deuterated product was detected when the solvent was replaced by *t*BuOD (Scheme 4c). The results demonstrated that protonation of the Co-alkyl intermediate was probably not involved in this transformation and the hydrogen source was H_2. The hydrogenation of **1b** with H_2/D_2 mixture was also conducted, and some mono-deuterated product **2b-*d*$_1$** was observed, indicating that the hydrogen atoms in the product may origin from two molecules of hydrogen gas (for details, see the Supporting Information). Besides, a series of Co^{II}-catalyzed asymmetric hydrogenation of **1b** were conducted with (*S*,*S*)-Ph-BPE with different enantiopurities as the ligand under the standard reaction conditions. A linear effect was observed in this asymmetric reduction, indicating a 1:1 binding pattern between (*S*,*S*)-Ph-BPE and cobalt(II) stearate (Supporting Information, Figure S6).[16] EPR experiments were also conducted to monitor the process of asymmetric hydrogenation using **1b** as model substrate. Our EPR results suggested that a paramagnetic Co^{II} species could be involved in the catalytic cycle (Figures S7–S9).

DFT study. On the basis of the previous computational studies on asymmetric hydrogenation employing 3d metal catalysts[12f,17] and our control experiments (Scheme 4), systematic density functional theory (B3LYP-D3 (mainly)) calculations were conducted to understand the origin of the enantioselectivity.[18] Our computational results suggest that the active Co^{II}-carboxylate hydride intermediates (**A1$_R$** or **A1$_S$**) preferentially undergo hydrogen insertion into C1 atom of the substrate (Figure 2) via **^{2}ATS1$_S$** and **^{2}ATS1$_R$**, which were computed to be the rate-, regio- and stereo-determining step with the barriers of about 15.8–17.9 kcal mol^{-1} in solution by the PCM B3LYP-D3//B3LYP-D3 method. The most favorable transition state **^{2}ATS1$_S$** leading to the desired (*S*)-form final product **P$_S$** was computed to be lower in free energy than **^{2}ATS1$_R$** forming the (*R*)-form product **P$_R$** by about 2.1 kcal mol^{-1} in solution.[19,20a] This computational result (equivalent to 94.4% *ee*) is qualitatively consistent with the experimental result (90% *ee*, Scheme 2). Metallacycle intermediates **^{2}A2$_S$** and **^{2}A2$_R$** can be formed after this insertion. Coordination of one hydrogen molecule to **^{2}A2$_S$** and **^{2}A2$_R$** then takes place to form **^{2}A3$_S$** and **^{2}A3$_R$** before σ-bond metathesis via **^{2}ATS2$_S$** and **^{2}ATS2$_R$** to afford the final products and Co^{II}-hydride species. Alternatively, more stable intermediates **^{4}A2$_S$** and **^{4}A3$_S$** can be formed after spin transition prior to **^{4}ATS2$_S$**. Such spin crossing is supported by our PCM B3LYP-D3//B3LYP-D3, PCM PBE0-D3//PBE0-D3 and PCM M06-L//M06-L methods (Table S7). Finally, ligand exchange of the product **P$_S$** or **P$_R$** by another substrate molecule completes the catalytic cycle and regenerates the active species **^{4}A1$_S$** or **^{4}A1$_R$**.[20b]

(Relative) distortion/interaction analysis[5b,21] further suggests that, compared to favorable **^{2}ATS1$_S$**, a larger distortion energy in **^{2}ATS1$_R$** plays the dominant role in the enantioselectivity (Figure 3b). In this connection, the phenyl group of the substrate is oriented into a close (top left) quadrant of the catalyst in **^{2}ATS1$_S$**, in which one phenyl group of the chiral ligand adapts to stack with the phenyl group of the substrate (Figure 3a). Whereas, owing to the Co^{II}-carboxylate chelation, the phenyl group of the substrate is forced to be positioned into the two right quadrants in **^{2}ATS1$_R$**, in which the two phenyl groups have a poor geometric complementarity. The steric map can also show the steric hindrance of the chiral ligand in **^{4}A1$_R$**, **^{2}ATS1$_S$** and **^{2}ATS1$_R$** (Figure 3c).[22] Indeed, the steric repulsion can be partly attributed to a shorter H-H distance between the substrate and ligand in **^{2}ATS1$_R$** (1.96 Å vs. 2.12 Å in **^{2}ATS1$_S$**; Figure 3a). Moreover, their free energy difference was slightly increased by 0.2 kcal mol^{-1} in the absence of dispersion correction (Table S18). These computational results and our additional calculations (replacement of the phenyl groups by a smaller methyl group(s) and its substitution effect evaluated by isodesmic-reaction approach;[23] Figure S13) support that the steric effect between phenyl groups of the ligand and the substrate should play a more critical role in the observed enantioselectivity.

Based on our combined mechanistic and DFT (Figure 2) investigations, a plausible mechanism of cobalt(II)-catalyzed asymmetric hydrogenation of tetrasubstituted α,β-unsaturated carboxylic acids was proposed (Scheme 5). After ligand exchange and heterolytic cleavage of hydrogen, the cobalt(II) monohydride species **^{4}A1$_S$** is formed and then enters the catalytic cycle.[12b] Metallacycle intermediates **^{2}A2$_S$** can be formed after the migratory insertion of cobalt(II) monohydride **^{4}A1$_S$** via transition state **^{2}ATS1$_S$**. The migratory insertion is suggested to be the rate-, regio- and stereo-determining step. Coordination of one hydrogen molecule to **^{2}A2$_S$** then takes place to form **^{4}A3$_S$**. Subsequently, Co^{II}-hydride species **^{4}A4$_S$** is produced via σ-bond metathesis (**^{4}ATS2$_S$**). The ligand exchange of **^{4}A4$_S$** with another unsaturated carboxylate substrate **1a** releases the less acidic hydrogenation product **2a** and regenerates the cobalt(II) hydride species **^{4}A1$_S$**.



Scheme 4. Mechanistic studies for cobalt(II)-catalyzed asymmetric hydrogenation.

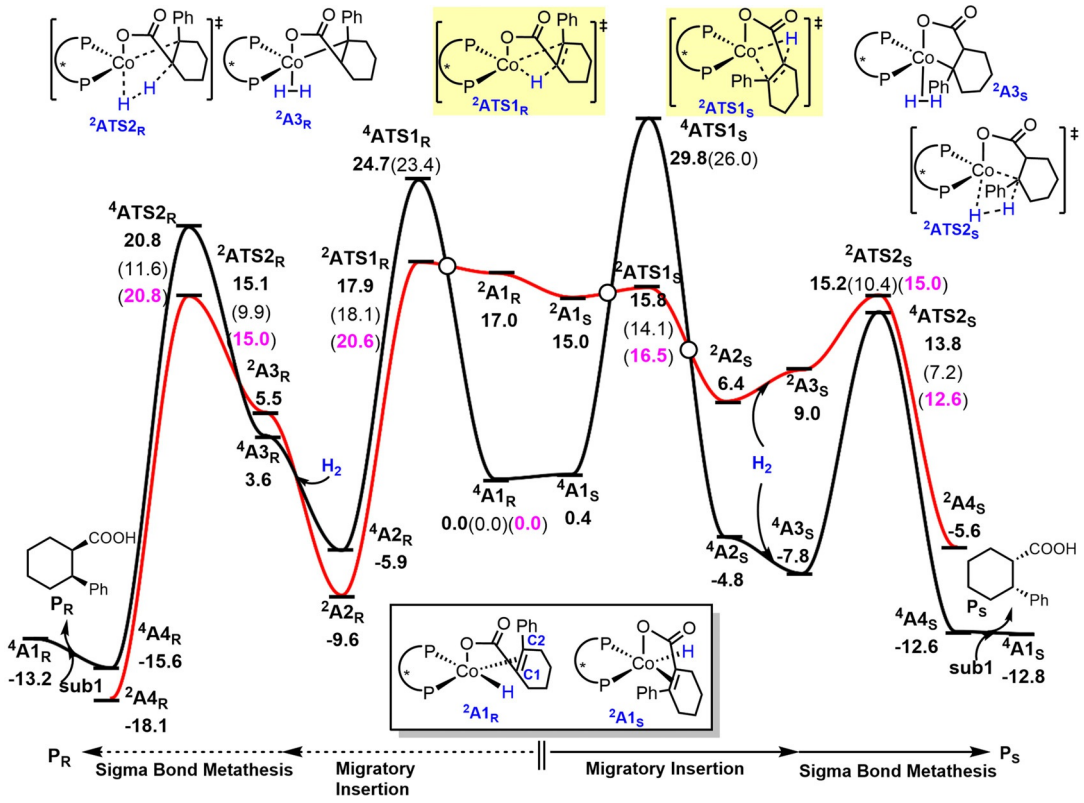


Figure 2. Free energy profile for the most favorable path (Path **A**) of the Co^{II}-catalyzed enantioselective hydrogenation with the initial hydrogen insertion into the C1 atom to form $\mathbf{P_S}$ and $\mathbf{P_R}$ products in doublet (red line) and quartet (black line) states in *t*BuOH solvent by the PCM B3LYP-D3//B3LYP-D3 (in bold), PCM PBE0-D3//PBE0-D3 (in parentheses) and PCM B3LYP-D3 (in bold purple, in parentheses) methods.

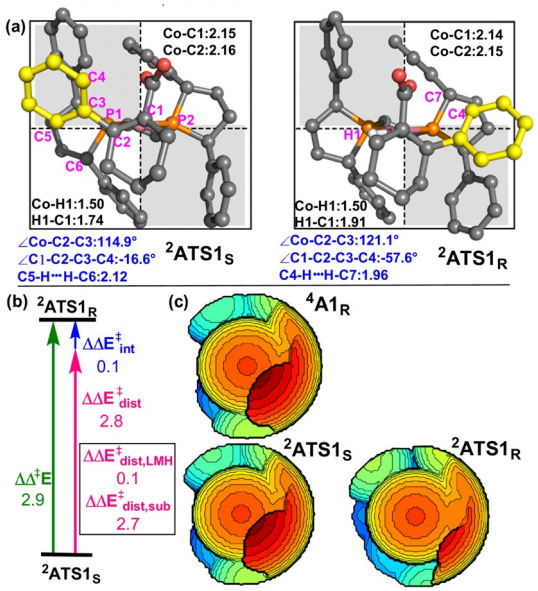
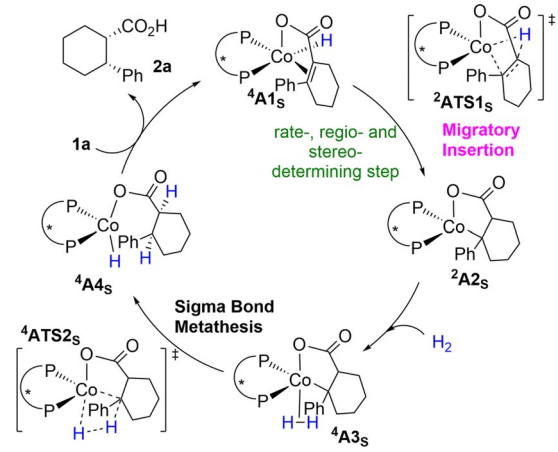


Figure 3. a) The optimized key rate-, regio- and enantio-determining transition states in doublet state in the gas phase by the B3LYP-D3 method. The key distances (Å), key angles (°), and dihedral angles (°) are given. Unimportant hydrogen atoms are not shown for clarity. b) Relative distortion-interaction energy analysis on the two key transition states with relative distortion energy for the metal hydride and ligand ($E^{\ddagger}_{dist,LMH}$), relative distortion energy for the substrate ($E^{\ddagger}_{dist,sub}$) and relative interaction energy ($E^{\ddagger}_{int}$) using ^{2}**ATS1$_S$** as the reference point by the PCM B3LYP-D3//B3LYP-D3 method. c) Steric map for ^{4}**A1$_R$**, ^{2}**ATS1$_S$** and ^{2}**ATS1$_R$** (more bulky (red), less bulky (green)).



Scheme 5. Proposed catalytic cycle.

Conclusion

In conclusion, we have developed a highly efficient and enantioselective hydrogenation of tetrasubstituted unsaturated α,β-unsaturated carboxylic acids (up to 98% yield and 99% *ee*) employing an earth-abundant cobalt(II)-catalyst. The [Co]/BPE system not only works well for challenging endocyclic substrates, but also shows comparable results with noble metal-catalyzed hydrogenations in the case of acyclic tetrasubstituted substrates. Mechanistic investigations were conducted through combined control experiment, deuterium-

labeling experiments and DFT calculations. Our results revealed that hydrogen was activated through σ-bond metathesis rather than oxidative addition (Scheme 5). In addition, our DFT calculations suggested that the migratory insertion serves as the rate-, regio- and stereo-determining step, and the steric effect between phenyl groups of the ligand and the substrate play a critical role in the enantiocontrol of this transformation.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cobalt · DFT calculations · mechanisms · tetrasubstituted unsaturated carboxylic acids

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[18] For computational details, see the Supporting Information.

[19] The rate-determining step was also supported by the PBE0-D3 and B3LYP-D3 methods using larger basis sets. The computed free-energy barrier gap is about 1.8–4.0 kcal mol^{-1} by these PBE0-D3 and B3LYP-D3 methods (Table S7).

[20] a) In comparison, path B involving the initial hydrogen insertion into C2 atom (Figure S11) requires higher reaction barriers than the most favorable path A via ^{2}**ATS1$_{S}$** by ~3.3–11.1 kcal mol^{-1}. Likewise, path B also kinetically favors the formation of the major product **P$_{S}$** with a lower reaction barrier of 7.8 kcal mol^{-1} than **P$_{R}$**. b) The other pathways involving Co^{II}/Co^{0} or a neutral Co^{I}-hydride species can be excluded, due to their higher reaction barriers (Supporting Information, Scheme S1, Figure S27).

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