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Diastereo- and Enantioselective Asymmetric Hydrogenation of α-Amido-β-keto Phosphonates via Dynamic Kinetic Resolution

Xiaoming Tao,[†] Wanfang Li,[†] Xiaoming Li,[†] Xiaomin Xie,[†] and Zhaoguo Zhang*[,†,‡]

School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, 345 Lingling Road, Shanghai 200032, China

zhaoguo@sjtu.edu.cn

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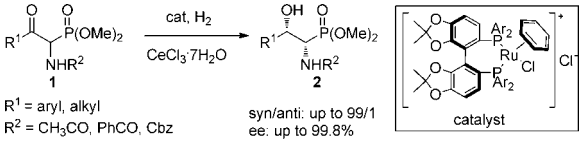
ABSTRACT



Dynamic kinetic resolution of various α-amido-β-keto phosphonates via asymmetric hydrogenation proceeded efficiently to give the corresponding β-hydroxy-α-amido phosphonates in high diastereo- and enantioselectivities (up to 99:1 syn/anti, 99.8% ee). The addition of catalytic amounts of $CeCl_3 \cdot 7H_2O$ is necessary to achieve both good selectivity and catalytic efficiency under mild reaction conditions.

Chiral β-hydroxy-α-amino phosphonates have received considerable attention in the past decades because of their prevalence in bioorganic and medicinal chemistry owing to their unique biological activities as well as their potential uses as peptide mimics and haptens of catalytic antibodies (Figure 1).[1] Presently, a number of methods are available for the synthesis of optically pure and enriched β-hydroxy-α-amino phosphonates,[2] via resolution, enzymatic methods, or asymmetric C−C and C−P bond-forming reactions. However, these synthetic routes suffered from either low stereoselectivity or poor efficiency. Accordingly, the search for effective, highly stereoselective, and atom-economic processes to obtain β-hydroxy-α-amino phosphonates is of great significance.

Ruthenium-catalyzed asymmetric hydrogenation via dynamic kinetic resolution (DKR) has turned out to be an elegant and powerful synthetic tool to control two adjacent stereogenic centers with high levels of enantioselectivity and diastereoselectivity in one single chemical operation.[3] This reaction was reported by Noyori et al.[4] in 1989 and Genêt et al.[5] in 1991 for the synthesis of threonine. The hydrogenation of α-acetamido-β-keto esters and

[†] Shanghai Jiao Tong University.
[‡] Shanghai Institute of Organic Chemistry.

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more generally of noncyclic α-amino-β-keto esters with Ru(II) catalysts afforded the corresponding β-hydroxy esters with excellent diastereoisomeric and enantiomeric excesses.[6] The stereochemical course of the hydrogenation reaction is highly dependent on the nature of the protected amino groups. In the current paradigm, hydrogenation of the *N*-acyl-protected α-amido-β-keto esters yields the *syn* diastereomer,[7] whereas the hydrochloride salt of α-amino-β-keto esters afforded the *anti* diastereomer.[8] However, up to now, the only example of an efficient DKR of an α-acetamido-β-keto phosphonates with Ru-BINAP system afforded the corresponding *syn* α-acetamido-β-hydroxy phosphonates was reported by Noyori et al. in 1995.[9] Therefore, asymmetric hydrogenation of α-amido-β-keto phosphonates is still a challenging work.

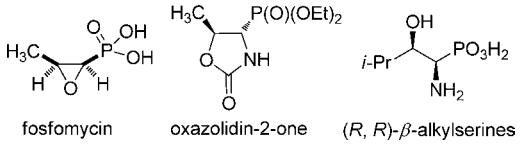

Figure 1. Biologically active β-hydroxy-α-amino phosphonates.

Our group has designed some atropisomeric C_2-symmetric biaryl biphosphine-SunPhos ligands and explored their applications in asymmetric hydrogenation of functionalized ketones.[10] In this paper, we disclose a general and highly diastereo- and enantioselective hydrogenation reaction of α-amido-β-keto phosphonates.

The catalyst was prepared from $[RuCl_2(benzene)]_2$ and (*S*)-SunPhos (Figure 2) by refluxing them in degassed dichloromethane/ethanol (v/v = 1:1) for 1.5 h, and then the solvent was removed under reduced pressure.[10a] The asymmetric hydrogenation was carried out with 1 mol % of [RuCl(benzene)(*S*)-SunPhos]Cl under 10 bar of H_2 at 50 °C in MeOH for 24 h with dimethyl (1-acetamido-2-oxo-2-phenylethyl)phosphonate (**1a**) as the standard substrate. We obtained full conversions and excellent diastereoisomeric and enantiomeric excesses of the desired product **2a**[11] (Table 1, entry 1, syn/anti 97:3, ee 98.0%). Because subtle changes in geometric, steric, and/or electronic properties of chiral ligands can lead to dramatic variations of reactivity and stereselectivity,[12] (*S*)-Tol-SunPhos and two commercially available chiral bidentate ligands, (*S*)-SegPhos and (*S*)-MeO-Biphep, were also tested under the same reaction conditions (Figure 2). They showed lower activity, and the diastereo- and enantioselectivities varied to some extent. As illustrated in Table 1, (*R*)-Tol-SunPhos (entry 2, syn/anti 94:6, ee 99.9%), (*S*)-SegPhos (entry 3, syn/anti 89:11, ee 95.7%), and (*S*)-Meo-Biphep (entry 4, syn/anti 89:11, ee 96.7%) were inferior to (*S*)-SunPhos. On the basis of the above results, (*S*)-SunPhos was the ligand of choice.

Results of the optimization of solvents, hydrogen pressure, and reaction temperatures are summarized in Table 1. Solvent is important for the catalytic efficiency and diastereoisomeric and enantiomeric excesses of the asymmetric hydrogenation reaction (Table 1, entries 1, 5–8). Protic solvents resulted in high catalytic activities and diastereoisomeric and enantiomeric excesses, providing

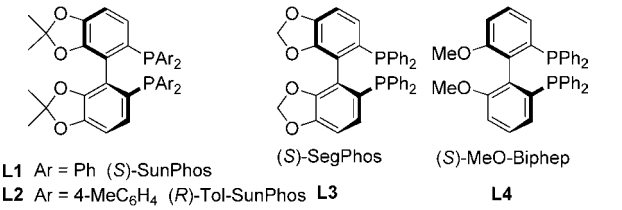

Figure 2. Structures of chiral bidentate ligands.

complete conversions of **1a** to **2a** with good to excellent syn/anti ratios ranging from 95:5 to 97:3 and ee's up to 98.2%. Aprotic solvents such as dichloromethane or THF gave **2a** with up to 99.0% ee but lower diastereoselectivities (Table 1, entries 7 and 8). The results depicted in Table 1 showed that the efficiency and diastereoisomeric and enantiomeric excesses of the hydrogenation were strongly dependent on the temperature (Table 1, entries 1 and 9–11).[13] Lower reaction temperature remarkably decreased the reaction rate and diastereoisomeric and enantiomeric excesses, while higher reaction temperature slightly decreased

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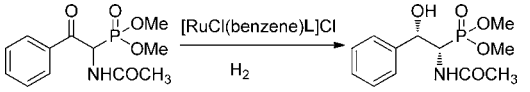
enantioselectivity. However, the efficiency and diastereoisomeric and enantiomeric excesses were not affected by the hydrogen pressure in our optimization.

Table 1. Optimization of Ligands and Reaction Conditions[a]



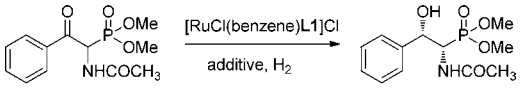
1a 2a

entry	ligand	solvent	syn/anti[b]	ee of syn[b] (%)
1	**L1**	MeOH	97:3	98.0
2	**L2**	MeOH	94:6	99.9
3[c]	**L3**	MeOH	89:11	95.7
4[d]	**L4**	MeOH	89:11	96.7
5	**L1**	EtOH	96:4	97.7
6	**L1**	*i*-PrOH	95:5	98.2
7	**L1**	CH_2Cl_2	87:13	98.1
8	**L1**	THF	85:15	99.0
9[e]	**L1**	MeOH	95:5	94.4
10[f]	**L1**	MeOH	97:3	98.7
11[g]	**L1**	MeOH	98:2	96.6
12[h]	**L1**	MeOH	97:3	97.8
13[i]	**L1**	MeOH	97:3	98.0

[a] Unless otherwise stated, all reactions were carried out with a substrate (1 mmol) concentration of 0.5 M in solvent under 10 bar of H_2 at 50 °C for 24 h, S/C = 100:1. Conversion: >99%. [b] Determined by HPLC on a Chiralpak AD-H column. [c] Conversion: 90%. [d] Conversion: 94%. [e] At 30 °C, conversion: 80%. [f] At 70 °C. [g] At 90 °C. [h] Under 30 bar. [i] Under 50 bar.

It has been reported that additives played some crucial roles in improving the reactivity and diastereo- and enantioselectivity in many asymmetric reactions.[14] In our preliminary work, we used Lewis acids or aqueous solutions of Brønsted acids as additives in the asymmetric hydrogenation of α-ketoesters and achieved better results.[10c,e] Accordingly, we evaluated several additives for the asymmetric hydrogenation of **1a** by using 1 mol % of [RuCl(benzene)(*S*)-SunPhos]Cl as catalyst and 5 mol % of additives in an attempt to promote the diastereo- and enantioselectivity. Lewis acids are among the most useful reagents in reactions with ketones as substrates. For example, $CeCl_3 \cdot 7H_2O$ was used in the selective reduction of the carbonyl group of α,β-unsaturated ketones with $NaBH_4$.[15] When Lewis acids were used as additives in the hydrogenation of our model substrate **1a** with ruthenium as the catalyst (Table 2, entries 3−6), improved diastereoselectivities (syn/anti 98:2−99:1) were obtained and the enantioselectivity remained excellent. The best results were achieved with $CeCl_3 \cdot 7H_2O$ as additive; perfect enantioselectivity and diastereoselectivity were obtained (Table 2, entries 3). There was no detectable difference between anhydrous $CeCl_3$ and $CeCl_3 \cdot 7H_2O$ as additives. The diastereo- and enantioselectivities decreased slightly when aqueous solutions of Brønsted acids, except for HBF_4, were tested (entries 7−10), where the diastereoselectivity was better than those without additives (entry 7 vs 1, syn/anti 98:2 vs 97:3). When iodine was used as the additive, the enantioselectivity remained but the diastereoselectivity increased slightly to 98:2 (entry 11).

Table 2. Effects of Additives on the DKR of **1a**[a]



1a 2a

entry	additive	syn/anti[b]	ee of syn[b] (%)
1	none	97:3	98.0
2	H_2O	97:3	97.4
3	$CeCl_3 \cdot 7H_2O$	99:1	98.8
4	$CeCl_3$	99:1	98.6
5	$ZnCl_2$	98:2	98.1
6	$BF_3 \cdot Et_2O$	99:1	97.2
7	HBF_4 aq	98:2	99.9
8	HF aq	97:3	97.2
9	HCl aq	96:4	94.5
10	HBr aq	96:4	94.7
11	I_2	98:2	97.9

[a] Unless otherwise stated, all reactions were carried out with a substrate (1 mmol) concentration of 0.5 M in MeOH under 10 bar of H_2 at 50 °C for 24 h, S/C/additive = 100:1:5. Conversion: >99%. [b] Determined by HPLC on a Chiralpak AD-H column.

On the basis of these results, the optimized reaction conditions were therefore set as the following: 1 mol % of [RuCl(benzene)**L1**]Cl as the catalyst, $CeCl_3 \cdot 7H_2O$ as the additive, MeOH as the solvent with a substrate concentration of 0.5 M, and 10 bar of H_2 at 50 °C.

Under the optimized reaction conditions, a variety of protected α-amido-β-keto phosphonates were hydrogenated, and the results are depicted in Table 3. The diastereo- and enantioselectivities were highly dependent on the amino protecting groups: benzoyl-protected substrate (**1c**) gave low diastereoselectivity and high enantioselectivity (entry 3, syn/anti 55:45, ee 96.5%); when benzyloxycarbonyl was employed as the amino protecting group, diastereo- and enantioselectivity for the hydrogenation turned out to be very high (entry 2, syn/anti 95:5, ee 99.5%); the acetyl-protected substrate (**1a**) had accomplished the highest diastereo- and enantioselectivity (entry 1, syn/anti 99:1, ee 98.8%). Therefore, acetyl-protected substrates were chosen in the following investigation. A series of acetyl-protected α-amido-β-keto phosphonates bearing a different substituent at the *para* position on the phenyl group were studied. The results showed that the electron

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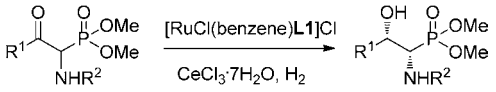
Table 3. Asymmetric Hydrogenation of α-Amido-β-keto Phosphonates[a]



1 2

1a, **1d-1o**: $R^2 = CH_3CO$; **1b**: R^2 = Cbz; **1c**: R^2 = PhCO

entry	1	R^1	2 syn/anti[b]	2 ee of syn[b] (%)
1[c]	**1a**	C_6H_5	99:1	98.8
2[d]	**1b**	C_6H_5	95:5	99.5
3	**1c**	C_6H_5	55:45	96.5
4	**1d**	*o*-$CH_3C_6H_4$	95:5	93.2
5	**1e**	*m*-$CH_3C_6H_4$	95:5	97.3
6	**1f**	*p*-$CH_3C_6H_4$	94:6	94.2
7	**1g**	*p*-$OMeC_6H_4$	94:6	99.8
8	**1h**	*p*-F-C_6H_4	76:24	95.6
9	**1i**	*p*-ClC_6H_4	96:4	95.5
10	**1j**	*p*-BrC_6H_4	98:2	95.0
11	**1k**	*p*-$CF_3C_6H_4$	96:4	97.5
12	**1l**	2-furyl	97:3	93.6
13[c]	**1m**	CH_3	98:2	95.2
14[e]	**1m**	CH_3	97:3	94.0
15	**1n**	C_2H_5	98:2	92.5
16	**1o**	$CH(CH_3)_2$	94:6	91.7
17	**1p**	$C_6H_5CH_2$	75:25	95.9

[a] Unless otherwise stated, all reactions were carried out with a substrate (1 mmol) concentration of 0.5 M in MeOH under 10 bar of H_2 at 50 °C for 24 h. S/C/additive = 100:1:5. Conversion: >99%. [b] Determined by HPLC. [c] Absolute configurations of **2a** and **2m** were assigned as (1*S*, 2*S*) on the basis of their optical rotation and ^{31}P NMR (see ref 9); the configuration of other products can be assigned as (1*S*, 2*S*) according to the well-established general trend (see ref 8). [d] Absolute configuration was not known. [e] S/C/additive = 10000:1:10.

density of the aromatic ring has a strong effect on the diastereo- and enantioselectivities (entries 6–11, syn/anti 76:24–98:2, ee 94.2–99.8%). The strong electron-donating groups (MeO) on the aromatic ring afforded the corresponding product (**2g**) in 94:6 syn/anti in the presence of $CeCl_3 \cdot 7H_2O$ (entry 7), while the electron-withdrawing groups (F) on the aromatic ring decreased the diastereoselectivity (entry 8, syn/anti 76:24). Electronic influences of the *para* substituents were presumed to affect the coplanarity of the benzene rings with C=O in the transition state,[16] thereby generating an asymmetric bias. Simple *ortho*- and *meta*-substituted substrates were also hydrogenated to give the products with excellent diastereo- and enantioselectivities (entries 4 and 5). Heteroaryl group was also tolerated and excellent diastereo- and enantioselectivities were obtained (entry 12).

Hydrogenation of an aliphatic analogue also gave moderate to excellent diastereo- and enantioselectivities (Table 3, entries 13–16, syn/anti 75:25–98:2, ee 91.7–95.9%). Asymmetric hydrogenation of dimethyl (1-acetamido-2-oxopropyl)phosphonate (**1m**) afforded the corresponding alcohol (**2m**) in 98:2 syn/anti and 95.2% ee (entry 13).[11] Enantiopure **2m** has been applied in the practical synthesis of fosfomycin.[17] Furthermore, the reaction proceeded smoothly on multigram scale with excellent diastereo- and enantiofacial discrimination; up to 97:3 syn/anti and 94.0% ee under 10 bar of hydrogen pressure and 50 °C using a catalyst loading of 0.01 mol % of [RuCl(benzene)(*S*)-SunPhos]Cl (entry 14) were obtained.

In conclusion, we have developed a convenient and general protocol for the diastereo- and enantioselective hydrogenation of a variety of α-amido-β-keto phosphonates via dynamic kinetic resolution, and excellent diastereo- and enantioselectivity were obtained. Additives play a crucial role in improving the diastereo- and enantioselectivity in our reaction. In the presence of $CeCl_3 \cdot 7H_2O$ as the additive, dramatically increased diastereoisomeric and enantiomeric excesses up to 99:1 syn/anti and 99.8% ee were achieved.

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Supporting Information Available. Experimental details of substrate synthesis and NMR and/or HPLC data of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.