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# Enantioselective Ruthenium(II)/Xyl-SunPhos/Daipen-Catalyzed Hydrogenation of γ-Ketoamides

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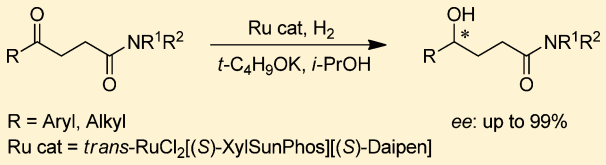
Supporting Information

**ABSTRACT:** A series of γ-hydroxy amides were synthesized with high enantioselectivities (up to 99%) using asymmetric hydrogenation of the corresponding γ-ketoamides in the presence of Ru-Xyl-SunPhos-Daipen catalyst providing key building blocks for a variety of naturally occurring and biologically active compounds.




## INTRODUCTION

Enantiomerically pure γ-hydroxy acid derivatives are important synthetic building blocks which can be easily transformed into a series of natural, pharmaceutical, and agrochemical compounds.[1] Currently, a number of methods are available for the synthesis of enantiomerically enriched γ-hydroxy acid derivatives via enzymatic reduction,[2] kinetic resolution,[3] asymmetric hydrosilylation,[4] hydroboration,[5] and other methods.[6] However, these synthetic routes suffered from either low efficiency or poor enantioselectivity. Accordingly, the search for effective and highly enantioselective approaches to access enantiomerically pure γ-hydroxy acid derivatives is of significance.

Catalytic asymmetric hydrogenation of ketones is one of the most practical and direct methods to prepare chiral alcohols and has attracted much attention both in academia and industry.[7] Both functionalized and nonfunctionalized ketones can be enantioselectively hydrogenated using efficient catalytic systems, and many effective chiral diphosphines have been developed for this important transformation.[8] Although the asymmetric hydrogenation of α- and β-ketoacid derivatives has been studied,[9] only a few approaches based on asymmetric hydrogenation of γ-ketoacid derivatives have been reported so far.[1g,10] In 1990, Noyori and co-workers described the first asymmetric hydrogenation of 4-oxo carboxylates catalyzed by $Ru(OCOCH_3)_2$[(*S*)-BINAP] in the presence of HCl at 100 atm for 110 h affording a mixture of γ-hydroxy carboxylates and γ-lactones.[10a] Later, Vinogradov and co-workers reported the enantioselective hydrogenation of levulinates in the presence of the Ru(II)-BINAP with 10 equiv of HCl to afford enantiomerically pure γ-lactone derivatives with 95% yield and 99% ee under an $H_2$ pressure of 60−70 atm.[10e] In 2008, a much simpler catalytic system, $RuCl_3$−BINAP-HCl, was used to achieve the asymmetric hydrogenation of γ-ketoesters.[10f] However, most of the hydrogenation methods employed high hydrogen pressure and long reaction time and were only effective for a limited substrate scope, yielding either γ-lactones or a mixture of γ-hydroxy carboxylates and γ-lactones. Consequently, using asymmetric hydrogenation to synthesize γ-hydroxy acid derivatives is still a challenging work.

It is well established that hydrogenation of functionalized ketones involves a chelating ring transition state.[9d,11] The seven-membered chelating ring transition state of γ-ketoesters with ruthenium is considered less stable than those of the five-membered ring transition state of α-ketoesters and a six-membered transition state of β-ketoesters. In order to enhance the reactivity of γ-functionalized ketones, we envisaged utilizing the hydrogenation of γ-ketoamides, which have a stronger coordination ability compared to esters and a lower tendency to form γ-lactones as reported by Brückner and ourselves.[12]

Our groups have been involved in an ongoing program toward the development of catalysts for asymmetric hydrogenation of ketone derivatives and their applications in organic synthesis including α- and β-keto acid derivatives, highly functionalized ketones, and simple ketones.[13] We report herein the application of diphosphine−ruthenium−diamine catalyst systems for the enantioselective synthesis of γ-hydroxy amides.

## RESULTS AND DISCUSSION

First, γ-keto Weinreb amides were chosen as standard substrates[14] in order to enhance the coordination ability of the $C(O)NR^1R^2$ amide moiety bearing methoxy and methyl groups ($R^1$= Me, $R^2$ = OMe) and because the resulting γ-hydroxy Weinreb amides could be easily converted to the corresponding γ-hydroxy ketones through nucleophilic addition using organometallic reagents, or reduced to chiral diols.

*N*-Methoxy-*N*-methyl-4-oxo-4-phenylbutanamide (**1a**) was chosen as the model substrate, and $[Ru(cymene)Cl_2]_2$-(*S*)-Sunphos was first set as the catalyst to investigate the

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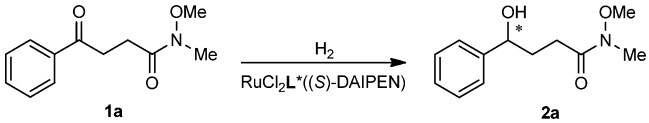
hydrogenation reaction. When the reaction was conducted in alcohols, low conversions were observed because of the formation of the Weinreb amine side product which probably poisoned the catalyst as previously reported.[12c] Although THF proved to be the solvent of choice for asymmetric hydrogenation of $\beta$-keto Weinreb amides,[12c] low conversion and poor enantioselectivity were obtained for the hydrogenation of **1a**. Aprotic solvents with weak coordinating ability, such as dichloromethane and 1,2-dichloroethane, were not efficient for this transformation. Unlike Noyori's work,[10a] no improvement was seen when HCl was added.

Considering the weak chelating ability of $\gamma$-keto acid derivatives to coordinate the Ru, we carried out the hydrogenation reaction using $RuCl_2$(diphosphine)(diamine) bifunctional catalyst which was developed by Noyori and coworkers and has been widely used in the hydrogenation of nonfunctionalized ketones.[15] Pleasingly, the hydrogenation of **1a** gave complete conversion with 85% ee at a S/C = 100 under 10 atm of hydrogen pressure at 30 °C in *i*-PrOH in the presence of *t*-$C_4H_9OK$ by employing $RuCl_2$[(*S*)-SunPhos][(*S*)-Daipen] as catalyst (Table 1, entry 1). However, when methyl 4-oxo-4-phenylbutanoate was reduced under the same reaction conditions, a mixture of products was obtained with 40% conversion.

**Table 1. Asymmetric Hydrogenation of $\gamma$-Keto Weinreb Amide Using Diphosphine−Ruthenium−Diamine Catalyst**[a]




**1a** **2a**

| entry | ligand | *T* (°C) | *P* (atm) | conv[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | (*S*)-SunPhos | 30 | 10 | 100 | 85 |
| 2 | (*S*)-BINAP | 30 | 10 | 100 | 93 |
| 3 | (*S*)-SegPhos | 30 | 10 | 73 | 83 |
| 4 | (*S*)-SYNPHOS | 30 | 10 | 96 | 87 |
| 5 | (*S*)-C3-Tunephos | 30 | 10 | 88 | 82 |
| 6 | **L1** | 30 | 10 | 100 | −51 |
| 7 | **L2** | 30 | 10 | 100 | 99 |
| 8[d] | **L3** | 30 | 10 | 53 | 1 |
| 9[e] | **L2** | 30 | | 20 | 99 |
| 10 | **L2** | 30 | 30 | 100 | 98 |
| 11 | **L2** | 30 | 50 | 100 | 98 |
| 12[d] | **L2** | 10 | 10 | 95 | 98 |
| 13 | **L2** | 50 | 10 | 100 | 98 |

[a]Unless otherwise stated, all reactions were carried out with a substrate (0.5 mmol) concentration of 0.25 M in *i*-PrOH at 30 °C for 15 h. Substrate/catalyst/*t*-BuOK = 100/1/5. [b]Determined by HPLC on a chiral AD-H column. [c]Determined by NMR analysis. [d]Reaction time: 30 h. [e]Without $H_2$.

Optimizations of the reaction conditions were performed for asymmetric hydrogenation of *N*-methoxy-*N*-methyl-4-oxo-4-phenylbutanamide (**1a**) including ligands, reaction temperatures and hydrogen pressures (Table 1). Although good enantioselectivities were obtained under the same reaction conditions using several commercially available chiral bidentate ligands, such as (*S*)-BINAP, (*S*)-SEGPhos, (*S*)-C3-TunePhos, and (*S*)-SYNPHOS (Figure 1, Table 1, entries 1−5), (*S*)-BINAP gave the highest ee value of 93% (Table 1, entry 2). Because minor changes of chiral ligands in geometric, steric, and electronic properties can lead to dramatic differences of

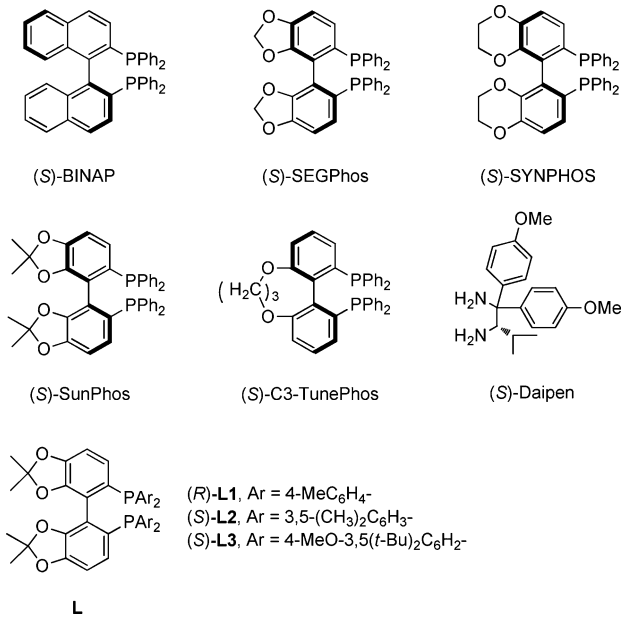



**Figure 1.** Structures of chiral bidentate ligands.

enantioselectivity, we tested the hydrogenation with ligands **L1**−**L3** (Table 1, entries 6−8). The best result was obtained using Xyl-SunPhos (**L2**), which provided the corresponding alcohol in full conversion and 99% ee (Table 1, entry 7). When the more sterically hindered ligand **L3** was used, the reaction led to poor enantioselectivity and conversion, and a racemic product was obtained with 53% conversion (Table 1, entry 8).

To verify whether the reaction involved a hydrogenation or transfer hydrogenation process, we conducted the reaction without $H_2$. Under the same reaction conditions, the product was obtained with 99% ee and 20% conversion (Table 1, entry 9). Apparently, the hydrogenation is much faster than transfer hydrogenation in this transformation. Increasing the $H_2$ pressure from 10 to 30 atm provided an equivalent reactivity and enantioselectivity, and a higher hydrogen pressure of 50 atm resulted in equivalent enantiomeric excess and conversion to 30 atm (Table 1, entry 11). It was interesting to observe that increasing or decreasing the reaction temperature did not obviously change the enantioselectivity but did slightly modify the reaction rate (Table 1, entries 12 and 13).

The optimized reaction conditions were therefore set as follows: $RuCl_2$[(*S*)-Xyl-SunPhos][(*S*)-Daipen] as the catalyst in *i*-PrOH and *t*-$C_4H_9OK$ as the base under 10 atm of $H_2$ at 30 °C for 15 h.

Under the optimized reaction conditions, a wide range of $\gamma$-keto Weinreb amides were hydrogenated, and the results are depicted in Table 2. The model substrate **1a** was hydrogenated to give a full conversion and 99% ee (Table 2, entry 1). To our delight, substrates with electron-donating groups and electron-withdrawing groups at the *para* position of the phenyl moiety were hydrogenated in full conversions with good to excellent enantioselectivities as high as 99%, and a wide tolerance of functional groups was observed (Table 2, entries 2−7). Substrates with a substituent at the *meta* position of the phenyl ring did not show any negative effect on the reaction. As a result, the hydrogenation of **1h** afforded the corresponding alcohol with complete conversion and 99% ee (Table 2, entry 8). However, the substrates possessing *ortho* substituents on the aromatic ring showed a different behavior considering both


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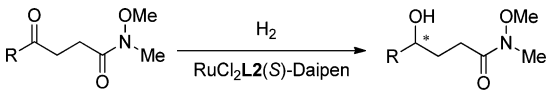
**Table 2. Asymmetric Hydrogenation of γ-Keto Weinreb Amides[a]**




1 2

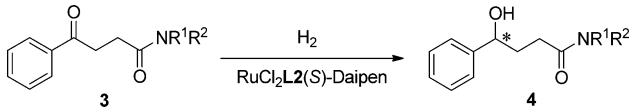
| entry | 1 | R | conv[b] (%) | yield[c] (%) | ee[d] (%) |
|---|---|---|---|---|---|
| 1 | **1a** | $C_6H_5$ | 100 | 92 | 99 |
| 2 | **1b** | 4-$MeC_6H_4$ | 100 | 92 | 98 |
| 3 | **1c** | 4-$OMeC_6H_4$ | 100 | 92 | 99 |
| 4 | **1d** | 4-$CF_3C_6H_4$ | 100 | 91 | 98 |
| 5 | **1e** | 4-$FC_6H_4$ | 100 | 92 | 99 |
| 6 | **1f** | 4-$ClC_6H_4$ | 100 | 91 | 99 |
| 7 | **1g** | 4-$BrC_6H_4$ | 100 | 91 | 99 |
| 8 | **1h** | 3-$MeC_6H_4$ | 100 | 91 | 99 |
| 9[e] | **1i** | 2-$MeC_6H_4$ | 100 | 90 | 97 |
| 10[e] | **1j** | 2-$OMeC_6H_4$ | 45 | 40 | 70 |
| 11[e] | **1k** | 2,4-$Me_2C_6H_4$ | 100 | 90 | 97 |
| 12 | **1l** | 2-naphthyl | 100 | 92 | 98 |
| 13 | **1m** | 2-furyl | 100 | 91 | 98 |
| 14 | **1n** | Me | 100 | 89 | 5 |
| 15[e] | **1o** | $C_6H_5CH_2$ | 80 | 72 | 8 |

[a]Unless otherwise stated, all reactions were carried out under 10 atm of $H_2$ for 15 h at 30 °C using 0.5 mmol of the substrate **1** in *i*-PrOH (0.5 M) containing the [$RuCl_2$(*S*)-Xyl-SunPhos(*S*)-Daipen] and *t*-$C_4H_9OK$. Substrate/catalyst/base = 100/1/5. [b]Determined by NMR analysis. [c]Isolated yield by column chromatography and trace of lactone was obtained. [d]Determined by HPLC on a ChiralPak column. [e]For 30 h.

reactivity and enantioselectivity. For a noncoordinating *o*-Me-substituted substrate **1i**, the reactivity dropped dramatically because of the steric effect but with an equivalent ee value (Table 2, entry 9). For the *o*-OMe-substituted γ-keto Weinreb amides (**1j**), the reaction afforded the desired product with much lower conversion and enantioselectivity because of the coordinating ability of the *o*-MeO group (Table 2, entry 10). Although the reaction time was prolonged to 30 h, the hydrogenation of **1j** could not give a full conversion. The substrate **1k** with two methyl group on the *ortho*- and *para*-position of the aryl gave results similar to those of **1i** (Table 2, entry 11). Asymmetric hydrogenation of substrates bearing other aromatic rings, such as **1l** and **1m**, led to the corresponding γ-hydroxy Weinreb amides with 98% and 98% ee, respectively (Table 2, entries 12 and 13). It was noteworthy that the alcohol resulting from hydrogenation of **1m** was obtained with higher yield and enantioselectivity (91% yield and 98% ee) compared to that prepared by the transfer hydrogenation process (87% yield and 91% ee). Compound **2m** was an important intermediate to synthesize nakiterpiosin.[1g] Unfortunately, the alkyl-substituted **1n** and the benzyl-substituted **1o** were hydrogenated with much lower ee (Table 2, entries 14 and 15), and for the compound **1o**, low conversion was observed even when the hydrogenation was conducted for 30 h.

Following the above reaction conditions, the scope of the reaction was then extended to other γ-ketoamides, and excellent enantioselectivities and yields were obtained for **3a**–**f**, with ee values ranging from 96% to 99% (Table 3). Moreover, *N*-cyclohexyl-4-hydroxy-4-phenylbutanamide **4f**, which was used by Yang and co-workers for the syntheses of a series of γ-aminoxy peptides, could be obtained by

**Table 3. Asymmetric Hydrogenation of γ-Ketoamides[a]**




3 4

| entry | 3 | $R^1$ | $R^2$ | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | **3a** | Me | Me | 97 | 99 |
| 2 | **3b** | Et | Et | 97 | 96 |
| 3 | **3c** | $-(CH_2)_4-$ | | 98 | 97 |
| 4 | **3d** | $-CH_2CH_2OCH_2CH_2-$ | | 97 | 97 |
| 5 | **3e** | H | Ph | 97 | 98 |
| 6 | **3f** | H | Cy | 98 | 97 |
| 7[d] | **3g** | H | H | 8 | 98 |

[a]Unless otherwise stated, all reactions were carried out under 10 atm of $H_2$ for 15 h at 30 °C using 0.5 mmol of the substrate **3** in *i*-PrOH (0.5 M) containing the [$RuCl_2$(*S*)-Xyl-SunPhos(*S*)-Daipen] and *t*-$C_4H_9OK$ with 100% conversion. Substrate/catalyst/base = 100/1/5. [b]Isolated yield by column chromatography [c]ee values were determined by HPLC. [d]12% conversion.

asymmetric hydrogenation of **3f** with 97% ee and up to a TON of 1000 instead of the low-yielding DIP-Cl or baker's yeast reduction of the γ-keto *tert*-butyl esters.[1f] However, when the substrate **3g** was hydrogenated, it gave a 98% ee with only 12% conversion and the hydrogenation reaction gave a complicated mixture (Table 3, entry 7).

## CONCLUSION

In summary, we have successfully achieved a highly enantioselective hydrogenation of a series of functionalized γ-keto amides with excellent yields and enantioselectivities up to 99% using a Ru/diphosphine/diamine catalyst system. This practical method has a broad substrate scope, and the corresponding γ-hydroxy amides, obtained under mild reaction conditions, provide valuable building blocks for the preparation of pharmaceutically and biologically relevant compounds.

## EXPERIMENTAL SECTION

**General Methods.** Commercially available reagents were used throughout without further purification beyond that detailed below: DMF and *i*-PrOH used in catalyst preparation and hydrogenation were distilled over calcium hydride. PE = petroleum ether, EA = ethyl acetate. All reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques unless otherwise noted. $^1H$ NMR and $^{13}C$ NMR spectra were obtained on a 400 MHz NMR spectrometer. The chemical shifts of $^1H$ NMR were recorded in ppm downfield from tetramethylsilane (TMS) with the solvent resonance as the internal standard. The chemical shifts of $^{13}C$ NMR were recorded in ppm downfield using the central peak of $CDCl_3$ (77.00 ppm) as the internal standard. Coupling constants (*J*) are reported in hertz and refer to apparent peak multiplications. HRMS were performed under ESI ionization technique on a Waters Micromass Q-TOF Premier mass spectrometer. Flash column chromatography was performed on silica gel (300–400 mesh). $[\alpha]_D$ values were recorded at the D line (589 nm) of a sodium lamp in a 0.5 dm cell at 25 °C.

**Preparation of 1a–l,o.**[16,17] To *N*,*N*′-dimethoxy-*N*,*N*′-dimethyl-succinamide (5.0 g, 24.5 mmol) in THF (40 mL) under $N_2$ atmosphere was added dropwise the corresponding Grignard reagent (26.9 mmol). Upon consumption of the starting material, the reaction was quenched with 10% HCl, and THF was removed in vacuum. The resulting aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous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$MgSO_4$. Evaporation was carried out under reduced pressure after filtration. The crude product was purified by column chromatography (PE/EA = 2/1).

*N-Methoxy-N-methyl-4-oxo-4-phenylbutanamide (**1a**):*[18] white solid; 4.5 g, 83% yield; mp 58.9−59.4 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03−7.96 (m, 2H), 7.58−7.51 (m, 1H), 7.48−7.42 (m, 2H), 3.77 (s, 3H), 3.33 (t, $J$ = 6.8 Hz, 2H), 3.20 (s, 3H), 2.89 (t, $J$ = 6.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 198.8, 173.1, 136.6, 132.9, 128.4, 127.9, 61.1, 32.8, 32.1, 25.9.

*N-Methoxy-N-methyl-4-oxo-4-(p-tolyl)butanamide (**1b**):*[19] white solid; 3.7 g, 65% yield; mp 64.2−65.3 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.95−7.86 (m, 2H), 7.28−7.26 (m, 1H), 7.25−7.23 (m, 1H), 3.78 (s, 3H), 3.32 (t, $J$ = 6.8 Hz, 2H), 3.21 (s, 3H), 2.89 (t, $J$ = 6.8 Hz, 2H), 2.40 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 198.6, 173.3, 143.8, 134.2, 129.2, 128.1, 61.2, 32.8, 32.2, 26.0, 21.6.

*N-Methoxy-N-methyl-4-oxo-4-(4-methoxyphenyl)butanamide (**1c**):*[19] white solid; 3.5 g, 57% yield; mp 56.9−58.0 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.00−7.95 (m, 2H), 6.94−6.88 (m, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 3.28 (t, $J$ = 6.4 Hz, 2H), 3.19 (s, 3H), 2.87 (t, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.2, 173.2, 163.2, 130.1, 129.6, 113.4, 61.0, 55.2, 32.4, 32.0, 25.9.

*N-Methoxy-N-methyl-4-oxo-4-(4-(trifluoromethyl)phenyl)-butanamide (**1d**):*[19] white solid; 6.0 g, 85% yield; mp 98.9−100.1 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.10 (d, $J$ = 8.0 Hz, 2H), 7.72 (d, $J$ = 8.0 Hz, 2H), 3.78 (s, 3H), 3.33 (t, $J$ = 6.4 Hz, 2H), 3.20 (s, 3H), 2.93 (t, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 198.0, 172.8, 139.3, 134.1 (q, $J$ = 33.0 Hz), 128.3, 125.5 (d, $J$ = 3.2 Hz), 123.5 (q, $J$ = 270.8 Hz), 61.1, 33.0, 32.0, 26.0.

*N-Methoxy-N-methyl-4-oxo-4-(4-fluorophenyl)butanamide (**1e**):* white solid; 4.7 g, 80% yield; mp 44.8−46.3 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.07−7.98 (m, 2H), 7.15−7.06 (m, 2H), 3.76 (s, 3H), 3.29 (t, $J$ = 6.4 Hz, 2H), 3.19 (s, 3H), 2.88 (t, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.0, 172.8, 165.4 (d, $J$ = 252.7 Hz), 132.9, 130.4 (d, $J$ = 9.2 Hz), 115.2 (d, $J$ = 21.7 Hz), 60.9, 32.5, 31.9, 25.8; HRMS calcd for $C_{12}H_{14}FNNaO_3$ (M + Na)$^+$ 262.0855, found 262.0853.

*N-Methoxy-N-methyl-4-oxo-4-(4-chlorophenyl)butanamide (**1f**):*[19] white solid; 3.0 g, 48% yield; mp 63.9−65.3 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.98−7.91 (m, 2H), 7.47−7.39 (m, 2H), 3.77 (s, 3H), 3.29 (t, $J$ = 6.4 Hz, 2H), 3.20 (s, 3H), 2.90 (t, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.6, 172.9, 139.3, 135.0, 129.4, 128.7, 61.1, 32.7, 32.1, 25.9.

*N-Methoxy-N-methyl-4-oxo-4-(4-bromophenyl)butanamide (**1g**):* white solid; 2.1 g, 29% yield; mp 69.6−71.3 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.91−7.82 (m, 2H), 7.63−7.55 (m, 2H), 3.76 (s, 3H), 3.28 (t, $J$ = 6.6 Hz, 2H), 3.19 (s, 3H), 2.89 (t, $J$ = 6.2 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.8, 172.9, 135.3, 131.7, 129.5, 128.0, 61.1, 32.7, 32.1, 25.9; HRMS calcd for $C_{12}H_{14}BrNNaO_3$ (M + Na)$^+$ 322.0055, found 322.0049.

*N-Methoxy-N-methyl-4-oxo-4-(m-tolyl)butanamide (**1h**):*[19] white solid; 3.8 g, 66% yield; mp 50.2−51.3 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.85−7.75 (m, 2H), 7.41−7.30 (m, 2H), 3.77 (s, 3H), 3.32 (t, $J$ = 6.4 Hz, 2H), 3.20 (s, 3H), 2.89 (t, $J$ = 6.4 Hz, 2H), 2.40 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.0, 173.1, 138.1, 136.6, 133.6, 128.4, 128.2, 125.1, 61.1, 32.9, 32.1, 26.0, 21.2.

*N-Methoxy-N-methyl-4-oxo-4-(o-tolyl)butanamide (**1i**):*[19] colorless oil; 3.3 g, 57% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.75 (d, $J$ = 8.0 Hz, 1H), 7.34 (t, $J$ = 7.4 Hz, 1H), 7.22 (t, $J$ = 7.4 Hz, 2H), 3.75 (s, 3H), 3.21 (t, $J$ = 6.4 Hz, 2H), 3.19 (s, 3H), 2.87 (t, $J$ = 6.4 Hz, 2H), 2.48 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 202.5, 172.9, 137.5, 131.4, 130.8, 128.3, 125.3, 60.8, 35.3, 31.9, 26.0, 20.9.

*N-Methoxy-N-methyl-4-oxo-4-(2-methoxyphenyl)butanamide (**1j**):* yellow oil; 2.9 g, 47% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.75 (dd, $J$ = 8.0, 1.8 Hz, 1H), 7.45 (m, 1H), 7.03−6.92 (m, 2H), 3.91 (s, 3H), 3.76 (s, 3H), 3.35 (t, $J$ = 6.8 Hz, 2H), 3.20 (s, 3H), 2.85 (t, $J$ = 6.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.3, 173.2, 158.4, 133.2, 129.9, 127.3, 120.1, 111.2, 60.7, 55.1, 37.8, 31.7, 25.9; HRMS calcd for $C_{13}H_{17}NNaO_4$ (M + Na)$^+$ 274.1055, found 274.1050.

*N-Methoxy-N-methyl-4-(2,4-dimethylphenyl)-4-oxobutanamide (**1k**):* yellow oil; 3.6 g, 60% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.71 (d, $J$ = 8.0 Hz, 1H), 7.09−7.01 (m, 2H), 3.76 (s, 3H), 3.23 (t, $J$ = 6.6 Hz, 2H), 3.20 (s, 3H), 2.86 (t, $J$ = 6.6 Hz, 2H), 2.48 (s, 3H), 2.34 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 202.0, 173.3, 141.7, 138.4, 134.6, 132.6, 129.1, 126.2, 61.1, 35.2, 32.2, 26.2, 21.4, 21.2; HRMS calcd for $C_{14}H_{19}NNaO_3$ (M + Na)$^+$ 272.1263, found 272.1258.

*N-Methoxy-N-methyl-4-(naphthalen-2-yl)-4-oxobutanamide (**1l**):* white solid; 3.4 g, 51% yield; mp 83.7−85.4 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.56 (s, 1H), 8.06 (dd, $J$ = 8.8, 1.6 Hz, 1H), 7.97 (d, $J$ = 7.2 Hz, 1H), 7.89 (t, $J$ = 8.4 Hz, 2H), 7.58 (m, 2H), 3.80 (s, 3H), 3.49 (t, $J$ = 6.4 Hz, 2H), 3.23 (s, 3H), 2.97 (t, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 198.7, 173.1, 135.4, 133.9, 132.4, 129.7, 129.4, 128.2, 127.6, 126.6, 123.7, 61.1, 32.9, 32.1, 26.0; HRMS calcd for $C_{16}H_{17}NNaO_3$ (M + Na)$^+$ 294.1106, found 294.1104.

*N-Methoxy-N-methyl-4-oxo-5-phenylpentanamide (**1o**):* light yellow oil; 1.4 g, 24% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.29 (m, 2H), 7.27−7.20 (m, 3H), 3.77 (s, 2H), 3.70 (s, 3H), 3.16 (s, 3H), 2.78 (t, $J$ = 6.0 Hz, 2H), 2.69 (t, $J$ = 5.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 207.0, 172.7, 134.0, 129.2, 128.4, 126.6, 60.9, 49.8, 35.8, 31.9, 25.7; HRMS calcd for $C_{13}H_{17}NNaO_3$ (M + Na)$^+$ 258.1106, found 258.1104.

**Preparation of 4-(Furan-2-yl)-*N*-methoxy-*N*-methyl-4-oxobutanamide (1m).**[1g,20] Succinic anhydride (10.0 g, 100.0 mmol) was dissolved in $CH_2Cl_2$ (120 mL), and furan (13.6 g, 200.0 mmol) was added to the mixture. Then, $AlCl_3$ (13.3 g, 100.0 mmol) was added in portions to the mixture at 0 °C. The mixture was warmed to room temperature and stirred for 4 h. The mixture was poured into HCl (2 M, 100 mL) to acidify to pH = 2 at 0 °C, and the layers were partitioned. The aqueous layer was extracted with $CH_2Cl_2$ thoroughly, and the organic layers were washed with water and saturated brine, dried with $Na_2SO_4$, and concentrated in vacuo. After purification by flash chromatography, the 4-(furan-2-yl)-4-oxobutanoic acid was obtained. To a solution of 4-(furan-2-yl)-4-oxobutanoic acid (5.0 g, 29.7 mmol) in dry $CH_2Cl_2$ (100 mL) was added carbonyl diimidazole (5.8 g, 35.7 mmol), and the mixture was stirred for 1 h under room temperature. Then, *N*,*O*-dimethylhydroxylamine hydrochloride (3.5 g, 36.7 mmol) and $NEt_3$ (6.0 g, 59.5 mmol) were added to the mixture. After the mixture was stirred for overnight at 25 °C, water (100 mL) was added, and the aqueous phase was extracted with $CH_2Cl_2$ (50 mL × 3). The combined organic phases was washed with saturated brine (50 mL × 1) and dried over $Na_2SO_4$. The crude product was purified by column chromatography (PE/EA = 2/1) to give **1m** as light yellow oil (20% yield): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.58 (dd, $J$ = 1.6, 0.8 Hz, 1H), 7.22 (dd, $J$ = 3.6, 0.8 Hz, 1H), 6.52 (dd, $J$ = 3.6, 1.6 Hz, 1H), 3.75 (s, 3H), 3.23−3.14 (m, 5H), 2.87 (t, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 187.8, 172.7, 152.2, 146.1, 116.8, 111.9, 61.0, 32.4, 31.9, 25.5.

**Typical Procedure for the Preparation of 1n, 3a−f.**[21] 4-Oxopentanoic acid (5 g, 43.1 mmol) was added to *N*,*O*-dimethylhydroxylamine hydrochloride (5.0 g, 51.7 mmol) in $CH_2Cl_2$ (120 mL). To this mixture was added 1-ethyl-3-(3-(dimethylamino)-propyl)carbodiimide (9.9 g, 51.7 mmol) in one batch at 0 °C, and then $Et_3N$ (8.7 g, 86.1 mmol) was added dropwise over 10 min. The ice bath was removed and the temperature maintained at room temperature overnight. The mixture was poured into water (100 mL), and the aqueous phase was extracted with $CH_2Cl_2$ (50 mL × 3). The combined organic phase was washed with saturated brine and dried over $Na_2SO_4$. The crude product was purified by column chromatography (PE/EA = 2/1) to give **1n**. Similarly, compounds (**3a−f**) were prepared from 4-oxo-4-phenylbutanoic acid, and the corresponding amines and the products were purified by column chromatography (PE/EA = 2/1).

*N-Methoxy-N-methyl-4-oxopentanamide (**1n**):*[22] colorless oil; 3.7 g, 55% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.72 (s, 3H), 3.17 (s, 3H), 2.82−2.65 (m, 4H), 2.20 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 207.2, 172.8, 60.8, 37.1, 31.8, 29.7, 25.5.

*N,N-Dimethyl-4-oxo-4-phenylbutanamide (**3a**):*[23] colorless oil; 4.1 g, 72% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02−7.99 (m, 2H), 7.55−7.48 (M, 1H), 7.47−7.41 (m, 2H), 3.34 (t, $J$ = 6.6 Hz, 2H), 3.08 (s, 3H), 2.95 (s, 3H), 2.77 (t, $J$ = 6.6 Hz, 2H); $^{13}$C NMR (100 MHz,


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$CDCl_3$) δ 198.8, 171.2, 136.4, 132.6, 128.1, 127.63, 36.6, 35.0, 33.2, 26.8.

*N,N-Diethyl-4-oxo-4-phenylbutanamide (**3b**):*[24] light yellow oil; 5.2 g, 79% yield; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.02−7.99 (m, 2H), 7.80−7.74 (m, 1H), 7.48−7.39 (m, 2H), 3.45−3.30 (m, 6H), 2.76 (t, *J* = 6.6 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H)l $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.1, 170.5, 136.7, 132.8, 128.3, 127.8, 41.7, 40.1, 33.6, 26.9, 14.00, 12.9.

*1-Phenyl-4-(piperidin-1-yl)butane-1,4-dione (**3c**):*[25] white solid; 3.8 g, 56% yield; mp 49.8−52.1 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.05−7.98 (m, 2H), 7.57−7.73 (m, 1H), 7.49−7.42 (m, 2H), 3.55 (t, *J* = 5.6 Hz, 2H), 3.49 (t, *J* = 5.2 Hz, 2H), 3.34 (t, *J* = 6.8 Hz, 2H), 2.78 (t, *J* = 6.8 Hz, 2H), 1.69−1.58 (m, 4H), 1.56−1.51 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.1, 169.6, 136.6, 132.7, 128.3, 127.8, 46.2, 42.6, 33.4, 26.9, 26.1, 25.3, 24.3.

*1-Morpholino-4-phenylbutane-1,4-dione (**3d**):*[26] white solid; 3.5 g, 50% yield; mp 85.4−86.9 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.03−8.00 (m, 2H), 7.56−7.44 (m, 1H), 7.50−7.41 (m, 2H), 3.72 (t, *J* = 4.8 Hz, 2H), 3.68 (t, *J* = 4.6 Hz, 2H), 3.62 (t, *J* = 4.6 Hz, 2H), 3.58 (t, *J* = 4.8 Hz, 2H), 3.37 (t, *J* = 6.4 Hz, 2H), 2.77 (t, *J* = 6.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.9, 170.2, 136.6, 133.0, 128.4, 128.0, 66.7, 66.4, 45.69, 42.0, 33.4, 26.8.

*N-Phenyl-4-oxo-4-phenylbutanamide (**3e**):*[25] white solid; 4.5 g, 63% yield; mp 150.4−151.6 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.04−7.94 (m, 2H), 7.83 (s, 1H), 7.60−7.45 (m, 5H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 3.46 (t, *J* = 6.4 Hz, 2H), 2.82 (t, *J* = 6.2 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.3, 170.4, 138.0, 136.3, 133.4, 128.9, 128.6, 128.1, 124.1, 119.7, 34.1, 31.4.

*N-Cyclohexyl-4-oxo-4-phenylbutanamide (**3f**):*[27] white solid; 4.0 g, 51% yield; mp 102.1−103.0 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.00−7.97 (m, 2H), 7.58−7.54 (m, 1H), 7.49−7.42 (m, 2H), 5.61 (s, 1H), 3.79−3.70 (m, 1H), 3.36 (t, *J* = 6.6 Hz, 2H), 2.59 (t, *J* = 6.6 Hz, 2H), 1.96−1.85 (m, 2H), 1.76−1.65 (m, 2H), 1.62−1.57 (m, 1H), 1.40−1.29 (m, 2H), 1.22−1.08 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.2, 171.0, 136.6, 133.2, 128.6, 128.0, 48.2, 34.2, 33.1, 30.5, 25.5, 24.8.

**Preparation of 4-Oxo-4-phenylbutanamide (3g).**[1c,28] Methyl 4-oxo-4-phenylbutanoate (2.0 g, 10.4 mmol) was dissolved in MeOH (30 mL). Then, ammonium hydroxide (25−28%, 30 mL) was added to the mixture. The mixture was stirred for 12 h at 40 °C and concentrated in vacuo. The aqueous phase was extracted with $CH_2Cl_2$ (20 mL × 3).The combined organic phases were washed with water and saturated brine (20 mL × 1) and dried over $Na_2SO_4$. The crude product was purified by column chromatography (PE/EA = 1/3) to give **1m** as a light yellow solid: 0.97 g, 53% yield; mp 123.2−124.1 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.00−7.97 (m, 2H), 7.60−7.53 (m, 1H), 7.50−7.42 (m, 2H), 5.86 (s, 1H), 5.62 (s, 1H), 3.37 (t, *J* = 6.4 Hz, 2H), 2.67 (t, *J* = 6.4 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 199.0, 175.0, 136.3, 133.3, 128.6, 128.0, 33.8, 29.3.

**Typical Procedure for the Asymmetric Hydrogenation.** To a 25 mL Schlenk tube were added $[RuCl_2$ (cymene)$]_2$ (6.0 mg, 0.01 mmol) and (*S*)-Xyl-SunPhos (17.2 mg, 0.022 mmol). The tube was vacuumed and purged with nitrogen for three times before addition of freshly distilled and freeze-and-thaw degassed DMF (3 mL). The resulting mixture was heated at 100 °C for 10 min before it was cooled to room temperature, and then (*S*)-Daipen (6.8 mg, 0.022 mmol) was added under $N_2$. The tube was vacuumed and purged with nitrogen for three times before it was heated at 40 °C for 5 h. The solvent was removed under vacuum to give the catalyst as a yellow solid. The catalyst was dissolved in degassed *i*-PrOH (4 mL),and then the solution was equally charged into four vials which contained 0.5 mmol of substrates, *t*-BuOK (2.8 mg, 0.025 mmol), and 1 mL of *i*-PrOH. The vials were then transferred into 300 mL autoclaves. The autoclaves were purged three times with $H_2$, and the required pressure of $H_2$ was set. The autoclaves were stirred under specified reaction conditions. After being cooled to ambient temperature and careful release of the hydrogen, the autoclaves were opened and the solvent was evaporated. The reaction solution was purified by a silica gel column to give the corresponding hydrogenation products, which was then directly analyzed by HPLC to determine the enantiomeric excess.

*4-Hydroxy-N-methoxy-N-methyl-4-phenylbutanamide (**2a**):* colorless oil; 102.8 mg, 92% yield; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40−7.31 (m, 4H), 7.27−7.23 (m, 1H), 4.81−4.78 (m, 1H), 3.64 (s, 3H), 3.51 (b, 1H), 3.19 (s, 3H), 2.58 (t, *J* = 6.0 Hz, 2H), 2.14−2.03 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.7, 144.5, 128.1, 127.0, 125.6, 73.3, 61.0, 33.3, 32.0, 28.1; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 mL/min, 210 nm) $t_1$ = 14.2 min, $t_2$ = 15.3 min; $[\alpha]^{25}_D$ = +23.8 (*c* 1.52, $CH_2Cl_2$); HRMS calcd for $C_{12}H_{17}NNaO_3$ $(M + Na)^+$ 246.1106, found 246.1100. The absolute configuration of **2a** was assigned as *R* on the basis of the optical rotation of γ-phenyl-γ-butyrolactone **2a′**.[29,30]

*γ-Phenyl-γ-butyrolactone (**2a′**):*[29] colorless oil; 358.8 mg, 92% yield; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.43−7.31 (m, 5H), 5.54−5.50 (m, 1H), 2.73−2.60 (m, 3H), 2.28−2.12 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.8, 139.2, 128.5, 128.2, 125.1, 81.1, 30.7, 28.8; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 65/35, 0.7 mL/min, 210 nm) $t_1$ = 15.7 min, $t_2$ = 20.7 min; $[\alpha]^{26}_D$ = +37.1 (*c* 0.5, $CHCl_3$) [lit. $[\alpha]^{26}_D$ = +30.0 (*c* 0.5, $CHCl_3$), 97% ee for *R* enantiomer].

*4-Hydroxy-N-methoxy-N-methyl-4-(p-tolyl)butanamide (**2b**):* colorless oil; 108.6 mg, 91% yield; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 4.75−4.73 (m, 1H), 3.64 (s, 3H), 3.19 (s, 3H), 2.58 (t, *J* = 6.4 Hz, 2H), 2.33 (s, 3H), 2.12−2.05 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.7, 141.5, 136.6, 128.8, 125.5, 73.2, 61.0, 33.2, 32.0, 28.1, 20.9; HPLC (Chiralcel OJ-H column, hexane/*i*-PrOH = 88/12, 0.7 mL/min, 210 nm) $t_1$ = 29.1 min, $t_2$ = 30.1 min. $[\alpha]^{25}_D$ = +21.3 (*c* 1.20, $CH_2Cl_2$); HRMS calcd for $C_{13}H_{19}NNaO_3$ $(M + Na)^+$ 260.1263, found 260.1260.

*4-Hydroxy-N-methoxy-N-methyl-4-(4-methoxyphenyl)-butanamide (**2c**):* colorless oil; 116.1 mg, 92% yield; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32−7.27 (m, 2H), 6.89−6.86 (m, 2H), 4.78−4.70 (m, 1H), 3.80 (s, 3H), 3.65 (s, 3H), 3.27 (s, 1H), 3.19 (s, 3H), 2.59−2.56 (m, 2H), 2.09−2.04 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.7, 158.7, 136.7, 126.9, 113.6, 73.1, 61.1, 55.1, 33.3, 32.1, 28.3; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 70/30, 1.0 mL/min, 210 nm) $t_1$ = 11.1 min, $t_2$ = 16.0 min; $[\alpha]^{25}_D$ = +19.2 (*c* 1.03, $CH_2Cl_2$); HRMS calcd for $C_{13}H_{19}NNaO_4$ $(M + Na)^+$ 276.1212, found 276.1211.

*4-Hydroxy-N-methoxy-N-methyl-4-(4-(trifluoromethyl)phenyl)-butanamide (**2d**):* white solid; 132.9 mg, 91% yield; mp 81.7−83.6 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.59−7.47 (m, 2H), 4.87−4.85 (m, 1H), 4.17 (s, 1H), 3.65 (s, 3H), 3.20 (s, 3H), 2.60 (s, 2H), 2.16−1.98 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.6, 148.8, 129.2 (q, *J* = 32.0 Hz) 125.9, 125.1 (d, *J* = 3.4 Hz), 122.8, 72.8, 61.1, 33.2, 32.1, 28.1; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.5 mL/min, 210 nm) $t_1$ = 17.9 min, $t_2$ = 19.2 min; $[\alpha]^{25}_D$ = +11.4 (*c* 0.91, $CH_2Cl_2$); HRMS calcd for $C_{13}H_{16}F_3NNaO_3$ $(M + Na)^+$ 314.0980, found 314.0984.

*4-(4-Fluorophenyl)-4-hydroxy-N-methoxy-N-methylbutanamide (**2e**):* colorless oil; 111.3 mg, 92% yield; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37−7.30 (m, 2H), 7.05−6.98 (m, 2H), 4.80−4.77 (m, 1H), 3.69 (s, 1H), 3.65 (s, 3H), 3.20 (s, 3H), 2.61−2.58 (m, 2H), 2.11−2.00 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.6, 161.7 (d, *J* = 243.1 Hz) 140.3, 127.2 (d, *J* = 7.9 Hz), 114.8 (d, *J* = 21.1 Hz), 72.7, 61.0, 33.4, 32.0, 28.01; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 88/12, 0.7 mL/min, 210 nm) $t_1$ = 53.3 min, $t_2$ = 56.0 min; $[\alpha]^{25}_D$ = +21.6 (*c* 1.09, $CH_2Cl_2$); HRMS calcd for $C_{12}H_{16}FNNaO_3$ $(M + Na)^+$ 264.1012, found 264.1009.

*4-(4-Chlorophenyl)-4-hydroxy-N-methoxy-N-methylbutanamide (**2f**):* colorless oil; 117.4 mg, 91% yield; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 4H), 4.76−4.73 (m, 1H), 3.99 (s, 1H), 3.64 (s, 3H), 3.17 (s, 3H), 2.57−2.56 (m, 2H), 2.10−1.95 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.5, 143.1, 132.5, 128.2, 127.0, 72.5, 61.0, 33.22, 32.0, 28.0; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.5 mL/min, 210 nm) $t_1$ = 24.0 min, $t_2$ = 25.7 min; $[\alpha]^{25}_D$ = +17.4 (*c* 2.40, $CH_2Cl_2$); HRMS calcd for $C_{12}H_{16}ClNNaO_3$ $(M + Na)^+$ 280.0716, found 280.0718.

*4-(4-Bromophenyl)-4-hydroxy-N-methoxy-N-methylbutanamide (**2g**):* colorless oil; 137.0 mg, 91% yield; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.47−7.41 (m, 2H), 7.26−7.20 (m, 2H), 4.76−4.73 (m, 1H), 3.97 (s, 1H), 3.64 (s, 3H), 3.18 (s, 3H), 2.58−2.57 (m, 2H), 2.11−1.95 (m,


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2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.5, 143.6, 131.1, 127.4, 120.6, 72.5, 61.0, 33.2, 32.0, 27.9; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.5 mL/min, 210 nm) $t_1$ = 26.2 min, $t_2$ = 28.7 min; $[\alpha]^{25}_D$ = +16.2 (*c* 2.50, $CH_2Cl_2$); HRMS calcd for $C_{12}H_{16}BrNNaO_3$ $(M + Na)^+$ 324.0211, found 324.0201.

*4-Hydroxy-N-methoxy-N-methyl-4-(m-tolyl)butanamide* (**2h**): colorless oil; 108.3 mg, 91% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.23−7.05 (m, 4H), 4.74−4.71 (m, 1H), 3.63 (s, 3H), 3.18 (s, 3H), 2.57 (s, 2H), 2.34 (s, 3H), 2.12−1.99 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.7, 144.4, 137.7, 128.0, 127.8, 126.3, 122.7, 73.32, 61.00, 33.3, 32.0, 28.2, 21.3; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.5 mL/min, 210 nm) $t_1$ = 19.7 min, $t_2$ = 23.5 min; $[\alpha]^{25}_D$ = +22.6 (*c* 1.60, $CH_2Cl_2$); HRMS calcd for $C_{13}H_{19}NNaO_3$ $(M + Na)^+$ 260.1263, found 260.1261.

*4-Hydroxy-N-methoxy-N-methyl-4-(o-tolyl)butanamide* (**2i**): colorless oil; 106.5 mg, 90% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.53−7.51 (m, 1H), 7.25−7.10 (m, 3H), 5.03−5.00 (m, 1H), 3.67 (s, 3H), 3.33 (s, 1H), 3.20 (s, 3H), 2.71−2.56 (m, 2H), 2.34 (s, 3H), 2.11−1.95 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.8, 142.7, 134.1, 130.2, 126.8, 126.0, 125.1, 69.9, 61.1, 32.1, 31.9, 28.4, 18.9; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 90/10, 0.5 mL/min, 210 nm) $t_1$ = 30.6 min, $t_2$ = 34.3 min; $[\alpha]^{25}_D$ = +41.7 (*c* 1.50, $CH_2Cl_2$); HRMS calcd for $C_{13}H_{19}NNaO_3$ $(M + Na)^+$ 260.1263, found 260.1263.

*4-Hydroxy-N-methoxy-N-methyl-4-(2-methoxyphenyl)-butanamide* (**2j**): colorless oil; 51.1 mg, 40% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.38 m, 1H), 7.25−7.19 (m, 1H), 6.97−6.85 (m, 2H), 4.96 (t, *J* = 6.0 Hz, 1H), 3.83 (s, 3H), 3.65 (s, 3H), 3.19 (s, 3H), 2.72−2.53 (m, 2H), 2.12 (q, *J* = 6.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.0, 156.1, 132.2, 128.0, 126.7, 120.5, 110.2, 69.7, 61.0, 55.1, 32.1, 31.3, 28.5; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 mL/min, 210 nm) $t_1$ = 17.7 min, $t_2$ = 20.2 min; $[\alpha]^{25}_D$ = +34.9 (*c* 1.34, $CH_2Cl_2$); HRMS calcd for $C_{13}H_{19}NNaO_4$ $(M + Na)^+$ 276.1212, found 276.1213.

*4-Hydroxy-N-methoxy-N-methyl-4-(2,4-dimethylphenyl)-butanamide* (**2k**): colorless oil; 113.3 mg, 90% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37 (d, *J* = 7.6 Hz, 1H), 7.05−6.91 (m, 2H), 4.96−4.93 (m, 1H), 3.65 (s, 3H), 3.31 (s, 1H), 3.18 (s, 3H), 2.70−2.55 (m, 2H), 2.29 (s, 6H), 2.07−1.92 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.7, 139.6, 136.2, 133.9, 130.8, 126.5, 125.0, 69.6, 61.0, 31.9, 28.3, 20.8, 18.7; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.5 mL/min, 210 nm) $t_1$ = 21.2 min, $t_2$ = 23.2 min; $[\alpha]^{25}_D$ = +39.7 (*c* 1.60, $CH_2Cl_2$); HRMS calcd for $C_{14}H_{21}NO_3$ $(M + Na)^+$ 274.1419, found 274.1409.

*4-Hydroxy-N-methoxy-N-methyl-4-(naphthalen-2-yl)-butanamide* (**2l**): colorless oil; 125.6 mg, 92% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.86−7.79 (m, 4H), 7.53−7.41 (m, 3H), 4.99−4.98 (m, 1H), 3.73 (s, 1H), 3.62 (s, 3H), 3.20 (s, 3H), 2.62 (t, *J* = 5.2 Hz, 2H), 2.26−2.11 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.6, 141.9, 133.1, 132.6, 127.8, 127.7, 127.4, 125.8, 125.4, 124.2, 125.0, 73.2, 60.9, 33.1, 32.0, 28.0; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 mL/min, 210 nm) $t_1$ = 22.4 min, $t_2$ = 23.9 min; $[\alpha]^{25}_D$ = +12.5 (*c* 1.80, $CH_2Cl_2$); HRMS calcd for $C_{16}H_{19}NNaO_3$ $(M + Na)^+$ 296.1263, found 296.1262.

*4-Hydroxy-N-methoxy-N-methyl-4-(furan-2-yl)butanamide* (**2m**):[19] colorless oil; 103.8 mg, 91% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.34 (m, 1H), 6.36−6.19 (m, 2H), 4.78−4.75 (m, 1H), 3.65 (s, 3H), 3.17 (s, 3H), 2.59 (t, *J* = 6.4 Hz, 2H), 2.21−2.12 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.3, 156.5, 141.4, 109.8, 109.6, 105.5, 66.8, 61.0, 31.9, 29.9, 27.7; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 80/20, 1.0 mL/min, 210 nm) $t_1$ = 7.9 min, $t_2$ = 11.6 min; $[\alpha]^{25}_D$ = +7.8 (*c* 2.30, $CH_2Cl_2$).

*4-Hydroxy-N-methoxy-N-methylpentanamide* (**2n**):[31] colorless oil; 71.9 mg, 89% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.87−3.78 (m, 1H), 3.68 (s, 3H), 3.17 (s, 3H), 2.67−2.48 (m, 2H), 1.86−1.67 (m, 2H), 1.19 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.8, 67.3, 61.1, 33.3, 32.1, 28.3, 23.4. $[\alpha]^{25}_D$ = +0.2 (*c* 1.10, $CH_2Cl_2$).

*5-(Methoxy(methyl)amino)-5-oxopentan-2-yl-4-nitrobenzoate* (**2n′**). To the hydroxyl product (0.14 g, 0.9 mmol) in $CH_2Cl_2$ (5 mL) were added 4-nitrobenzoyl chloride (0.48 g, 2.7 mmol), pyridine (0.21 g, 2.7 mmol), and a catalytic amount of DMAP (0.01 g, 0.09 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h and then concentrated and flash column chromatographed to give the desired product: yellow oil; 191.3 mg, 71% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.31−8.27 (m, 2H), 8.23−8.18 (m, 2H), 5.31−5.15 (m, 1H), 3.62 (s, 3H), 3.14 (s, 3H), 2.54 (t, *J* = 7.6 Hz, 2H), 2.16−2.01 (m, 2H), 1.41 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.3, 164.1, 150.3, 135.9, 130.6, 127.2, 123.8, 123.4, 72.5, 61.1, 32.0, 30.5, 27.8, 20.0; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 80/20, 1.0 mL/min, 210 nm) $t_1$ = 19.0 min, $t_2$ = 27.1 min.

*4-Hydroxy-N-methoxy-N-methyl-5-phenylpentanamide* (**2o**): colorless oil; 85.6 mg, 72% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.33−7.28 (m, 2H), 7.25−7.19 (m, 3H), 3.86 (s, 1H), 3.68 (s, 3H), 3.19 (s, 3H), 2.79−2.77 (m, 2H), 2.72−2.53 (m, 3H), 1.99−1.86 (m, 1H), 1.80−1.70 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.5, 129.4, 128.5, 126.4, 72.4, 61.2, 44.2, 40.1, 32.2, 30.9, 28.5; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 90/10, 0.5 mL/min, 210 nm) $t_1$ = 26.6 min, $t_2$ = 31.0 min. $[\alpha]^{25}_D$ = +0.7 (*c* 0.28, $CH_2Cl_2$); HRMS calcd for $C_{13}H_{19}NNaO_3$ $(M + Na)^+$ 260.1263, found 260.1256.

*4-Hydroxy-N,N-dimethyl-4-phenylbutanamide* (**4a**):[27] colorless oil; 101.0 mg, 97% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39−7.30 (m, 4H), 7.26−7.22 (m, 1H), 4.81−4.77 (m, 1H), 4.29 (d, *J* = 3.6 Hz, 1H), 2.97 (s, 3H), 2.96 (s, 3H), 2.46 (t, *J* = 6.4 Hz, 2H), 2.16−2.02 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.5, 144.7, 128.0, 126.8, 125.5, 73.1, 37.1, 35.3, 33.7, 29.5; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.5 mL/min, 210 nm) $t_1$ = 19.0 min, $t_2$ = 21.8 min; $[\alpha]^{25}_D$ = +27.6 (*c* 1.70, $CH_2Cl_2$).

*N,N-Diethyl-4-hydroxy-4-phenylbutanamide* (**4b**): yellow oil; 114.3 mg, 97% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.41−7.30 (m, 4H), 7.26−7.21 (m, 1H), 4.82−4.80 (m, 1H), 4.50 (s, 1H), 3.44−3.34 (m, 2H), 3.27 (q, *J* = 7.2 Hz, 2H), 2.47 (t, *J* = 6.2 Hz, 2H), 2.19−2.03 (m, 2H), 1.13 (t, *J* = 7.2 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.5, 144.7, 127.8, 126.6, 125.4, 72.9, 41.8, 40.1, 33.8, 29.3, 29.1, 13.7, 12.7; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 mL/min, 210 nm) $t_1$ = 10.9 min, $t_2$ = 11.8 min; $[\alpha]^{25}_D$ = +30.0 (*c* 1.02, $CH_2Cl_2$); HRMS calcd for $C_{14}H_{21}NNaO_2$ $(M + Na)^+$ 258.1470, found 258.1465.

*4-Hydroxy-4-phenyl-1-(piperidin-1-yl)butan-1-one* (**4c**):[27] colorless oil; 121.3 mg, 98% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.31 (m, 4H), 7.27 (s, 1H), 7.27−7.22(m, 1H), 4.81−4.78 (m, 1H), 4.23 (s, 1H), 3.57 (t, *J* = 5.4 Hz, 2H), 3.36 (t, *J* = 5.4 Hz, 2H), 2.47 (t, *J* = 6.4 Hz, 2H), 2.17−2.03 (m, 2H), 1.71−1.60 (m, 3H), 1.57−1.50 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.7, 144.8, 128.1, 126.9, 125.6, 73.4, 46.6, 42.8, 33.9, 29.6, 26.2, 25.4, 24.3; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 90/10, 0.5 mL/min, 210 nm) $t_1$ = 34.4 min, $t_2$ = 39.4 min; $[\alpha]^{25}_D$ = +20.3 (*c* 1.17, $CH_2Cl_2$).

*4-Hydroxy-1-morpholino-4-phenylbutan-1-one* (**4d**):[27] white solid; 127.0 mg, 97% yield; mp 91.0−92.2 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.41−7.29 (m, 4H), 7.27−7.23 (m, 1H), 4.77 (dd, *J* = 7.6, 4.4 Hz, 1H), 3.66−3.59 (m, 6H), 3.41 (t, *J* = 4.8 Hz, 2H), 2.44 (t, *J* = 6.6 Hz, 2H), 2.16−2.02 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.9, 144.5, 128.1, 127.0, 125.5, 73.0, 66.5, 66.3, 45.7, 41.8, 33.8, 29.1; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.8 mL/min, 210 nm) $t_1$ = 18.2 min, $t_2$ = 20.9 min; $[\alpha]^{25}_D$ = +21.8 (*c* 1.01, $CH_2Cl_2$).

*N-Phenyl-4-hydroxy-4-phenylbutan-1-one* (**4e**):[26] white solid; 123.7 mg, 97% yield; mp 98.4−99.5 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.50 (d, *J* = 7.7 Hz, 3H), 7.40−7.28 (m, 6H), 7.11 (t, *J* = 7.4 Hz, 1H), 4.96−4.75 (m, 1H), 3.04 (br, 1H), 2.58−2.45 (m, 2H), 2.24−2.08 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.9, 144.1, 137.8, 128.9, 128.5, 127.5, 125.7, 124.3, 120.0, 73.5, 34.2, 33.9; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 90/10, 0.5 mL/min, 210 nm) $t_1$ = 33.9 min, $t_2$ = 36.3 min; $[\alpha]^{25}_D$ = +18.7 (*c* 1.66, $CH_2Cl_2$).

*N-Cyclohexyl-4-hydroxy-4-phenylbutanamide* (**4f**):[32] white solid; 127.7 mg, 98% yield; mp 83.5−85.2 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39−7.30 (m, 4H), 7.27−7.23 (m, 1H), 5.56 (br, 1H), 4.78−4.65 (m, 1H), 4.12 (br, 1H), 3.80−3.70 (m, 1H), 2.30 (t, *J* = 6.6 Hz, 2H), 2.11−1.98 (m, 1H), 1.92−1.88 (m, 2H), 1.72−1.59 (m, 3H), 1.40−1.30 (m, 2H), 1.19−1.04 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.7, 144.5, 128.2, 127.1, 125.6, 73.3, 48.3, 34.5, 33.0, 32.9, 25.3, 24.8; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 88/12, 0.7 mL/


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min, 210 nm) $t_1$ = 11.9 min, $t_2$ = 13.1 min; $[\alpha]^{25}_D$ = +33.0 (*c* 0.90, $CH_2Cl_2$).

*4-Hydroxy-4-phenylbutanamide (**4g**):*[1c] white solid; 7.2 mg, 8% yield; mp 82.7−83.5 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.32 (m, 4H), 7.29−7.26 (m, 1H), 5.58 (s, 1H), 5.42 (s, 1H), 4.83−4.79 (m, 1H), 3.22 (d, *J* = 3.6 Hz, 1H), 2.45−2.32 (m, 2H), 2.16−2.01 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 176.1, 144.3, 128.4, 127.4, 125.7, 73.5, 34.1, 32.0; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 80/20, 0.8 mL/min, 210 nm) $t_1$ = 8.9 min, $t_2$ = 12.0 min.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Details of the NMR and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) (a) Tschaen, D. M.; Simpson, P.; McSwine, D. J.; Reamer, R. A.; Verhoeven, T. R.; Shinkai, I.; Thompson, A. S. *J. Org. Chem.* **1992**, *57*, 7044. (b) Brealey, C.; Brown, T. J.; Facchini, V.; Handscombe, C.; Harris, N. V.; McCarthy, C.; McLay, I. M.; Porter, B.; Roach, A. G.; Sargent, C.; Smith, C.; Walsh, R. J. A.; Astles, P. C. *J. Med. Chem.* **1998**, *41*, 2732. (c) Hilborn, J. W.; Jurgens, A. R.; Fang, Q. K.; Byers, P.; Wald, S. A.; Lu, Z.-H.; Senanayake, C. H. *Tetrahedron Lett.* **2001**, *42*, 8919. (d) Swanson, L.; Ghosh, A. K. *J. Org. Chem.* **2003**, *68*, 9823. (e) Giroux, S.; Buffat, M.; Hanessian, S. *Org. Lett.* **2005**, *7*, 3989. (f) Chen, F.; Song, K.-S.; Wu, Y.-D.; Yang, D. *J. Am. Chem. Soc.* **2007**, *130*, 743. (g) Gao, S.-H.; Wang, Q.-L.; Chen, C. *J. Am. Chem. Soc.* **2008**, *131*, 1410.

(2) (a) Manzocchi, A.; Casati, R.; Fiecchi, A.; Santaniello, E. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2753. (b) Broussy, S.; Cheloha, R. W.; Berkowitz, D. B. *Org. Lett.* **2009**, *11*, 305.

(3) (a) Zuobi, K.; Boltansky, A.; Gutman, A. L. *Tetrahedron Lett.* **1987**, *28*, 3861. (b) Zuobi, K.; Bravdo, T.; Gutman, A. L. *J. Org. Chem.* **1990**, *55*, 3546. (c) Atkinson, R. F.; Almli, E. P.; Carr, M. D.; Van Huis, T. J.; Whittaker, M. R.; Taylor, S. K. *Tetrahedron: Asymmetry* **1995**, *6*, 157. (d) Fransson, A.-B. L.; Borén, L.; Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2005**, *70*, 2582. (e) Ketterer, C.; Wünsch, B. *Eur. J. Org. Chem.* **2012**, 2428.

(4) (a) Issenhuth, J.-T.; Dagorne, S.; Bellemin-Laponnaz, S. *C. R. Chimie* **2010**, *13*, 353. (b) Ogura, K.; Kouchi, Y.; Iwasaki, F.; Onomura, O.; Matsumura, Y. *Org. Lett.* **2006**, *8*, 3789. (c) Lower, A.; Kucejko, R. J.; Noson, K.; Lipshutz, B. H. *Org. Lett.* **2006**, *8*, 2969.

(5) (a) Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (b) Brown, H. C.; Pitre, S.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 17. (c) Pitre, S.; Brown, H. C.; Ramachandran, P. V. *J. Org. Chem.* **2002**, *67*, 5315.

(6) (a) Tomimori, K.; Oriyama, T.; Mukaiyama, T. *Chem. Lett.* **1985**, 813. (b) Applegate, G. A.; Cheloha, R. W.; Nelson, D. L.; Berkowitz, D. B. *Chem. Commun.* **2011**, *47*, 2420.

(7) (a) Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 5856. (b) Shang, G.; Li, W.; Zhang, X. In *Catalytic Asymmetric Synthesis*, 3rd ed.; Ojima, I., Ed.; John Wiley & Sons: Hoboken, NJ, 2010. (c) de Vries, J. G., Elsevier, C. J., Eds. *The Handbook of Homogeneous Hydrogenation*; Wiley-VCH: Weinheim, 2007. (d) Ager, D. J.; de Vries, A. H. M.; de Vries, J. G. *Chem. Soc. Rev.* **2012**, *41*, 3340−3380.

(8) (a) Ohkuma, T.; Noyori, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 40. (b) Sandoval, C. A.; Muñiz, K.; Ohkuma, T.; Noyori, R. *Philos. Trans. R. Soc. London, Ser. A* **2005**, *363*, 901. (c) Kawano, H.; Ikariya, T.; Ishii, Y.; Saburi, M.; Yoshikawa, S.; Uchida, Y.; Kumobayashi, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1571. (d) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163. (e) Heiser, B.; Broger, E. A.; Crameri, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 51. (f) Shao, L.-M.; Takeuchi, K.; Ikemoto, M.; Kawai, T.; Ogasawara, M.; Takeuchi, H.; Kawano, H.; Saburi, M. *J. Organomet. Chem.* **1992**, *435*, 133. (g) Hoke, J. B.; Hollis, S.; Stern, E. W. *J. Organomet. Chem.* **1993**, *455*, 193. (h) Ratovelomanana-Vidal, V.; Caño De Andrade, M. C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y.; Genêt, J.-P. *Tetrahedron Lett.* **1995**, *36*, 4801. (i) Ohta, T.; Tonomura, Y.; Nozaki, K.; Takaya, H.; Mashima, K. *Organometallics* **1996**, *15*, 1521.

(9) (a) Mashima, K.; Kusano, K.-h.; Sato, N.; Matsumura, Y.-i.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064. (b) Laneman, S. A.; Ager, D. J. *Tetrahedron: Asymmetry* **1997**, *8*, 3327. (c) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599. (d) Tang, W.-J.; Zhang, X.-M. *Chem. Rev.* **2003**, *103*, 3029.

(10) (a) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509. (b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (c) Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H.; Saito, T. *Adv. Synth. Catal.* **2001**, *343*, 264. (d) Benincori, T.; Rizzo, S.; Pilati, T.; Ponti, A.; Pagliarini, E.; Ratti, S.; Giuseppe, C.; de Ferra, L.; Sada, M.; Sannicolò, F. *Tetrahedron: Asymmetry* **2004**, *15*, 2289. (e) Starodubtseva, E. V.; Turova, O. V.; Gorshkova, L. S.; Ferapontov, V. A.; Vinogradov, M. G. *Russ. Chem. Bull., Int. Ed.* **2005**, *54*, 2374. (f) Starodubtseva, E. V.; Turova, O. V.; Gorshkova, L. S.; Ferapontov, V. A.; Struchkova, M. I.; Vinogradov, M. G. *Tetrahedron* **2008**, *64*, 11713.

(11) Vinogradov, M. G.; Starodubtseva, E. V.; Turova, O. V. *Russ. Chem. Rev.* **2008**, *77*, 725.

(12) (a) Kramer, R.; Brückner, R. *Chem.—Eur. J.* **2007**, *13*, 9076. (b) Kramer, R.; Brückner, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 6537. (c) Li, W.-F.; Ma, X.; Fan, W.-Z.; Tao, X.-M.; Li, X.-M.; Xie, X.-M.; Zhang, Z.-G. *Org. Lett.* **2011**, *13*, 3876.

(13) (a) Wan, X.-B.; Meng, Q.-H.; Zhang, H.-W; Sun, Y.-H.; Fan, W.-Z.; Zhang, Z.-G. *Org. Lett.* **2007**, *9*, 5613. (b) Meng, Q.-H.; Sun, Y.-H.; Ratovelomanana-Vidal, V.; Genêt, J. P.; Zhang, Z.-G. *J. Org. Chem.* **2008**, *73*, 3842. (c) Tao, X.-M.; Li, W.-F.; Ma, X.; Li, X.-M.; Fan, W.-Z.; Xie, X.-M.; Ayad, T.; Ratovelomanana-Vidal, V.; Zhang, Z.-G. *J. Org. Chem.* **2011**, *77*, 612. (d) Fan, W.-Z.; Li, W.-F.; Ma, X.; Tao, X.-M.; Li, X.-M.; Yao, Y.; Xie, X.-M.; Zhang, Z.-G. *Chem. Commun.* **2012**, *48*, 4247. (e) Ma, X.; Li, W.-F.; Li, X.-M.; Tao, X.-M.; Fan, W.-Z.; Xie, X.-M.; Ayad, T.; Ratovelomanana-Vidal, V.; Zhang, Z.-G. *Chem. Commun.* **2012**, *48*, 5352. (f) Ma, X.; Li, W.-F.; Fan, W.-Z.; Tao, X.-M.; Li, X.-M.; Yao, Y.; Zhu, L.-F.; Chen, H.-H.; Xie, X.-M.; Zhang, Z.-G. *Chin. J. Org. Chem.* **2012**, *32*, 1353. (g) Zhao, M.-M.; Li, W.-F.; Ma, X.; Fan, W.-Z.; Tao, X.-M.; Li, X.-M.; Xie, X.-M.; Zhang, Z.-G. *Sci. China. Chem.* **2013**, *56*, 342.

(14) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Jacks, W. S.; Turner, J. A. *J. Org. Chem.* **1989**, *54*, 4229. (c) Commeureuc, A. G. J.; Snaddon, T. N.; McGuire, T. M.; Khan, T. A.; Hisler, K.; Dewis, M. L.; Carling, R.; Murphy, J. A. *Org. Lett.* **2005**, *7*, 1427.

(15) (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675. (b) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529. (c) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703.

(16) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374.

(17) Marvin, M.; Sharma, R.; Sibi, M. P. *J. Org. Chem.* **1995**, *60*, 5016.

(18) Grzyb, J. A.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 7485.

(19) Quan, F.; Huang, D.-F.; Xu, C.-M.; Zhang, Z.-C.; Niu, T.; Feng, H.-J.; Xu, L.-Y.; Hu, Y.-L. *Chin. J. Org. Chem.* **2009**, *29*, 450.
(20) Yin, B.-L.; Xu, H.-H.; Chiu, M.-H.; Wu, Y.-L; Chen, L. *Chin. J. Org. Chem.* **2004**, *22*, 92.
(21) Myers, M. C.; Wang, J.-L.; Iera, J. A.; Bang, J.-K.; Hara, T.; Saito, S. i.; Zambetti, G. P.; Appella, D. H. *J. Am. Chem. Soc.* **2005**, *127*, 6152.
(22) Sundermann, K. F.; Burlingame, M. A.; Myles, D. C.; Freeze, B. S.; Xian, M.; Brouard, I.; Smith, A. B., III; Shaw, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 6532.
(23) Shibata, Y.; Suda, T.; Hagiwara, Y.; Hirano, M.; Tanaka, K. *Org. Lett.* **2007**, *9*, 1215.
(24) Kondo, J.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 825.
(25) Bai, J.-F; Zambroń, B. K.; Vogel, P. *Org. Lett.* **2014**, *16*, 604.
(26) Allen, C. L.; Chhatwal, A. R.; Williams, J. M. J. *Chem. Commun.* **2012**, *48*, 666.
(27) Cromwell, N. H.; Cook, K. E. *J. Am. Chem. Soc.* **1958**, *80*, 4573.
(28) Chern, C.-Y.; Huang, Y.-P.; Kan, W. M. *Tetrahedron Lett.* **2003**, *44*, 1039.
(29) Ogura, K.; Kouchi, Y.; Iwasaki, F.; Onomura, O.; Matsumura, Y. *Org. Lett.* **2006**, *8*, 3789.
(30) Chandrakumar, A.; Prasad, K. R. *Tetrahedron* **2007**, *63*, 1798.
(31) Nonaka, H.; Maeda, N.; Kobayashi, Y. *Tetrahedron Lett.* **2007**, *48*, 5601.
(32) Sekiguchi, H.; Nishio, T. *Tetrahedron* **1999**, *55*, 5017.