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Ru-catalyzed highly enantioselective hydrogenation of α-keto Weinreb amides

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Asymmetric hydrogenation of α-keto Weinreb amides has been realized with [Ru((*S*)-Sunphos)(benzene)Cl]Cl as the catalyst and $CeCl_3 \cdot 7H_2O$ as the additive. A series of enantiopure α-hydroxy Weinreb amides (up to 97% ee) have been obtained. Catalytic amount of $CeCl_3 \cdot 7H_2O$ is essential for the high reactivity and enantioselectivity and the ratio of $CeCl_3 \cdot 7H_2O$ to [Ru((*S*)-Sunphos)(benzene)Cl]Cl plays an important role in the hydrogenation reaction.

asymmetric hydrogenation, α-keto Weinreb amides, $CeCl_3 \cdot 7H_2O$

1 Introduction

Weinreb amides [1] are important acylation reagents. They can be easily converted to ketones through nucleophilic addition with many organometallic reagents without the hazard of over addition to form tertiary alcohols. Their applications in organic synthesis have been widely demonstrated [2–7]. Enantiomerically pure α-hydroxy Weinreb amides are key intermediates for many pharmaceuticals, agrochemicals, and biologically relevant compounds because they provide useful precursors for α-hydroxy ketones or aldehydes which usually obtained from benzoin condensation [8, 9] or asymmetric hydrogenation of 1,2-diones [10]. For example, natural products like Calyculin A [11], Kurasoin A and B (Figure 1) [12] can be prepared from several chiral α-hydroxy Weinreb amides which routinely obtained from α-hydroxy acids, esters or acyl chlorides with commercially available *N*,*O*-dimethylhydroxylamine hydrochloride [11, 12]. However, these synthetic routes suffer from poor efficiency and enantioselectivity, and need over stoichiometric amount of activating agents. For example, to obtain the α-hydroxy Weinreb amides, $AlMe_3$ or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride is usually employed to activate the acids. Accordingly, the search for highly efficient and atom economic processes to obtain such chiral moieties is of great significance. Obviously, the enantioselective hydrogenation of α-keto Weinreb amides is the most straightforward method to provide these important chiral blocks. However, only a few examples

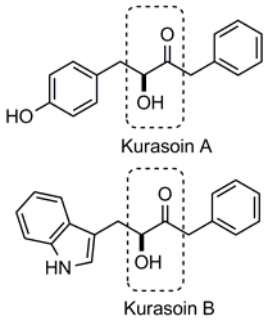

Figure 1 Structures of Kurasoin A and Kurasoin B.

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were reported on the enantioselective hydrogenation of α-keto amides and the efficiency and substrate scope were rather limited [13–15]. During our previous research, we found that α-keto esters could be smoothly hydrogenated catalyzed by [Ru((*S*)-Sunphos)(benzene)Cl]Cl in the presence of $CeCl_3 \cdot 7H_2O$ [16–18], here we report our recent work on the asymmetric hydrogenation of a series of α-keto Weinreb amides.

2 Experimental

2.1 General experimental section

Commercially available reagents were used without further purification other than those detailed below. The solvents used in catalyst preparation and hydrogenation reactions were pretreated by the following procedures: Ethanol was distilled over magnesium under nitrogen; THF was distilled over sodium under nitrogen; CH_2Cl_2 was distilled over calcium hydride. All reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques unless otherwise noted. ^{1}H and ^{13}C NMR spectra were obtained on a 400 MHz NMR spectrometer. The chemical shifts for ^{1}H NMR were recorded in ppm downfield from tetramethylsilane (TMS) with the solvent resonance as the internal standard. The chemical shifts for ^{13}C NMR were recorded in ppm downfield using the central peak of $CDCl_3$ as the internal standard. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplications. Specific rotations were operated at 25 °C (*A* = 589 nm). Flash column chromatography was performed on silica gel (300–400 mesh).

2.2 General procedure for the synthesis of 1

To *N*,*N*′-dimethoxy-*N*,*N*′-dimethyloxalamide (5.0 g, 28.4 mmol) in THF (40 mL) under N_2 atmosphere was added dropwise the corresponding Grignard reagent (42.5 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 $MgSO_4$. Evaporation was carried out under reduced pressure after filtration. The crude product was purified by column chromatography.

*N-methoxy-N-methyl-2-oxo-2-phenylacetamide (**1a**) [26]*

White solid; M.p.: 56.1–57.2 °C; 19.7 g, 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 1.0 Hz, 1H), 7.90 (t, *J* = 1.6 Hz, 1H), 7.67–7.61 (m, 1H), 7.54–7.48 (m, 2H), 3.64 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.1, 167.4, 134.8, 132.9, 129.5, 129.1, 62.2, 31.5.

*N-methoxy-N-methyl-2-oxo-2-(o-tolyl)acetamide (**1b**)*

White solid; M.p.: 80.5–81.8 °C; 5.1 g, 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.9 Hz, 1H), 7.56–7.41 (m, 1H), 7.29 (dd, *J* = 16.8, 9.1 Hz, 2H), 3.64 (s, 3H), 3.33 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 168.3, 141.0, 133.7, 132.5, 132.4, 131.7, 126.2, 62.1, 31.7, 21.6. HRMS calcd. for $C_{11}H_{14}NO_3$ $(M+H)^+$: 208.0974, found: 208.0969.

*N-methoxy-N-methyl-2-(2-methoxyphenyl)-2-oxoacetamide (**1c**) [27]*

Colorless oil; 5.4 g, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.56 (m, 1H), 7.08 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 3.64 (s, 3H), 3.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.4, 170.1, 160.6, 136.6, 136.2, 130.8, 130.3, 122.6, 121.2, 112.6, 61.6, 56.7, 32.3.

*N-methoxy-N-methyl-2-oxo-2-(p-tolyl)acetamide (**1d**) [26]*

White solid; M.p.: 111.1–112.3 °C; 4.9 g, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.30 (s, 2H), 3.64 (s, 3H), 3.35 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 167.6, 146.0, 130.5, 129.7, 62.2, 31.5, 22.0.

*N-Methoxy-N-methyl-2-(4-methoxyphenyl)-2-oxoacetamide (**1e**) [26]*

White solid; M.p.: 41.5–43.4 °C; 5.7 g, 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.9 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 3.88 (s, 3H), 3.65 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.7, 167.8, 164.9, 132.5, 131.9, 126.0, 114.5, 62.2, 55.8, 31.5.

*N-methoxy-N-methyl-2-oxo-2-(4-(trifluoromethyl)phenyl)acetamide (**1f**)*

White solid; M.p.: 80.7–81.8 °C; 6.6 g, 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 3.66 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.9, 166.6, 165.9, 159.8, 136.2, 135.9, 135.6, 135.3, 130.5, 129.8, 127.9, 127.6, 126.1, 124.9, 122.2, 119.5, 116.2, 95.8, 95.2, 62.3, 39.8, 36.1, 31.6. HRMS calcd. for $C_{11}H_{11}F_3NO_3$ $(M+H)^+$: 262.0691, found: 262.0677.

*N-methoxy-N-methyl-2-oxo-2-(4-(trifluoromethoxy)phenyl)-acetamide (**1g**)*

Yellow oil; 6.7 g, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–7.94 (m, 2H), 7.33 (dd, *J* = 8.8, 0.8 Hz, 2H), 3.67 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.4, 166.8, 153.6, 132.2, 131.5, 131.1, 124.2, 121.6, 120.7, 119.0, 62.1. HRMS calcd for $C_{11}H_{11}F_3NO_4$ $(M+H)^+$: 278.0640, found: 278.0629.

*N-methoxy-N-methyl-2-(naphthalen-2-yl)-2-oxoacetamide (**1h**)*

White solid; M.p.: 101.2–102.3 °C; 6.1 g, 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.02–7.86 (m, 4H), 7.64 (m, 1H), 7.60–7.54 (m, 1H), 3.67 (s, 3H), 3.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 167.2, 136.1, 132.4, 132.2, 130.0, 129.6, 129.1, 128.8, 127.8, 126.9, 123.3, 77.3,

77.0, 76.6, 61.97, 31.3. HRMS calcd. for $C_{14}H_{14}NO_3$ $(M+H)^+$: 244.0974, found: 244.0957.

*N-methoxy-N-methyl-2-oxo-2-(thiophen-2-yl)acetamide (**1i**) [26]*

Brown solid; M.p.: 59.2–61.0 °C; 3.1 g, 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 4.8, 1.2 Hz, 1H), 7.74 (dd, J = 3.8, 1.2 Hz, 1H), 7.18 (dd, J = 4.8, 4.0 Hz, 1H), 3.71 (s, 3H), 3.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.0, 166.3, 139.9, 136.4, 136.2, 128.8, 62.4, 31.7.

*N-methoxy-N-methyl-2-oxopropanamide (**1j**) [28]*

To pyruvate (5.0 g, 56.8 mmol) in CH_3CN (150 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (8.3 g, 85.1 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (14.1 g, 73.8 mmol). The mixture was cooled to 0 °C using an ice bath, and Et_3N (8.6 g, 85.1 mol) was added dropwise. After completing the addition of Et_3N, the reaction mixture was stirred at room temperature. Upon complete consumption of starting material monitored by TLC, the solvent was removed in vacuum. The aqueous solution was extracted with CH_2C1_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuum afforded **1g** (10.2 g, 83% yield): light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.21 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1, 167.8, 62.3, 31.4, 27.1.

*N-methoxy-N-methyl-2-oxo-4-phenylbutanamide (**1k**)*

To 2-oxo-4-phenylbutanoic acid (6.0 g, 33.6 mmol) in CH_3CN (150 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (4.9 g, 50.5 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (8.4 g, 43.8 mmol). The mixture was cooled to 0 °C using an ice bath, and Et_3N (5.1 g, 50.5 mol) was added dropwise. After completing addition of Et_3N, the reaction mixture was stirred at room temperature. Upon complete consumption of starting material by TLC, the solvent was removed in vacuum. The aqueous solution was extracted with CH_2C1_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuum afforded **1k** (6.3 g, 85% yield): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 7.23–7.17 (m, 3H), 3.60 (s, 3H), 3.19 (s, 3H), 3.06–3.01 (m, 2H), 3.00–2.95 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.8, 168.0, 140.4, 128.6, 126.4, 62.3, 41.1, 31.6, 28.0. HRMS calcd. for $C_{12}H_{16}NO_3$ $(M+H)^+$: 222.1130, found: 222.1117.

*N-methoxy-N-methyl-2-oxo-3-phenylpropanamide (**1l**) [26]*

Colorless oil; 3.8 g, 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.20 (m, 5H), 3.99 (s, 2H), 3.60 (s, 3H), 3.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 131.9, 130.1, 128.8, 127.6, 127.1, 62.4, 46.5, 31.7.

2.3 Typical procedure for the asymmetric hydrogenation

To a 25 mL Schlenk tube were added $[Ru(benzene)Cl_2]_2$ (15.0 mg, 0.03 mmol) and (*S*)-SunPhos (45 mg, 0.066 mmol). The tube was vacuumed and purged with nitrogen for three times before addition of freshly distilled and freeze-and-thaw degassed Ethanol/CH_2Cl_2 (3 mL/3 mL). The resulting mixture was heated at 50 °C for 1 h and then cooled to room temperature. The solvent was then removed under vacuum to give the catalyst as a yellow solid. The catalyst was dissolved in degassed ethanol (24 mL) and then the solution was equally divided into 12 vials which contained 1 mmol of substrates and $CeCl_3{\cdot}7H_2O$ (12 eq.). Then the vials were transferred into two 300 mL Parr 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 ee values were determined by HPLC after passing the samples through a short pad of silica gel eluted with petroleum ether and ethyl acetate.

*2-Hydroxy-N-methoxy-N-methyl-2-phenylacetamide (**2a**) [29]*

Colorless oil; 146.8 mg, 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 5.35 (d, J = 6.1 Hz, 1H), 4.28 (d, J = 6.4 Hz, 1H), 3.21 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.7, 64.1, 25.2. $[\alpha]_D^{25}$ = +115.8 (c = 0.56, $CHCl_3$) for the (*S*)-isomer. Reference: $[\alpha]_D^{25}$ = –86.7 (c = 5.6, $CHCl_3$) for the (*R*)-isomer [30].

*2-Hydroxy-N-methoxy-N-methyl-2-(o-tolyl)acetamide (**2b**)*

Light yellow solid; 130.7 mg, 62% yield; M.p.: 55.4–57.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.14 (m, 4H), 5.54 (d, J = 4.8 Hz, 1H), 4.16 (d, J = 5.6 Hz, 1H), 3.22 (s, 3H), 3.03 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 138.0, 136.6, 130.9, 128.5, 127.7, 126.6, 69.2, 60.4, 33.0, 19.2. HRMS calcd. for $C_{11}H_{15}NO_3Na$ $(M+Na)^+$: 232.0950, found: 232.0947. $[\alpha]_D^{25}$ = +123.3 (c = 1.05, CH_2Cl_2).

*2-Hydroxy-N-methoxy-2-(2-methoxyphenyl)-N-methylacetamide (**2c**)*

White solid; 160.8 mg, 71% yield; M.p.: 65.8–67.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.24 (m, 1H), 7.19 (dd, J = 7.5, 1.7 Hz, 1H), 6.92 (dd, J = 15.3, 7.9 Hz, 2H), 5.68 (d, J = 6.0 Hz, 1H), 4.16 (d, J = 5.6 Hz, 1H), 3.85 (s, 3H), 3.18 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 157.2, 129.8, 128.7, 128.3, 121.0, 111.3, 66.7, 60.7, 55.8, 33.0. HRMS calcd. for $C_{11}H_{15}NO_4Na$ $(M+Na)^+$: 248.0899, found: 248.0888. $[\alpha]_D^{25}$ = +114.4 (c = 1.60, CH_2Cl_2).

*2-Hydroxy-N-methoxy-N-methyl-2-(p-tolyl)acetamide (**2d**) [29]*

Light yellow solid; 158.6 mg, 76% yield; M.p.:

97.5–98.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 5.32–5.29 (m, 1H), 4.21 (d, J = 6.4 Hz, 1H), 3.22 (d, J = 14.5 Hz, 6H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 138.3, 136.9, 129.5, 127.6, 71.5, 60.9, 32.8, 21.4. $[\alpha]_D^{25}$ = +76.4 (c = 1.05, CH_2Cl_2).

*2-Hydroxy-N-methoxy-N-methyl-2-(4-methoxyphenyl)acetamide (**2e**)*

Yellow solid; 136.5 mg, 61% yield; M.p.: 75.5–77.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.24 (m, 2H), 6.88 (t, J = 2.4 Hz, 2.8, 1H), 6.87 (t, J = 2.6 Hz, 2.4 Hz, 1H), 5.31 (s, 1H), 4.21 (s, 1H), 3.79 (s, 3H), 3.22 (d, J = 12.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 159.7, 132.2, 128.9, 114.2, 71.2, 60.9, 55.4, 32.8. HRMS calcd. for $C_{11}H_{15}NO_4Na$ $(M+Na)^+$: 248.0899, found: 248.0893. $[\alpha]_D^{25}$ = +77.0 (c = 1.05, CH_2Cl_2).

*2-Hydroxy-N-methoxy-N-methyl-2-(4-(trifluoromethyl)phen-yl)acetamide (**2f**)*

White solid; 141.6mg, 54% yield; M.p.: 44.3–46.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 5.38 (d, J = 6.0 Hz, 1H), 4.43 (d, J = 6.5 Hz, 1H), 3.31 (s, 3H), 3.19 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 143.7, 131.0, 130.7, 130.4, 130.1, 128.0, 126.2, 125.6, 71.1, 60.9, 32.8. HRMS calcd for $C_{11}H_{13}F_3NO_3$ $(M+H)^+$: 264.0848, found: 264.0847. $[\alpha]_D^{25}$ = +52.4 (c = 0.66, CH_2Cl_2).

*2-Hydroxy-N-methoxy-N-methyl-2-(4-(trifluoromethoxy)phe-nyl)acetamide (**2g**)*

Yellow oil; 196.5 mg, 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.36 (m, 2H), 7.21 (d, J = 8.0 Hz, 2H), 5.35 (d, J = 6.4 Hz, 1H), 4.30 (d, J = 6.4 Hz, 1H), 3.30 (s, 3H), 3.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 149.2, 147.5, 138.5, 129.2, 128.2, 121.8, 121.2, 119.3, 70.8, 60.9, 32.8. HRMS calcd. for $C_{11}H_{12}F_3NO_4Na$ $(M+Na)^+$: 302.0616, found: 302.0608. $[\alpha]_D^{25}$ = +53.7 (c = 2.1, CH_2Cl_2).

*2-Hydroxy-N-methoxy-N-methyl-2-(naphthalen-2-yl)acetam-ide (**2h**)*

Yellow solid; 144.1mg, 59% yield; M.p.: 86.3–86.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.80 (m, 4H), 7.56–7.45 (m, 3H), 5.53 (s, 1H), 4.42 (d, J = 5.1 Hz, 1H), 2.9 (s, 3H), 2.6 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 137.2, 133.5, 133.4, 128.8, 128.3, 127.9, 127.1, 126.5, 125.2, 71.9, 60.9, 32.9. HRMS calcd. for $C_{14}H_{15}NO_3Na$ $(M+Na)^+$: 268.0950, found: 268.0946. $[\alpha]_D^{25}$ = +99.7 (c = 1.2, CH_2Cl_2).

*2-Hydroxy-N-methoxy-N-methyl-2-(thiophen-2-yl)acetamide (**2i**)*

Brown solid; 144.7mg, 72% yield; M.p.: 67.3–68.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.25 (m, 1H), 7.06–7.03 (m, 1H), 6.96 (dd, J = 5.1, 3.5 Hz, 1H), 5.64 (d, J = 6.4 Hz, 1H), 4.20 (d, J = 6.8 Hz, 1H), 3.40 (s, 3H), 3.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 142.8, 127.0, 126.2, 125.9, 66.5, 61.1, 32.9. HRMS calcd. for $C_8H_{11}NO_3SNa$ $(M+Na)^+$: 224.0357, found: 224.0355. $[\alpha]_D^{25}$ = +25.2 (c = 0.45, CH_2Cl_2).

*2-Hydroxy-N-methoxy-N-methylpropanamide (**2j**) [31]*

Colorless oil; 96.2 mg, 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54–4.42 (m, 1H), 3.71 (s, 3H), 3.34 (d, J = 7.9 Hz, 1H), 3.24 (s, 3H), 1.35 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 65.0, 61.4, 32.5, 21.0. $[\alpha]_D^{25}$ = –21.7 (c = 0.2, CH_2Cl_2).

*2-Hydroxy-N-methoxy-N-methyl-4-phenylbutanamide (**2k**)*

Colorless oil; 164.3 mg, 74% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 7.23–7.26 (m, 3H), 4.34–4.30 (m, 1H), 3.55 (s, 3H), 3.29 (d, J = 7.9 Hz, 1H), 3.20 (s, 3H), 2.89–2.70 (m, 2H), 2.10–2.02 (m, 1H), 1.85–1.76 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 141.6, 128.8, 128.5, 126.1, 68.0, 61.3, 36.3, 32.6, 31.5. HRMS calcd. for $C_{12}H_{17}NO_3$ $(M+H)^+$: 224.1287, found: 224.1294. $[\alpha]_D^{25}$ = +7.99 (c = 0.1, CH_2Cl_2).

*2-Hydroxy-N-methoxy-N-methyl-3-phenylpropanamide (**2l**) [32]*

Colorless oil; 198.7 mg, 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 4.62 (s, 1H), 3.72 (s, 3H), 3.31 (d, J = 7.7 Hz, 1H), 3.24 (s, 3H), 3.07 (d, J = 13.6 Hz, 1H), 2.85 (dd, J = 13.6, 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 137.5, 129.6, 128.5, 126.8, 69.9, 61.6, 41.2, 32.7. $[\alpha]_D^{25}$ = –11.69 (c = 0.2, CH_2Cl_2) for the (*S*)-isomer. Reference: $[\alpha]_D^{25}$ = –70.90 (c = 0.97, CH_2Cl_2) for the (*S*)-isomer [32].

*2-Hydroxy-N-methyl-2-phenylacetamide (**3a**) [33]*

White solid; 44.9 mg, 23% yield; M.p.: 52.4–63.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 6.26 (s, 1H), 4.98 (d, J = 3.5 Hz, 1H), 3.88 (d, J = 3.5 Hz, 1H), 2.78 (d, J = 5.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 139.4, 128.7, 128.5, 126.8, 74.1, 26.2.

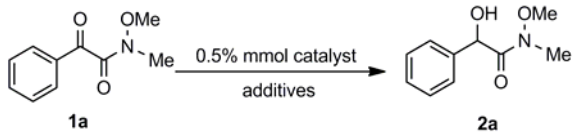
3 Results and discussion

Initially, *N*-methoxy-*N*-methyl-2-oxo-2-phenylacetamide **(1a)** was employed as the model substrate to optimize hydrogenation conditions (Table 1). The compound **1a** was tested first in ethanol under 10 atm of H_2 at 50 °C to provide **2a** with 23.7% ee over 20 h (Table 1, entry 1). The results in Table 1 showed that the stereoselective outcome of the hydrogenation was strongly dependent on the temperature and hydrogen pressure. Increasing the hydrogen pressure from 10 to 20 atm, the reaction provided a lower ee (Table 1, entry 2). Increasing the temperature from 50 to 70 °C resulted in both higher reaction rate and better enantioselectivity (Table 1, entry 3). However, a higher temperature of

90 °C with 10 atm of hydrogen pressure gave the product at the expense of both enantiomeric excess and conversion (Table 1, entry 4). At a lower or higher hydrogen pressure, such as 5 atm and 20 atm, the reaction provided lower ee values (Table 1, entries 5, 6). It is reported that catalytic amounts of additives play crucial roles in improving the reactivity and/or enantioselectivity of many asymmetric hydrogenation reactions [19–23] and it has been proved that $CeCl_3·7H_2O$ is useful for the hydrogenation of α-keto esters [16–18]. When $CeCl_3·7H_2O$ (6 eq. relative to catalyst) was added in this reaction under 10 atm of H_2 at 70 °C, the ee value of **2a** improved slightly (entry 3 vs. 7, Table 1). Unexpectedly, the trend of the effect of the hydrogen pressure was found to be opposite to that obtained without additive. The ee value dramatically increased to 94.7% when the hydrogen pressure was raised to 20 atm in the presence of $CeCl_3·7H_2O$ while decreased when the pressure went up to 30 atm (entry 8 vs. 9, Table 1). It was interesting that increasing or decreasing the reaction temperature led to lower conversion and poorer enantioselectivity (entries 10 and 11, Table 1). Further investigation revealed that the catalyst was unstable when the temperature was raised to 90 °C in the presence of $CeCl_3·7H_2O$. It was reported that the magnesium salts was able to chelate with the carbonyl and methoxy of the Weinreb amides [24], we tested some other additives such as $MgCl_2$ (entry 12, Table 1) and $ZnCl_2$ (entry 13, Table 1). It showed that these two additives gave lower ee values and conversions than $CeCl_3·7H_2O$. Notably, the amount of additive also played an important role in the enantioselectivity. The ee of **2a** increased from 94.7% to 97.3% when the amount of $CeCl_3·7H_2O$ was increased from 6 eq. to 12 eq. relative to the catalyst (entry 14, Table 1). However, the ee of **2a** decreased when the amount of $CeCl_3·7H_2O$ was increased to 20 eq. relative to the catalyst (entry 15, Table 1). The solvents also played important roles in the asymmetric hydrogenation of many functionalized ketones. EtOH was proved to be the best solvent in this hydrogenation reaction (entries 16–19, Table 1). MeOH could also give a high ee but with low yield. Based on these results, the optimized reaction conditions were therefore set as the following: EtOH as the solvent, 20 atm of H_2, 12 eq. of $CeCl_3·7H_2O$ relative to [Ru((*S*)-Sunphos)(benzene)Cl]Cl as the additive at 70 °C.

Having the optimized reaction conditions in hand, we then extended the substrate scope to other Weinreb amides (Table 2). Most aryl amides were hydrogenated in good to excellent ee values. Substitution at *ortho*-position on phenyl ring led to lower ee because of the steric effect. For example, ee values of *ortho*-methyl **1b** and methoxy **1c** were 75.9% and 73.6%, respectively (entries 2, 3, Table 2). The *para*-substituted substrates gave moderate to good enantiomeric excesses and the electronic nature of the *para*-substituent did not show distinct influence on enantioselectivity (entries 4–7, Table 2). The naphthyl substituted substrate **1h** also

Table 1 Optimization of the reaction conditions[a)]



1a **2a**

Entry	Solvent	Pressure (atm)	Temperature (°C)	Additive	Conversion[b)] (%)	ee [c)] (%)
1	EtOH	10	50	none	42.5	23.7
2	EtOH	20	50	none	67.3	15.1
3	EtOH	10	70	none	56.8	54.9
4	EtOH	10	90	none	23.4	29.8
5	EtOH	5	70	none	51.3	11.5
6	EtOH	20	70	none	68.6	15.6
7	EtOH	10	70	$CeCl_3·7H_2O$	64.4	67.3
8	EtOH	20	70	$CeCl_3·7H_2O$	95.0	94.7
9	EtOH	30	70	$CeCl_3·7H_2O$	100.0	91.9
10	EtOH	20	50	$CeCl_3·7H_2O$	92.6	80.8
11	EtOH	20	90	$CeCl_3·7H_2O$	51.9	49.3
12	EtOH	20	70	$MgCl_2$	37.5	31.5
13	EtOH	20	70	$ZnCl_2$	79.2	9.9
14	EtOH	20	70	$CeCl_3·7H_2O$	100.0	97.3[d)]
15	EtOH	20	70	$CeCl_3·7H_2O$	77.2	62.5[e)]
16	MeOH	20	70	$CeCl_3·7H_2O$	96.1	89.0
17	i-PrOH	20	70	$CeCl_3·7H_2O$	86.1	20.5
18	CH_2Cl_2	20	70	$CeCl_3·7H_2O$	20.4	66.1
19	THF	20	70	$CeCl_3·7H_2O$	76.5	77.6

a) All reaction were carried out with a substrate (1 mmol) concentration of 0.5 M for 20 h, substrate/catalyst/additive = 200/1/6; b) conversions of **2a** were determined by ^{1}H NMR; c) ee values were determined by HPLC on a chiral OD-H column; d) catalyst/additive = 1/12; e) catalyst/additive = 1/20.

Table 2 Asymmetric hydrogenation of α-keto Weinreb amides[a)]

Entry	1	R	2	
			Yield (%) [b)]	ee (%) [c)]
1	**1a**	C_6H_5	75	97.3
2	**1b**	2-Me-C_6H_4	62	75.9
3	**1c**	2-MeO-C_6H_4	71	73.6
4	**1d**	4-Me-C_6H_4	76	89.1
5	**1e**	4-MeO-C_6H_4	61	97.1
6	**1f**	4-CF_3-C_6H_4	54	88.8
7	**1g**	4-CF_3O-C_6H_4	70	92.9
8	**1h**	2-naphthyl	59	91.9
9	**1i**	2-thienyl	72	91.2
10	**1j**	Me	72	46.6
11	**1k**	$PhCH_2CH_2$	74	49.3
12	**1l**	$PhCH_2$	95	13.1

a) All reactions were carried out in EtOH with a substrate concentration of 0.5 M at 70 °C and 20 atm of H_2 for 20 h. Substrate/[Ru((*S*)-Sunphos) (benzene)Cl]Cl/additive: 200/1/12, 100% conversion; b) yields were determined by ^{1}H NMR; c) the ee values were determined by HPLC.

gave high ee values. The hydrogenation of thienyl substituted substrate **1i** (entry 9, Table 2) displayed well though with a sulfur atom at *meta*-position. Unfortunately, the alkyl substituted substrates **1j**, **1k** and the benzyl substituted substrate **1l** were hydrogenated in much lower ee.

It was also noticeable that the isolated yields of hydrogenations were only 60–75%. ^{1}H NMR analysis of the reaction mixture showed that part of (15–30%) the *N*-methoxy was removed during the hydrogenation reactions to generate compound **3**. In general, the removal of *N*-methoxy was reported in the presence of lithium based organometallic reagents [25]. To make sure whether the methoxy group of Weinreb amide was removed before or after the hydrogenation reaction, further investigation was conducted. When product **2a** was hydrogenated under the same conditions, compound **3a** was detected. Analysis of original reaction products showed that the ee values of **2a** and **3a** were different (**2a**, 80.8% ee vs. **3a**, 18.2% ee, Table 1, entry 10), revealing that removal of the methoxy group after the hydrogenation reaction is not the only pathway, and the substrates could also be demethoxylated under the reaction conditions before hydrogenation.

4 Conclusion

In conclusion, we have developed an efficient catalytic system for the asymmetric hydrogenation of α-keto Weinreb amides. $CeCl_3 \cdot 7H_2O$ as an additive was essential for the high conversion and enantioselectivity. The hydrogenation products provided valuable chiral blocks for the preparation of chiral hydroxy ketones.

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