Catalytic asymmetric hydrogenation of α-amino-β-keto ester hydrochlorides using homogeneous chiral nickel-bisphosphine complexes through DKR†

Yasumasa Hamada,* Yu Koseki, Takefumi Fujii, Tsukuru Maeda, Takuya Hibino and Kazuishi Makino

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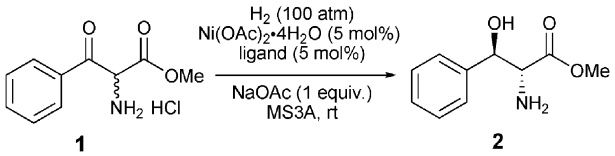
Homogeneous chiral nickel-bisphosphine complexes catalyze the asymmetric hydrogenation of α-amino-β-keto ester hydrochlorides through dynamic kinetic resolution to efficiently afford *anti*-β-hydroxy-α-amino esters with high diastereo- and enantioselectivities.

Nickel, one of abundant and cheap base transition metals, has attracted a great deal of attention in catalytic organic synthesis.[1] In the area of catalytic hydrogenation using nickel catalysts, the heterogeneous catalysts represented by Raney nickel have been well studied, and the asymmetric synthesis using heterogeneous nickel catalysts modified by a chiral auxiliary has also been investigated.[2] Recently, the first use of homogeneous nickel-bisphosphine complexes for the catalytic hydrogenation of simple alkenes has been reported.[3,4] Although homogeneous chiral nickel-bisphosphine complexes have been used in various asymmetric syntheses,[5] the asymmetric hydrogenation using these complexes remains a formidable challenge. In addition, the development of sustainable methods using abundant and cheap base transition metals is desirable.

We[6–8] and others[9] have reported the efficient asymmetric hydrogenations of α-amino-β-keto ester hydrochlorides using chiral ruthenium, rhodium, and iridium catalysts for the enantio- and diastereoselective synthesis of *anti*-β-hydroxy-α-amino acids through dynamic kinetic resolution (DKR).[10–12] *anti*-β-Hydroxy-α-amino acids are valuable constituents of a variety of natural products and medicinally important compounds.[13] We now describe the successful asymmetric hydrogenation using homogeneous chiral nickel-bisphosphine catalysts through DKR for the stereoselective synthesis of *anti*-β-hydroxy-α-amino esters from chirally labile α-amino-β-keto ester hydrochlorides.

Our investigation commenced with the screening of nickel salts and chiral ligands for the reaction of the readily available substrate **1**[14] as shown in Scheme 1. The initial experiments were confronted with the problem of reproducibility because the activity of the nickel catalysts was sensitive to the presence of air and moisture. This problem was overcome by using an argon-filled glove-bag during the assembling of the reaction apparatus and the addition of molecular sieves 3A to the reaction media. After extensive experiments, a combination of nickel acetate and ferrocenylphosphine **3a**[15] has been proven to be the best couple for the hydrogenation. The chiral nickel catalyst was directly prepared in the reaction media without prior preparation of the catalyst complex.



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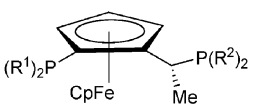
Scheme 1 Homogeneous Ni-catalyzed asymmetric hydrogenation.

Using this combination, the effects of solvents and ligands were examined as shown in Table 1. Most of the solvents were ineffective for this hydrogenation. Fortunately, when acetic acid in the presence of sodium acetate[16] (1 equiv.) was employed, the reaction proceeded to give the product in 65% yield with a complete *anti*-selectivity and 82% ee (entry 3). Encouraged by this result, a further investigation revealed that a mixture of trifluoroethanol and acetic acid (1:4) was suitable for this hydrogenation that led to the full conversion

Table 1 Effects of solvent and ligands



(*R*,*S*)-**3a**: R^1 = Ph, R^2 = Cy (*R*,*S*)-**3b**: R^1 = Ph, R^2 = t-Bu
(*R*,*S*)-**3c**: R^1 = Ph, R^2 = 3,5-diMePh (*R*,*S*)-**3d**: R^1 = Cy, R^2 = Cy
(*R*,*S*)-**3e**: R^1 = t-Bu, R^2 = Cy (*R*,*S*)-**3f**: R^1 = 3,5-diCF_3Ph, R^2 = Cy
(*R*,*S*)-**3g**: R^1 = 3,5-diMe-4-MeOPh, R^2 = Cy

Entry	Solvent	Ligand	*t*/h	Yield (%)	*anti*/*syn*[a]	ee[b] (%)
1	$PhCH_3$	**3a**	12	NR	—	—
2	TFE	**3a**	12	NR	—	—
3	AcOH	**3a**	12	65	>99/1	82
4	EtOH/AcOH (1/4)	**3a**	12	NR	—	—
5	TFE/AcOH (4/1)	**3a**	12	71	>99/1	71
6	TFE/AcOH (1/1)	**3a**	12	100	>99/1	81
7	TFE/AcOH (1/4)	**3a**	12	87	>99/1	84
8	TFE/AcOH (1/4)	**3b**	6	Trace	—	—
9	TFE/AcOH (1/4)	**3c**	24	NR	—	—
10	TFE/AcOH (1/4)	**3d**	48	48	96/4	9
11	TFE/AcOH (1/4)	**3e**	24	NR	—	—
12	TFE/AcOH (1/4)	**3f**	26	NR	—	—
13	TFE/AcOH (1/4)	**3g**	24	100	>99/1	92

[a] Estimated by ^{1}H NMR spectra. [b] Determined after *N*-benzoylation.

Graduate School of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Inage-ku, Chiba, 263-8522, Japan. E-mail: hamada@p.chiba-u.ac.jp; Fax: +81-(0)43-290-2987; Tel: +81-(0)43-290-2987

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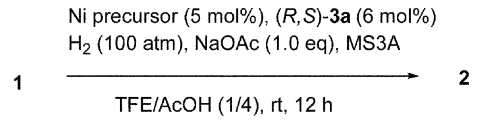
Table 2 Nickel precursors



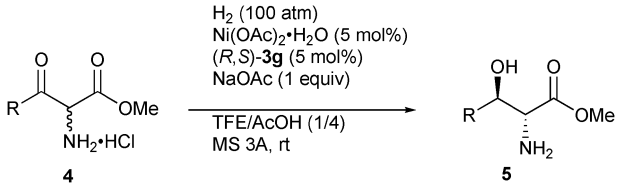
Entry	Ni precursor	Yield[a] (%)	*anti*/*syn*[a]	ee[a] (%)
1	Ni $(OAc)_2{\cdot}4H_2O$	84	>99/1	85
2	Ni $(acac)_2{\cdot}2H_2O$	62	>99/1	86
3	$NiCl_2$	80	>99/1	85
4	$NiCl_2{\cdot}6H_2O$	87	>99/1	86
5	$NiCl_2(PPh_3)_2$	50	>99/1	84
6	$NiBr_2$	84	>99/1	85
7	$Ni(NO_3)_2{\cdot}6H_2O$	86	>99/1	85
8	[Ni(cod)$_2$]	17	87/13	82

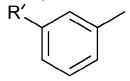
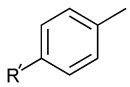
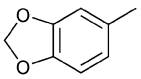
[a] Determined after *N*-benzoylation.

of the substrate with an excellent enantioselectivity and complete diastereoselectivity (entry 7). Interestingly, when the trifluoroethanol in the mixed solvent was substituted with ethanol (entry 4) or trifluoroethanol itself was used as the solvent (entry 2), no reaction was observed. With the best solvent in hand, we reexamined the nickel salts (Table 2). Although all the examined bivalent nickel salts were found to be applicable and gave a comparable stereoselectivity, we employed nickel acetate tetrahydrate with a nonhygroscopic property from a practical point of view.[17] In order to enhance the enantioselectivity, we next examined several chiral phosphine ligands. Most of the commercially available chiral phosphines resulted in little or no reaction, while the Josiphos type ligands produced the active catalysts.[18] Among them, the substituents on the two phosphorus atoms influenced the activity of the catalysts (Table 1, entries 7–13). The aromatic group with electron-donating group(s) at the phosphorus on the ferrocenyl ring and cyclohexyl group at the side chain were essential for the catalytic activity along with an excellent diastereoselectivity and enantioselectivity. Finally, when the hydrogenation was performed using a combination of nickel acetate (5 mol%) and the (*R*,*S*)-ferrocenyl ligand **3g** in the presence of sodium acetate in a mixture of trifluoroethanol and acetic acid under 100 atm of hydrogen for 24 h, the substrate was smoothly converted and the *anti*-β-hydroxy-α-amino acid ester **2** was obtained in quantitative yield with complete diastereoselectivity and 92% ee.[19]

For the scope and limitations of the hydrogenation under the optimized conditions, a series of substrates **4** with different substituents were subjected to hydrogenation as shown in Table 3. Excellent diastereoselectivities and enantioselectivities were obtained for the aromatic substrates. Compared to the iridium-catalyzed hydrogenation,[8] somewhat superior results with respect to the enantioselectivity and reactivity were obtained using the hindered substrate and halogen-containing substrates. The *o*-tolyl substrate did not react during the Ir-catalyzed hydrogenation, but was a good substrate for the nickel-catalyzed hydrogenation (entry 1). In the case of the Ir-catalyzed hydrogenation, the existence of an electron-withdrawing group on the aromatic ring hampered the hydrogenation and caused a low enantioselectivity. However, these were excellent substrates for the present hydrogenation (entries 4–6,

Table 3 Various β-hydroxy-α-amino acide esters



Entry	R	R′	Time	Yield[a]	*anti*/*syn*	ee[b] (%)
1	*o*-tolyl		7 d	90	>99/1	81
2		H	24 h	98	>99/1	92
3		Me	24 h	83	>99/1	93
4		F	24 h	88	>99/1	89
5		Cl	24 h	91	>99/1	92
6		Br	24 h	91	>99/1	92
7		Me	24 h	82	>99/1	93
8		*t*-Bu	24 h	90	>99/1	92
9[d]		OBn	4 d	94	>99/1	91
10[c]		NO_2	24 h	80	>99/1	91
11		CO_2Me	48 h	82	>99/1	88
12[d]			4 d	90	>99/1	89
13	2-Naphthyl		24 h	92	>99/1	90
14[d]	2-Thienyl		7 d	79	>99/1	95
15	Cyclohexyl		24 h	8 (16)[e]	>99/1	81
16	*t*-Butyl		24 h	21	>99/1	54

[a] Isolated yield after *N*-benzoylation. [b] Determined after *N*-benzoylation. [c] NO_2/NH_2 = ≥ 9/1. [d] 10 Mol% catalyst was used. [e] Yield in AcOH.

10, 11). Conventionally, the Raney nickel catalyst has been used for dehalogenation and desulfurization, but the homogeneous nickel complex catalyzes the hydrogenation without any interaction in the presence of halogen and sulfur atoms to afford the corresponding β-hydroxy-α-amino acid esters with excellent enantioselectivity (entries 4–6, 14). Although a nitro group is sensitive to reducing conditions, the hydrogenation of the nitro-containing substrate chemoselectively proceeded to give the corresponding product along with a small amount of the aniline derivative (entry 10). In contrast to the aromatic substrates, the reaction of the aliphatic substrates was slow and the enantioselectivities were moderate (entries 15 and 16). In order to explore the potential of the homogeneous chiral nickel-bisphosphine complex, we examined the asymmetric hydrogenation of several substrates. The ketonic substrates, methyl benzoylacetate and acetophenone, were smoothly hydrogenated but the enantioselectivities of the products were low or moderate. Although the activity of the chiral nickel-catalyst in the above asymmetric hydrogenation is moderate, the results of the present reaction are noteworthy because this represents not only the first use of homogeneous chiral nickel-phosphine complexes in asymmetric hydrogenation, but also the first example of nickel-catalyzed dynamic kinetic resolution.

We have succeeded in the development of a successful asymmetric hydrogenation using homogeneous chiral nickel-bisphosphine catalysts for the stereoselective synthesis of *anti*-β-hydroxy-α-amino esters. This reaction represents the first asymmetric hydrogenation using homogeneous chiral nickel-bisphosphine complexes. The present hydrogenation is superior to the iridium-catalyzed hydrogenation regarding the substrate

generality and enantioselectivity. It is noteworthy that such a complicated asymmetric hydrogenation smoothly proceeds with a combination of the cheap base metal, nickel, and commercially available phosphine ligands without using any precious transition-metal catalyst. Further investigations on the mechanistic details and potential applications of asymmetric hydrogenation using homogeneous chiral nickel catalysts are actively underway.

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16 Sodium acetate serves as the base for the generation of the acid-free substrate.

17 The examined nickel salts were purchased and used as received. The anhydrous nickel salts prepared from commercial nickel chloride and nickel acetate had a hygroscopic tendency.

18 The examined bisphosphines are follows: (+)-DIOP, (*S*,*S*)-Chiraphos, (*R*,*R*)-Me-Duphos, (*R*,*R*)-Et-BPE, (*R*,*R*)-Quinox P*, (*S*)-PHOX, (*R*,*S*)-PPFA, (*R*,*R*)-Walphos, (*R*,*S*)-Taniaphos, (*S*)-BINAP, and 1,2-bis(dicyclohexylphosphino)ethane.

19 Typical procedure for asymmetric hydrogenation (the reaction was carried out in a glassware placed in a stainless autoclave apparatus): A glass test tube was charged with $Ni(OAc)_2{\cdot}4H_2O$ (8.7 mg, 0.035 mmol), (*R*,*S*)-ferrocenyl ligand (**3g**, 24.9 mg, 0.035 mmol), the α-amino-β-keto ester hydrochloride (**1**, 161 mg, 0.70 mmol), sodium acetate (57.4 mg, 0.70 mmol), and molecular sieves 3A (70 mg), and then was flushed with argon. After trifluoroethanol (0.7 mL) and acetic acid (2.8 mL) were added, the resulting mixture was degassed by three freeze–thaw cycles. The glass test tube was transferred to a stainless steel autoclave in an argon-filled glove bag. The mixture was stirred at 25 °C under hydrogen pressure (100 atm) for 24 h. After hydrogen was carefully released, MeOH (3.5 mL) and aqueous HCl (1 M in H_2O, 1.4 mL) was added and the mixture was concentrated *in vacuo* to dryness below 40 °C. The resulting residue was dissolved in MeOH and the mixture was concentrated *in vacuo*. This operation was repeated three times. The residue was used for next step without any purification. Benzoic anhydride (158 mg, 0.70 mmol) followed by a solution of Et_3N (0.3 mL, 2.1 mmol) in THF (2.1 mL) were added dropwise to a solution of the above crude product in THF (3.5 mL) at 0 °C. After stirring the mixture at 25 °C for 12 h, the reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the *N*-benzoyl derivative of **2** (204 mg, 98%). The diastereomeric ratio was determined by ^1H NMR. The enantiomeric excess was determined by chiral HPLC.

