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Letter

Cobalt-Catalyzed Efficient Asymmetric Hydrogenation of α-Primary Amino Ketones

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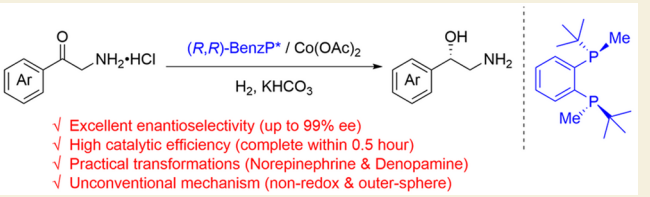
ABSTRACT: Based on an amino-group-assisted coordination strategy and a proton-shuttle-activated outer-sphere mode, the cobalt-catalyzed asymmetric hydrogenation of α-primary amino ketones has been developed, resulting in the efficient synthesis of chiral vicinal amino alcohols bearing functionalized aryl rings in high yields and enantioselectivities (up to 99% enantiomeric excess (ee)) within 0.5 h.



KEYWORDS: *amino ketones, assisted coordination, asymmetric hydrogenation, cobalt catalysis, vicinal amino alcohols*

Transition-metal-catalyzed asymmetric hydrogenation (AH) represents one of the most elegant ways to construct chiral molecules.[1,2] Compared to the well-developed rare metal-catalyzed version, earth-abundant metal-catalyzed asymmetric hydrogenation has attracted growing interest and already witnessed competent or even more remarkable results.[3−9] Within this newly emerging field, cobalt-catalyzed asymmetric hydrogenation has developed precipitously in the past decade.[10−12]

Based on a series of differentiated cobalt catalytic systems, a wide variety of alkene substrates, bearing largely unfunctionalized groups (UFG) as well as functionalized groups (FG) including acylamino, carboxyl, and azolyl, can be hydrogenated with excellent enantioselectivities and yields (Scheme 1a, up).[13−24] From the data recorded, bis(phosphine) (PP) ligands are more suitable for the latter and often achieve a higher catalytic efficiency (up to 2000 TON). It is important to note that the assisted coordinating groups such as a pyrazolyl with *N*-coordination are critical for the high efficiency in the cobalt-catalyzed asymmetric hydrogenation of functionalized olefins, which enables the reaction to proceed smoothly at ambient temperature and pressure and to complete quickly within 1 h (Scheme 1a, down).[19]

However, for cobalt-catalyzed asymmetric hydrogenation of double bonds containing heteroatoms, the catalytic efficiency is relatively lower, and much fewer achievements have been made, either with relatively lower catalytic efficiency or with harsh conditions (Scheme 1b and c, up).[25−30] To tackle this issue, the assisted coordination strategy has been introduced to enable the cobalt-catalyzed asymmetric hydrogenation of the C═N bond with high efficiency (up to 2000 TON). The success of this reaction relied on the presence of an NHBz group in the substrates, with the hydrogenation efficiency improved by its assisted *O*-coordination to the cobalt atom and its nonbonding interaction with the ligand (Scheme 1b, down).[26] These results coupled with our understanding of the catalytic mechanism propelled us to envisage that cobalt-catalyzed efficient asymmetric hydrogenation of the C═O bond may no longer be out of reach. Compared with the traditional acyl and hydroxyl groups using the oxygen atom as the coordinating atom, the imino and amino groups using the nitrogen atom as the coordinating atom are considered to form stronger coordinate bonds.[19] In particular, the simple primary amino group (NH_2) has the least steric hindrance and, thus, is more favorable for coordination bond formation. This is conducive to improving the stability of cobalt complexes that are relatively sensitive to the coordination space.[19,31,32]

Herein, we report a highly efficient cobalt-catalyzed asymmetric hydrogenation of NH_2-substituted ketones (Scheme 1c, down). Notably, there is no report on the cobalt-catalyzed asymmetric hydrogenation using NH_2 as an assisted coordinating group.[33−39] By avoiding the protection and deprotection steps, we expect to further improve the synthetic efficiency and transforming simplicity of chiral vicinal amino alcohols, which are irreplaceable synthetic skeletons and core building blocks of many bioactive compounds (Figure 1).

First, commercially available 2-aminoacetophenone hydrochloride (**1a**) was chosen as the model substrate to optimize reaction conditions (Table 1 and see Table S1 for details). During the preliminary screening, the spontaneous and simultaneous generation of binary condensed byproducts pyrrole and pyrazine was observed when the base K_2CO_3 was added.[40,41] Among the chiral diphosphine ligands evaluated, (*S*,*S*)-BDPP (**L1**), (*R*)-BINAP (**L2**), and (*R*,*Sp*)-

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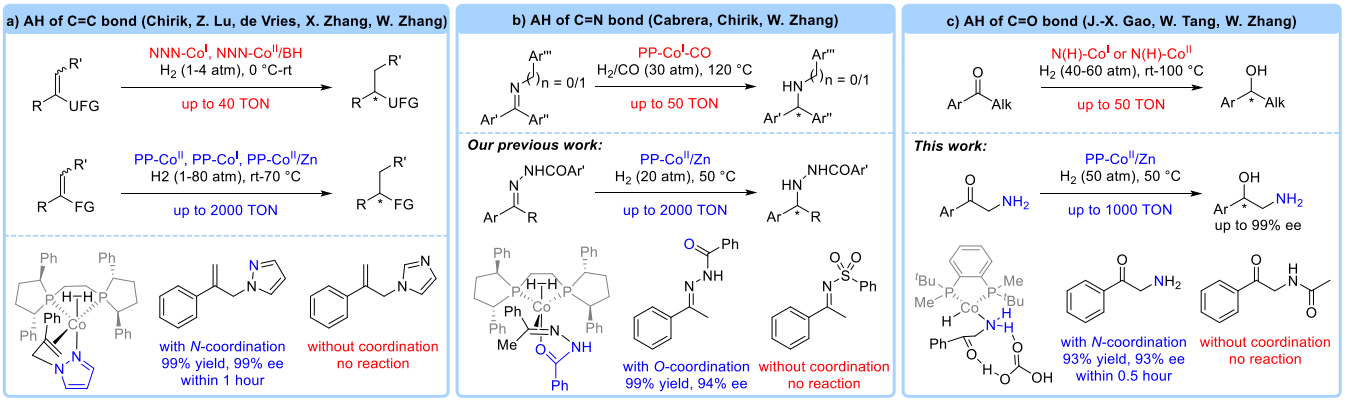
Scheme 1. Cobalt-Catalyzed Asymmetric Hydrogenation



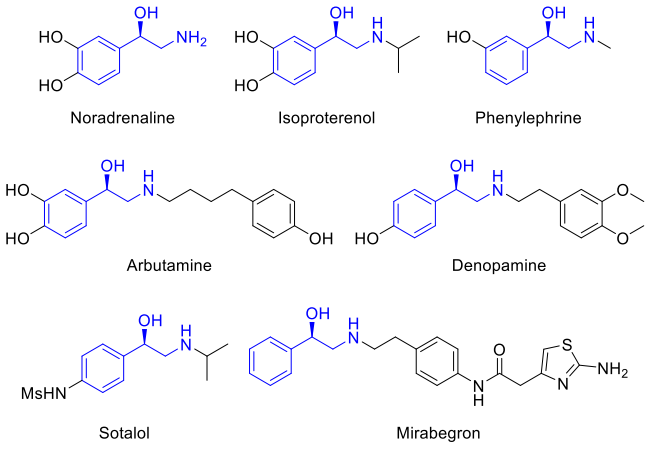


Figure 1. Chiral vicinal amino alcohols with bioactivities.

JosiPhos (**L3**) did not promote hydrogenation at all, while the electron-rich ligands (*S*,*S*)-Ph-BPE (**L4**), (*R*,*R*)-Me-DuPhos (**L5**), and (*R*,*R*)-BenzP* (**L6**) gave desired product **2a** with acceptable yields and good enantioselectivities (Table 1, entries 1−6). After investigating the effects of solvents and cobalt sources using (*R*,*R*)-BenzP* (**L6**) as the optimal ligand, we found that MeOH is the best solvent and Co(OAc)$_2$ becomes a better cobalt source (entry 7). After screening of bases, KHCO$_3$ gave the best results in both yield and enantioselectivity (entry 8). In the absence of a base, the conversion and ee value decreased slightly (entry 9). Then, the comparative advantage of the primary amino group was verified by comparing the hydrogenation performance of ketones with different substituents (entries 8−15). When the amino group was protected, the corresponding product could be well obtained regardless of whether the protecting group is acetyl (**1a-Ac**), benzoyl (**1a-Bz**), or *tert*-butoxycarbonyl (**1a-Boc**; entries 10−12). Less than 10% conversion was obtained when the primary amino group was removed (**1a-Ket**) or replaced by a hydroxyl group (**1a−OH**; entries 13, 14). Extending the carbon chain between NH$_2$ and C═O groups gave a maintained conversion but led to a dramatic decrease in the ee value (**1a-C2**; entry 15). Other reaction conditions such as temperature, hydrogen pressure, and reaction time were also studied and compared. Without the addition of zinc dust, the yield of **2a** is significantly reduced, although the enantioselectivity is maintained (entry 16). Increasing the reaction temperature and hydrogen pressure can further improve the yield of **2a** but will reduce the enantioselectivity (entries 17−19). To our surprise, facilitated by stoichiometric KHCO$_3$, the hydrogenation reaction was so efficient that it could be completed in less than 0.5 h with maintained yield and enantioselectivity (entries 20, 21).

With the optimized reaction conditions in hand, we began to explore the substrate scope of the α-primary amino ketones (Scheme 2). Most hydrogenated products (**2a−2z**) were obtained in high yields with good to excellent enantioselectivities (84−99% ee). For *para*- and *meta*-substituted substrates, both electron-donating and electron-withdrawing groups were well tolerated (**2a−2n**). And for **2h−2k** with a halogen substituent at the *para* position, the ee value went up as the electronegativities abated, with **2j** and **2k** obtained with the highest ee of 99%. However, with *ortho* substituents, the ee values of the corresponding products **2o** and **2p** decreased significantly. Disubstituted substrates gave good results, as well (**2q−2v**). Notably, norepinephrine **2s**, bearing two unprotected phenolic hydroxyl groups, an important neurotransmitter and cardiopulmonary resuscitation and antishock drug, could be directly obtained with 94% ee. Naphthyl and heteroaryl substrates were also amenable to the reaction conditions, affording the corresponding products (**2w−2z**) with satisfactory yields and enantioselectivities. However, certain substrate types gave relatively lower activity and were ineffective even after 24 h (**2aa−2ac**). When there was a strong electron-withdrawing substituent on the phenyl ring, such as trifluoromethyl (**2aa**), the yield dropped to 70% with a satisfactory enantioselectivity of 95% ee, and when the phenyl ring was substituted by chloride at the *meta*-positions (**2ab**), only 40% yield was obtained with 88% ee. Also, when there was a large steric-hindered substituent on the phenyl ring such as *tert*-butyl (**2ac**), only an 85% yield and 63% ee were obtained. In addition, the *N*-methyl-substituted substrate also went through the reaction smoothly, providing **2a-Me** in 90% yield and 98% ee. The absolute configuration of **2j** was determined to be *S* by single-crystal X-ray diffraction (see Supporting Information for details), and the other products were then assigned accordingly.

To demonstrate the practicality of this methodology, the hydrogenation reaction was performed on the gram scale, giving the desired product **2l** with complete conversion and a maintained ee value. Also, the reaction could be conducted under a substrate/catalyst (S/C) ratio of 1000 with identical results (Scheme 3a). Subsequently, using common reaction conditions, amine **2l** could be coupled with 2-(3,4-dimethoxyphenyl)acetic acid to form amide **3l**. Reduction of **3l** by LiAlH$_4$ completed the synthesis of the enantiomer of

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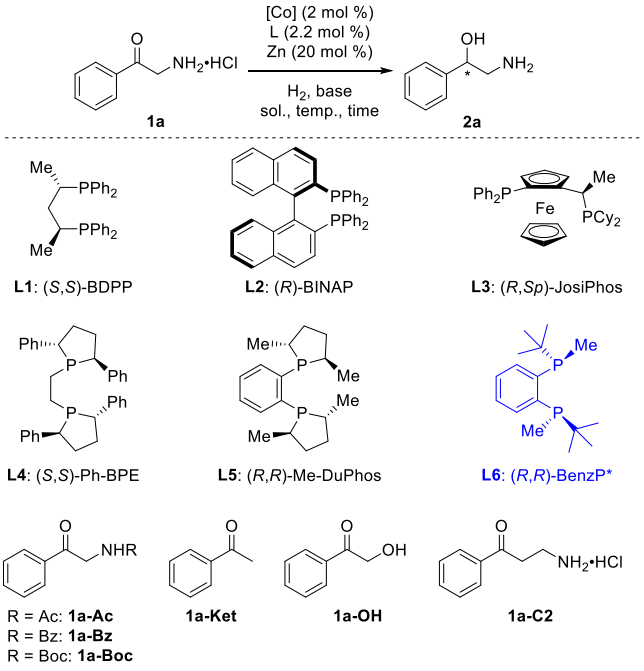
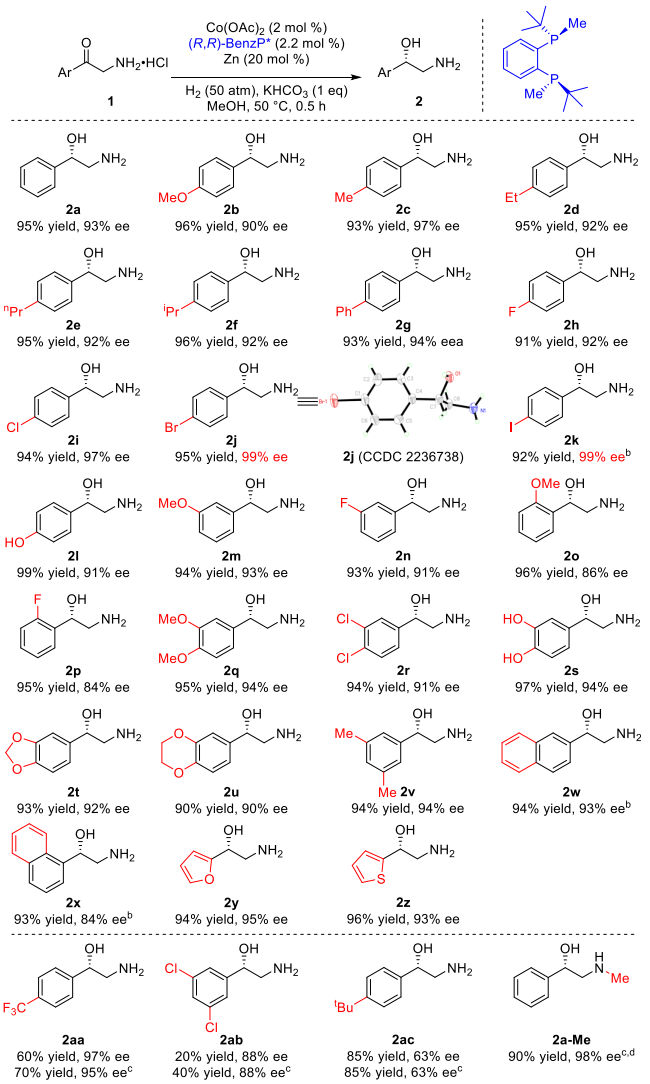
Table 1. Conditions Optimization



entry[a]	sub.	lig.	[Co]	base	conv. %[b]	ee %[c]
1	**1a**	**L1**	$CoCl_2$	K_2CO_3	trace	-
2	**1a**	**L2**	$CoCl_2$	K_2CO_3	NP	-
3	**1a**	**L3**	$CoCl_2$	K_2CO_3	trace	-
4	**1a**	**L4**	$CoCl_2$	K_2CO_3	65	63
5	**1a**	**L5**	$CoCl_2$	K_2CO_3	79	79
6	**1a**	**L6**	$CoCl_2$	K_2CO_3	55	91
7	**1a**	**L6**	$Co(OAc)_2$	K_2CO_3	77	93
8	**1a**	**L6**	$Co(OAc)_2$	$KHCO_3$	90	93
9	**1a**	**L6**	$Co(OAc)_2$	-	85	91
10	**1a-Ac**	**L6**	$Co(OAc)_2$	-	NP	-
11	**1a-Bz**	**L6**	$Co(OAc)_2$	-	NP	-
12	**1a-Boc**	**L6**	$Co(OAc)_2$	-	7	-
13	**1a-Ket**	**L6**	$Co(OAc)_2$	-	5	-
14	**1a-OH**	**L6**	$Co(OAc)_2$	-	10	71
15	**1a-C2**	**L6**	$Co(OAc)_2$	$KHCO_3$	90	58
16[d]	**1a**	**L6**	$Co(OAc)_2$	$KHCO_3$	29	93
17[e]	**1a**	**L6**	$Co(OAc)_2$	$KHCO_3$	85	93
18[f]	**1a**	**L6**	$Co(OAc)_2$	$KHCO_3$	91	89
19[g]	**1a**	**L6**	$Co(OAc)_2$	$KHCO_3$	93	92
20[g,h]	**1a**	**L6**	$Co(OAc)_2$	$KHCO_3$	96	93
21[g,h]	**1a**	**L6**	$Co(OAc)_2$	-	21	91

[a]Conditions: **1a** (0.2 mmol), [Co] (2.0 mol %), ligand (2.2 mol %), Zn (20 mol %), H_2 (40 atm), base (1 equiv), MeOH (1.0 mL), 50 °C, 24 h, unless otherwise noted. [b]The conversions of **2a** were calculated from ^{1}H NMR spectra. NP = no product. [c]The ee values were determined by HPLC using a chiral column. [d]Without Zn. [e]40 °C. [f]60 °C. [g]H_2 (50 atm). [h]0.5 h (stirring for 10 min at 50 °C and cooling down for 20 min).

Scheme 2. Substrate Scope[a]



[a]Conditions: 1 (0.4 mmol), $Co(OAc)_2$ (2 mol %), (*R*,*R*)-BenzP* (2.2 mol %), Zn (20 mol %), $KHCO_3$ (1 equiv), H_2 (50 atm), MeOH (2 mL), 50 °C, 0.5 h, unless otherwise noted; Yields of isolated products given; ee values determined by HPLC using chiral columns [b]1 h. [c]24 h. [d]40 atm.

denopamine, a selective β-adrenoceptor agonist that is clinically effective in congestive cardiomyopathy (Scheme 3a).[42] The amino and hydroxyl groups of **2a** could be acylated sequentially with BzCl and Ac_2O respectively to give **2a-Bz** and **3a** without any loss in enantioselectivity (Scheme 3b, up).[43] Similarly, by modified reaction conditions, acylation of **2a** gave monoacylated product **4a** in 50% yield and 94% ee, which is a key intermediate for the synthesis of the enantiomer of a selective β_3-adrenoceptor agonist named mirabegron (Scheme 3b, down).[44] Apart from acylation, hydrogenated product **2q** went through reductive alkylation with acetone/$NaBH_3CN$ successfully, providing compound **3q** in high yield and good enantioselectivity. Deprotection of methyl groups in compound **3q** can give the enantiomer of a potent β-adrenergic agonist named isoproterenol (Scheme 3c).[45]

To gain further insight into the reaction mechanism, a series of deuterium labeling experiments were conducted (see Scheme S1 for details). The results demonstrate that

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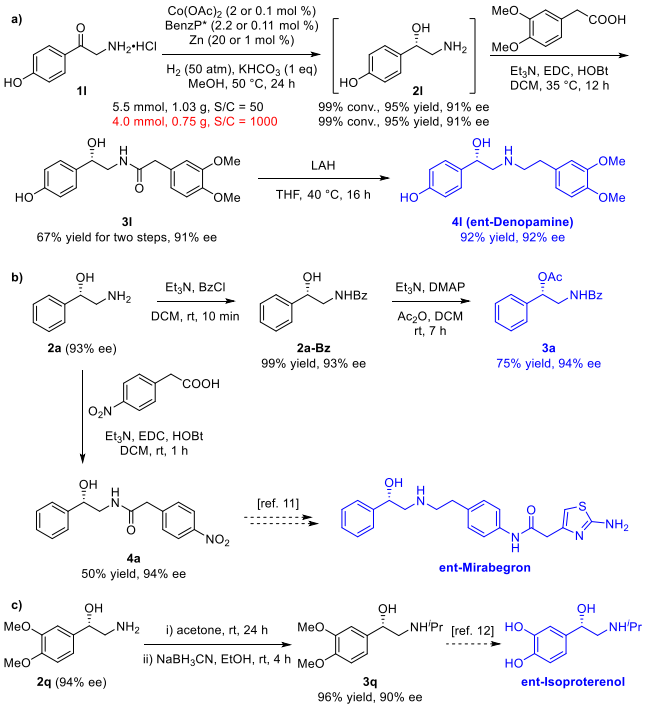
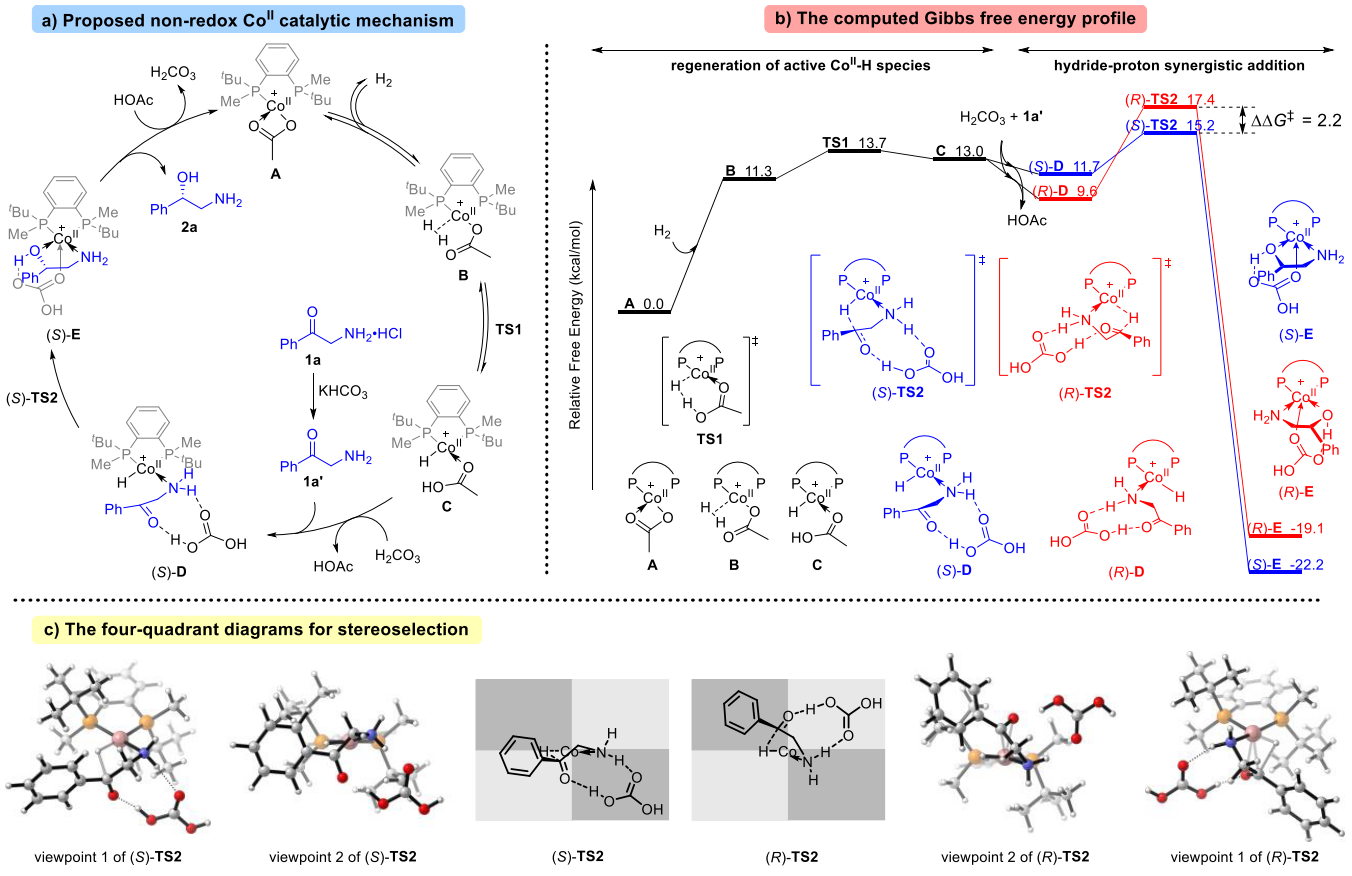
Scheme 3. Scaleup and Practical Applications



hydrogenation proceeds only via the ketone state rather than in its enol and enamine tautomer states. It also confirmed that H_2 is the hydrogen source and not MeOH. When probing into the role of base in the reaction, we found that compared to base species like Et_3N or KOH, $KHCO_3$ has a promotion effect on the reaction, the loading of which can be reduced to a catalytic amount (0.1 equiv) without affecting the reaction results for standard substrate **1a** (see Supporting Information 4.2 for details). As for the role of additives, we found that zinc acts as a promoter for the hydrogenation reaction, probably acting as Zn^{2+} Lewis acid[18] instead of taking effect at the catalyst preformulation stage (see Supporting Information 4.3 for details).

Based on the aforementioned experiments and density functional theory (DFT) calculations, a nonredox Co^{II} catalytic cycle and its energy profile are presented in Scheme 4. The mechanism mainly includes two parts: the formation of active Co^{II}–H species **C** and the reduction of the substrate **1a**. A molecule of hydrogen is first coordinated to the starting Co^{II} complex **A** then undergoes heterolytic cleavage under the action of acetate. The resulting active Co^{II}–H species **C** is converted to complex **D** through a series of ligand exchanges. Then, the carbon–oxygen double bond is reduced to a single bond through a hydride-proton synergistic addition transition state, **TS2**, in which the carbonic acid molecule plays as a proton shuttle in helping the C=O activation and proton transfer. The neutralized substrate **1a′** can combine with the cobalt center through two alternative chiral surfaces, therefore, producing two enantiomeric products (*S*)-**2a** and (*R*)-**2a**, and the $\Delta\Delta G^{\ddagger}$ of responding transition states is 2.2 kcal/mol,

Scheme 4. DFT Calculations[a]



[a]The unit of Gibbs free energy is kcal/mol. PBE0-D3/def2TZVP, SMD (methanol), 323.15 K, 50 atm.

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JACS Au 2023, 3, 2981–2986

which is matched with the experimental ee value (93% ee). Finally, the catalyst-product adduct **E** can release a molecule of the expected product **2a** and regenerate the initial Co^{II} complex **A**. For reference, several alternative mechanisms are also computed and proven to be unreasonable (see Schemes S2 and S6 for details). It is worth noting that the above mechanism is different from the "NH effect" activated outer-sphere mechanisms because the C═O bond in the transition state **TS2** is activated by the proton shuttle but not via the interaction with the M-NH.[11,46]

The four-quadrant diagram analysis (Scheme 4c) is also conducted to provide more information for the stereoselection. It is shown that the benzoyl group of (*R*)-**TS2** is located in the area with greater hindrance than that of (*S*)-**TS2**. In addition, the difference of distortion energy between the two transition states is 6.1 kcal/mol ($\Delta E = E_{dis(R)} - E_{dis(S)}$, see Supporting Information 8.3 for details), which further elucidates that steric hindrance is the main reason for the energy difference between the two stereoisomers ($\Delta\Delta G^{\ddagger}$ = 2.2 kcal/mol, matching with the 93% ee value).

In conclusion, an efficient cobalt-catalyzed asymmetric hydrogenation of the C═O bond has been realized, assisted by NH_2 coordination, affording chiral vicinal amino alcohols in high yields and with excellent enantioselectivities (up to 99% ee). The hydrogenation could be conducted on the gram scale with a low catalyst loading (up to 1000 S/C), and the resulting products could be further applied in various transformations. The mechanistic studies suggested a nonredox cobalt(II) catalytic cycle and a proton shuttle activated outer-sphere reaction mode.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.3c00524.

Synthetic details for substrates, procedures for hydrogenation reactions, spectra of NMR and HPLC data, computational details (PDF)

Crystallographic data for **2j** (CIF)

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Author Contributions

[§]H. Y., Y. H., and Y. Z. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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