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Iridium-Catalyzed Asymmetric Hydrogenation of Racemic β-Keto Lactams via Dynamic Kinetic Resolution

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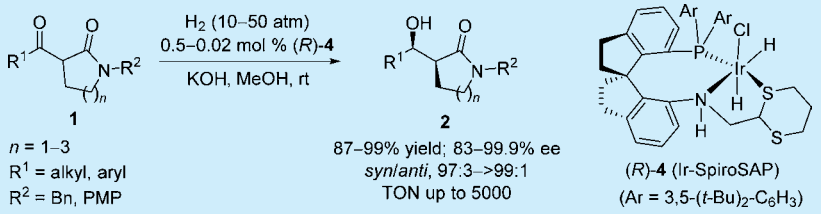
Supporting Information



ABSTRACT: A highly efficient Ir-catalyzed asymmetric hydrogenation of racemic β-keto lactams via dynamic kinetic resolution (DKR) for the synthesis of optically active β-hydroxyl lactams has been described. With the Ir-SpiroSAP catalyst, a series of racemic β-keto lactams including β-keto γ-, δ-, and ε-lactams were hydrogenated to chiral β-hydroxy lactams in high yields (87−99%) with excellent enantio- and diastereoselectivity (83−99.9% ee, *syn*/*anti*: 97:3−>99:1) at low catalyst loading under mild reaction conditions. This efficient method has been successfully applied in the synthesis of the chiral intermediate of fluoroquinolone antibiotic premafloxacine.

The development of catalytic asymmetric reactions that are both highly efficient and selective is an important and challenging task in organic synthesis. The Ru(diphosphine)-catalyzed asymmetric hydrogenation of racemic α-substituted β-ketoesters via dynamic kinetic resolution (DKR), initiated by Noyori[1] and Genêt,[2] has been demonstrated to be an efficient and reliable method for the synthesis of chiral β-hydroxy esters with two contiguous stereocenters.[3] Hattori et al.[4] expanded this method to the asymmetric hydrogenation of racemic α-acetyl γ-lactam, 1-benzyl-3-acetylpyrrolidin-2-one to optically active β-hydroxy γ-lactam and provided an enantioselective approach to 2-(*N*-imidoylpyrrolidinyl) carbapenems, which shows higher activity than imipenem against *Staphylococcus aureus* (MRSA). Subsequently, researchers of Pfizer[5] and Eli Lilly[6] used Ru-catalyzed asymmetric hydrogenation of racemic α-acyl γ-lactams via DKR for the preparation of pyrrolidine-containing chiral drugs such as PF-00951966, a novel broad-spectrum fluoroquinolone antibiotic,[7] and serotonin norepinephrine reuptake inhibitors (Scheme 1).[8] However, the catalyst loading is still high (S/C < 300) and the substrate scope of reaction needs improvement.[9]

Recently, we developed several chiral spiro iridium catalysts bearing P−N−N type ligands SpiroPAP (**3**)[10] and P−N−S type ligands SpiroSAP (**4**),[11] which are extremely efficient for the asymmetric hydrogenation of β-keto esters to optically active β-hydroxy esters.[10c,11] When we evaluated these spiro iridium catalysts for the hydrogenation of racemic α-acyl lactams to β-hydroxy lactams, we found that the catalyst Ir-(*R*)-SpiroSAP ((*R*)-**4**) shows excellent selectivities (up to 99.9% ee, >99:1 *syn*/*anti*-selectivity) with turnover numbers (TON) up to 5000 (Scheme 1). We herein describe the catalytic asymmetric hydrogenation of racemic α-acyl lactams **1** with chiral spiro iridium catalysts SpiroSAP for the synthesis of chiral β-hydroxy lactams **2**.

The hydrogenation of racemic 1-benzyl-3-acetylpyrrolidin-2-one (**1a**) was initially performed under the reaction conditions of 10 atm of H_2, *t*-BuOK as a base in MeOH at S/C = 1000. The catalyst (*R*)-**3** gave 100% conversion within 0.5 h with moderate enantioselectivity (*syn*-isomer, 76% ee; *anti*-isomer, 29% ee) and *syn*/*anti*-selectivity (*syn*/*anti* = 80:20) (Table 1, entry 1). Gratifyingly, the catalyst (*R*)-**4** bearing a 1,3-dithiane moiety shows very high activity and enantioselectivity in the hydrogenation of **1a**. The hydrogenation was completed within 0.5 h and afforded (3*S*,1′*R*)-**2a** in 100% conversion with 99.7% ee and >99:1 *syn*/*anti*-selectivity (entry 2). The absolute configuration of (3*S*,1′*R*)-**2a** was determined by X-ray diffraction analysis of its single crystal (see Supporting Information (SI)). The effect of solvent on the reaction was examined with catalyst (*R*)-**4**. The hydrogenations in EtOH and *n*-PrOH gave comparable conversion and selectivity, but required a longer reaction time (entries 3 and 4). However, the reaction in *i*-PrOH was slow (31% conversion after 4 h, entry 5). No hydrogenation was observed in toluene (entry 6). The hydrogenation reaction also proceeded smoothly with KOH, NaOH, or K_2CO_3 as a base, affording **2a** with excellent enantio- and diastereoselectivity (entries 8−10). However, low conversions were observed in the reactions using *t*-BuONa, Na_2CO_3, or Et_3N as a base (entries 7, 11, and 12). When the

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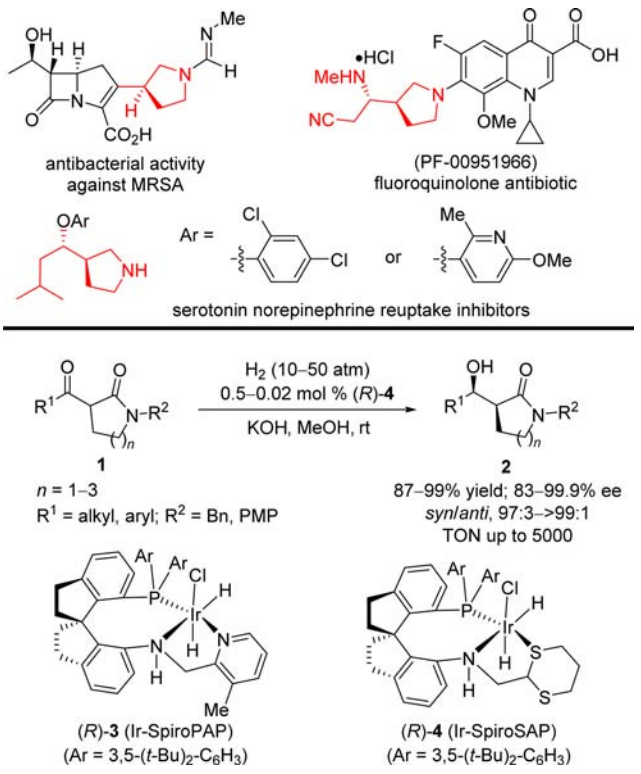
Scheme 1. Asymmetric Hydrogenation of Racemic β-Keto γ-Lactams via DKR

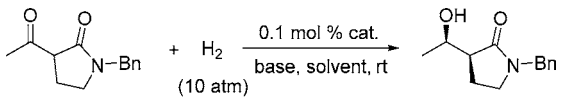


catalyst loading was decreased from 0.1 to 0.02 mol % (S/C = 5000) the reaction still gave full conversion with 99.4% ee and 95:5 *syn*/*anti*-selectivity at 50 atm of H_2 pressure (initial) and 20 h (entry 13).

Under the optimal reaction conditions, a variety of racemic γ-lactams with different α-acyl groups **1a**–**l** were hydrogenated to the corresponding optically active chiral β-hydroxyl γ-lactams **2a**–**i** in high yield (88–96%) with excellent enantioselectivity (98–99.9% ee) and *syn*/*anti*-selectivity (*syn*/*anti*: 98:2–>99:1) (Table 2, entries 1–12). Changing protecting group at the N-atom of lactam substrates has a strong effect on the reaction rate, but has little effect on the selectivity of the reaction. However, no hydrogenation reaction was observed when nonprotected lactams were used. The reaction exhibits good tolerance for the functional groups. The substrates containing an olefin (**1h**) and an ester group (**1i** and **1k**) also gave desired products in high yield and selectivities (entries 8, 9, and 11). Because the hydroxyl and ester groups in **2i** easily form a lactone in acidic workup, the hydrogenation product of γ-lactam **1i** is a lactone–lactam, 1-benzyl-3-(5-oxotetrahydrofuran-2-yl)pyrrolidin-2-one (**2i**, entry 9). The β-keto δ-lactams **1m**–**q** can also be hydrogenated to the corresponding β-hydroxy δ-lactams **1m**–**q** in high yield (96–99%) with excellent diastereoselectivity (*syn*/*anti* = 97:3–99:1) and enantioselectivity (98–99.9% ee) (entries 13–17). However, the β-keto-ε-lactam (**1r**) showed lower enantioselectivity (83% ee) in the hydrogenation reaction (entry 18). In addition, the catalyst (*R*)-**4** is also efficient for the asymmetric hydrogenation of racemic acyclic β-keto amides such as *N*,*N*-dibenzyl-2-methyl-3-oxobutanamide, resulting in the corresponding β-hydroxy amide in a high yield (98%, 24 h) with good *syn*-selectivity (*syn*/*anti*: 89:11), however, with low enantioselectivity (*syn*-isomer, 44% ee, *anti*-isomer, 5% ee) (see SI).

The β-keto lactams were able to epimerize through an enol intermediate under basic conditions, which is why the asymmetric hydrogenation lactams **1** via DKR can be achieved. To answer if the hydrogenation of β-keto lactam **1** occurs on its ketone or enol form, we performed a hydrogenation of *rac*-**1a** with D_2 under identical reaction conditions (Scheme 2). The ^{1}H NMR analysis showed that the hydrogenation product contains 72% deuterium at the 1′-position and 7% deuterium at the α-position of lactam. This result supported that the hydrogenation of β-keto lactams **1** occurs on its ketone form (Scheme 2, a). The minor deuteration at the α-position of lactam came from the hydrogen–deuterium exchange of substrate under the reaction conditions.

Table 1. Asymmetric Hydrogenation of 1a: Optimization of Reaction Conditions[a]



1a **2a**

entry	cat.	solvent	base	time (h)	conv (%)[b]	*syn*/*anti*[c]	ee (%)[c]
1	(*R*)-**3**	MeOH	*t*-BuOK	0.5	100	80:20	76 (29)[d]
2	(*R*)-**4**	MeOH	*t*-BuOK	0.5	100	>99:1	99.7
3	(*R*)-**4**	EtOH	*t*-BuOK	2	100	>99:1	98
4	(*R*)-**4**	*n*-PrOH	*t*-BuOK	2.5	100	>99:1	97
5	(*R*)-**4**	*i*-PrOH	*t*-BuOK	4	31	98:2	97
6	(*R*)-**4**	toluene	*t*-BuOK	15	<5	–	–
7	(*R*)-**4**	MeOH	*t*-BuONa	4	85	>99:1	99.3
8	(*R*)-**4**	MeOH	KOH	0.5	100	>99:1	99.7
9	(*R*)-**4**	MeOH	NaOH	1.5	100	>99:1	99.1
10	(*R*)-**4**	MeOH	K_2CO_3	0.6	100	>99:1	99.6
11	(*R*)-**4**	MeOH	Na_2CO_3	4	52	>99:1	99.5
12	(*R*)-**4**	MeOH	Et_3N	4	88	>99:1	99.9
13[e]	(*R*)-**4**	MeOH	KOH	20	100	95:5	99.4

[a]Reaction conditions: 1.0 mmol scale, [**1a**] = 1.0 M, 1.0 μmol catalyst, [base] = 0.1 M, 1.0 mL of solvent, room temperature (25–30 °C). [b]Determined by ^{1}H NMR spectroscopy. [c]The ee value of *syn*-isomer, determined by HPLC using a Chiralcel AD-H column. [d]The ee value of the *anti*-isomer is in parentheses. [e]5.0 mmol scale, S/C = 5000, 50 atm of H_2 (initial).

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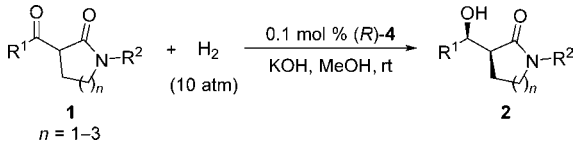
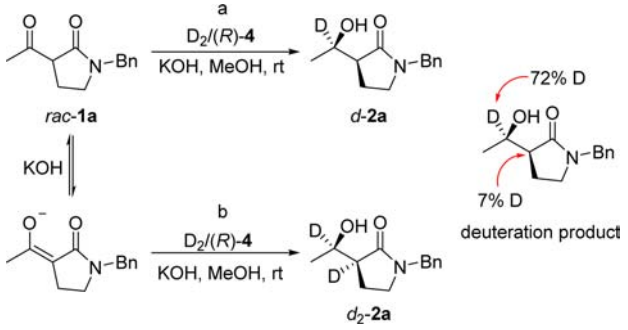
Table 2. Asymmetric Hydrogenation of Racemic α-Acyl Lactams 1 with (*R*)-4[a]



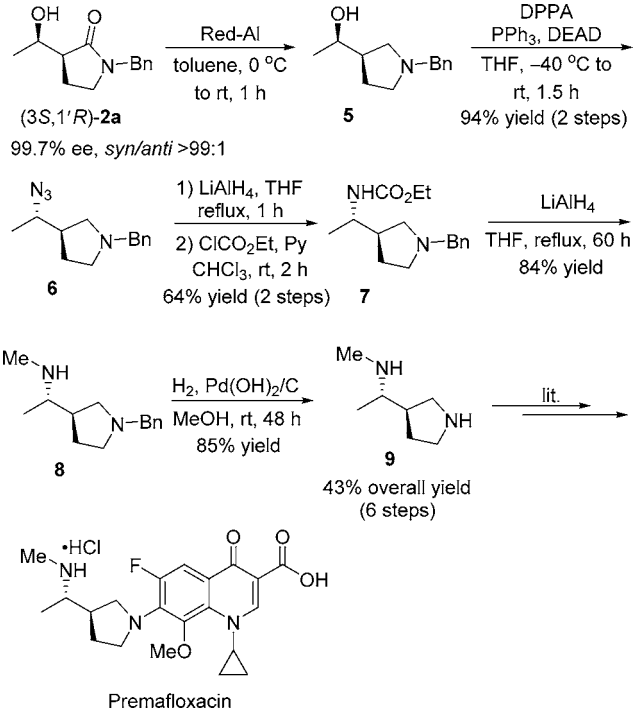
entry	1	R^1	R^2	n	time (h)	yield (%)[b]	*syn*/*anti*[c]	ee (%)[d]
1	**1a**	Me	Bn	1	0.5	94	>99:1	99.7
2	**1b**	Me	PMP	1	8	92	>99:1	99.9
3	**1c**	Et	Bn	1	0.5	95	>99:1	99.9
4	**1d**	*n*-Pr	Bn	1	3	95	>99:1	99.6
5	**1e**	Bn	Bn	1	2	94	>99:1	99.7
6	**1f**	Cy	Bn	1	3	90	>99:1	99.9
7[e]	**1g**	*i*-Bu	Bn	1	24	91	>99:1	98
8[f]	**1h**	$Me_2CCH(CH_2)_2$	Bn	1	24	95	>99:1	99
9[g]	**1i**	$MeO_2C(CH_2)_2$	Bn	1	4	88	>99:1	99.9
10	**1j**	C_6H_5	Bn	1	4	91	>99:1	99.9
11	**1k**	4-$MeOCOC_6H_4$	Bn	1	12	88	98:2	99.9
12[e]	**1l**	2-furyl	Bn	1	20	96	98:2	99.4
13	**1m**	Me	Bn	2	4	96	99:1	99.6
14[h]	**1n**	*n*-Pr	Bn	2	24	97	>99:1	99.9
15[h]	**1o**	Bn	Bn	2	24	97	97:3	98
16[h]	**1p**	C_6H_5	Bn	2	24	99	98:2	98
17[e]	**1q**	3-ClC_6H_4	Bn	2	24	91	>99:1	99
18[h]	**1r**	Me	Bn	3	24	87	97:3	83

[a]Reaction conditions were the same as those described in Table 1, entry 8. [b]Isolated yield. [c]Determined by HPLC. [d]The ee value of *syn*-isomer, determined by HPLC. [e]50 atm. [f]0.2 mol % of (*R*)-**4**, 50 atm. [g]Lactone-lactam product was obtained after acidic workup. [h]0.5 mol % of (*R*)-**4**, 50 atm of H_2.

Scheme 2. Hydrogenation of *rac*-1a with D_2



Scheme 3. Enantioselective Synthesis of (*S*)-*N*-Methyl-1-((*R*)-pyrrolidin-3-yl)ethan-1-amine (9)



To demonstrate the utility of this highly efficient method, we used the hydrogenation product (3*S*,1′*R*)-**2a** to synthesize (*S*)-*N*-methyl-1-((*R*)-pyrrolidin-3-yl)ethan-1-amine (**9**, Scheme 3), a key chiral intermediate to access fluoroquinolone antibiotic premafloxacin.[12] The reduction of γ-lactam (3*S*,1′*R*)-**2a** (99.7% ee, *syn*/*anti* > 99:1) with Red-Al was followed by a Mitsunobu reaction to yield azide **6** in 94% yield. Azide **6** was reduced with $LiAlH_4$, and the resulting amine reacted with ethyl chloroformate to afford carbamate **7** in 64% yield. The reduction of carbamate **7** with $LiAlH_4$ and removal of the benzyl protecting group by hydrogenation with $Pd(OH)_2/C$ produced chiral intermediate **9** in 71% yield. Thus, we accomplished the enantioselective synthesis of (*S*)-*N*-methyl-1-((*R*)-pyrrolidin-3-yl)ethan-1-amine (**9**) in 43% overall yield.

In conclusion, we have developed a highly efficient Ir-catalyzed asymmetric hydrogenation of racemic β-keto lactams via DKR for the synthesis of optically active β-hydroxyl lactams. With the Ir-SpiroSAP catalyst, a series of racemic β-keto lactams including β-keto γ-, δ-, and ε-lactams were hydrogenated to chiral β-hydroxy lactams in high yields with excellent enantio- and diastereoselectivity at a low catalyst loading under mild reaction conditions. This reaction provides an efficient and practical method for the synthesis of chiral β-hydroxyl lactams with two contiguous stereocenters.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03397.

Experiment procedures and the characterizations of the substrates and products (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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