Asymmetric Catalysis

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Development of Chiral Spiro P-N-S Ligands for Iridium-Catalyzed Asymmetric Hydrogenation of β-Alkyl-β-Ketoesters**

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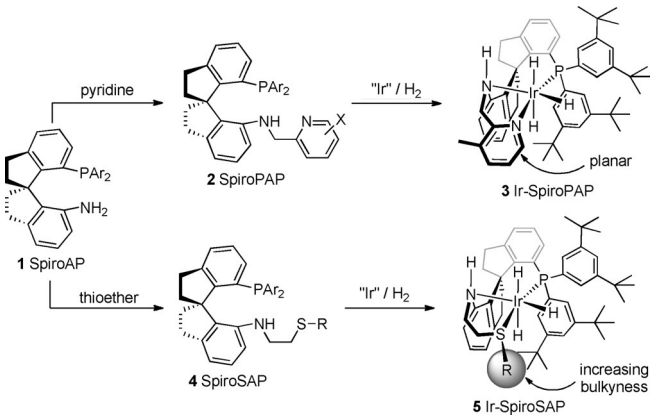
Abstract: *The chiral tridentate spiro P-N-S ligands (SpiroSAP) were developed, and their iridium complexes were prepared. Introduction of a 1,3-dithiane moiety into the ligand resulted in a highly efficient chiral iridium catalyst for asymmetric hydrogenation of β-alkyl-β-ketoesters, producing chiral β-alkyl-β-hydroxyesters with excellent enantioselectivities (95–99.9 % ee) and turnover numbers of up to 355 000.*

Transition-metal-catalyzed asymmetric hydrogenation of unsaturated compounds is a powerful tool for the synthesis of chiral molecules in optically active form. Many chiral ligands have been developed for asymmetric hydrogenation of diverse substrates such as olefins, ketones, and imines.[1] Most of the efficient chiral ligands reported to date have been chiral phosphorus (P) ligands,[2] nitrogen (N) ligands,[3] or mixed P-N ligands.[4] In contrast, only a few efficient chiral sulfur containing ligands, mainly P-S ligands, have been developed for highly enantioselective hydrogenation reactions.[5] Introduction of a thioether moiety into the chiral ligand is believed to beneficially alter the chiral environment around the metal of the catalyst; specifically, coordination of the S atom to the metal not only exerts steric and electronic effects but also converts the S atom to a new stereogenic center.[6]

Recently, we developed some chiral spiro pyridine-aminophosphine ligands, referred to as SpiroPAP ligands, that exhibit extraordinary activity and enantioselectivity in iridium-catalyzed hydrogenation of aromatic ketones and β-aryl-β-ketoesters.[7] However, when we used the SpiroPAP ligands for iridium-catalyzed asymmetric hydrogenation of β-alkyl-β-ketoesters to afford β-hydroxyesters, only moderate enantioselectivity was obtained.[8] Owing to the importance of chiral β-hydroxyesters in the synthesis of chiral drugs and natural products,[9] we explored new ligands and catalysts in the hope of achieving the asymmetric hydrogenation of β-alkyl-β-ketoesters. On the basis of the structure of Ir-SpiroPAP (**3**) and the fact that the pyridine moiety in **3** is vital for obtaining high activity and high enantioselectivity in the hydrogenation of aromatic ketones and β-aryl-β-ketoesters, we speculated that the enantioselectivity of the hydrogenation of β-alkyl-β-ketoesters could be increased by replacing the planar pyridine moiety in **3** with a thioether group, the steric bulk of which could be adjusted. Herein we report the syntheses of new tridentate spiro P-N-S ligands, SpiroSAP (**4**), and their applications for iridium-catalyzed asymmetric hydrogenation of β-alkyl-β-ketoesters (Scheme 1).



Scheme 1. The design of chiral spiro iridium catalysts with SpiroSAP ligands.

SpiroSAP ligands (*R*)-**4a–i** were synthesized from chiral spiro aminophosphines (*R*)-**1**[10] by acylation with 2-alkylthio- or arylthio-substituted acetyl chlorides and subsequent reduction with $LiAlH_4$ in the presence of $AlCl_3$. SpiroSAP ligands (*R*)-**4j** and (*R*)-**4k** were synthesized by reductive alkylation of (*R*)-**1** with 2,2-dimethoxyacetaldehyde with $NaBH(OAc)_3$ or H_2/Pd-C, followed by transdithioacetalization of the acetal group with 1,3-propanedithiol in the presence of indium(III) trichloride (Scheme 2).

Ir-SpiroSAP catalysts **5** were prepared by complexation of ligands (*R*)-**4** with an iridium precursor under H_2 pressure (Scheme 3). For example, the reaction of (*R*)-**4a** and $[Ir(cod)Cl]_2$ (cod = cyclooctadiene) in ethanol under 10 atm of H_2 at room temperature gave catalyst (*R*)-**5a** (96 % yield) as a light yellow solid. The ^1H NMR spectrum of (*R*)-**5a** exhibits two groups of double-doublets; and the ^{31}P NMR spectrum exhibits a triplet. These NMR results indicate the formation of an iridium dihydride $[Ir(H)_2((R)\text{-}\mathbf{4a})Cl]$. However, the reaction of (*R*)-**4k** with $[Ir(cod)Cl]_2$ under 30 atm of H_2 afforded iridium dihydride $[Ir(H)_2((R)\text{-}\mathbf{4k})Cl]$ as a mixture

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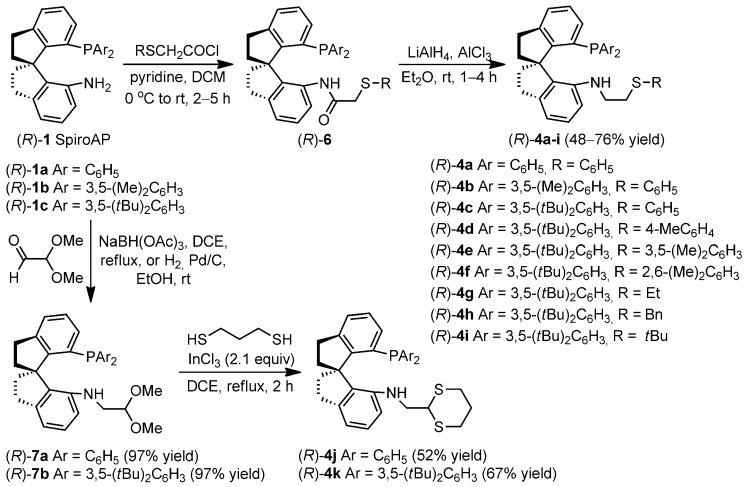
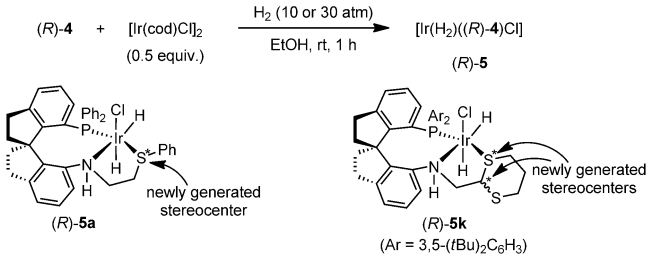


Scheme 2. The synthesis of SpiroSAP ligands (*R*)-**4**.

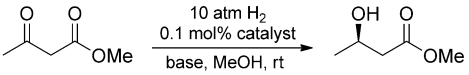


Scheme 3. The synthesis of Ir-SpiroSAP catalysts (*R*)-**5**.

of four stereoisomers in a 49:35:10:6 ratio (see Supporting Information). In the ^{1}H NMR spectrum of the mixture, the hydride hydrogens of the complexes appeared as eight groups of double-doublets in the chemical shift range of $\delta = -24.99$ to -23.37 ppm; and two groups of multiplets, at around $\delta =$ 19.76 and 20.40 ppm, were observed in the ^{31}P NMR spectrum. These results indicate that two new stereocenters were generated in (*R*)-**5k** (Scheme 3). Attempts to grow crystals of iridium dihydride complexes (*R*)-**5** for X-ray diffraction analysis were unsuccessful.

Iridium catalysts (*R*)-**5** were evaluated in the asymmetric hydrogenation of β-alkyl-β-ketoesters (Table 1). When methyl acetoacetate (**8a**) was hydrogenated in MeOH under 10 atm of H_2 in the presence of 0.1 mol% of (*R*)-**5a**, the desired product, methyl β-hydroxybutyrate ((*R*)-**9a**), was obtained in 69% *ee* with 100% conversion (entry 2). Compared with Ir-SpiroPAP ((*R*)-**3**), (*R*)-**5a** gave higher enantioselectivity, but the reaction rate was lower (compare entries 1 and 2). Introduction of substituents to the *P*-phenyl rings of (*R*)-**5** improved the enantioselectivity of the hydrogenation reaction (entries 3 and 4); for example, 3,5-*tert*-butyl-substituted catalyst (*R*)-**5c** gave 84% *ee* (entry 4). Introduction of a substituent to the *S*-phenyl ring of the catalyst did not affect the enantioselectivity but did decrease the reaction rate (entries 5–7). The reaction catalyzed by (*R*)-**5f**, which has a 2,6-$(Me)_2C_6H_3$ group on the *S* atom, did not go to completion (entry 7). When the aryl thioether moiety of the catalyst was replaced by an alkyl thioether, the reaction rate and conversion were comparable, but the enantioselectivity was decreased, owing to the steric bulk of the alkyl group (entries 8–10). The reaction catalyzed by (*R*)-**5i**, which has a *t*Bu substituent on the *S* atom, had the lowest enantioselectivity (47% *ee*, entry 10). We were delighted to find that introduction of a conformationally constrained 1,3-dithiane moiety into the catalyst remarkably improved the enantioselectivity of the reaction (entries 11 and 12), with catalyst (*R*)-**5k** giving the highest enantioselectivity (95% *ee*, entry 12). Reactions in which (*R*)-**5a** and (*R*)-**5k** were generated in situ showed conversions and enantioselectivities identical to those obtained with the pre-prepared catalysts.

Table 1: Optimizing the hydrogenation conditions for the asymmetric hydrogenation of β-alkyl-β-ketoester.[a]



Entry	Catalyst	Base	*t* [h]	Conv. [%][b]	*ee* [%][c]
1	(*R*)-**3**	*t*BuOK	0.5	100	53
2	(*R*)-**5a**	*t*BuOK	3	100	69
3	(*R*)-**5b**	*t*BuOK	3	100	76
4	(*R*)-**5c**	*t*BuOK	8.5	100	84
5	(*R*)-**5d**	*t*BuOK	3	100	83
6	(*R*)-**5e**	*t*BuOK	6	100	84
7	(*R*)-**5f**	*t*BuOK	24	70	84
8	(*R*)-**5g**	*t*BuOK	3	100	75
9	(*R*)-**5h**	*t*BuOK	2	100	82
10	(*R*)-**5i**	*t*BuOK	1.5	100	47
11	(*R*)-**5j**	*t*BuOK	8	100	87
12	(*R*)-**5k**	*t*BuOK	0.5	100	95
13	(*R*)-**5k**	NaOH	0.5	100	95
14[d]	(*R*)-**5k**	NaOH	4.5	100	95
15[e]	(*R*)-**5k**	NaOH	20	100	95
16[f]	(*R*)-**5k**	*t*BuOK	72	71 (68)	93

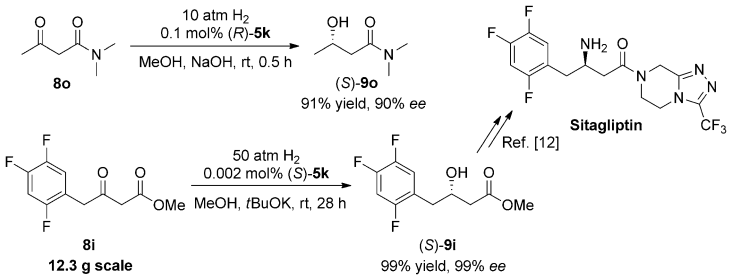
[a] Reaction conditions: 1.5 mmol scale, [**8a**] = 1.5 M, 0.05 mol% [Ir(cod)Cl]$_2$, 0.11 mol% ligand, [base] = 0.04 M, 1.0 mL MeOH. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by GC on a Supelco chiral β-dex-325. The absolute configuration of the product is *R*. [d] 1 atm H_2. [e] S/C = 100000 (0.001 mol%), 50 atm H_2 (initial). [f] S/C = 500000 (0.0002 mol%), 50 atm H_2 (initial). The value in parentheses is yield of isolated product.

The effect of the solvent on the reaction was examined with catalyst (*R*)-**5k** (see Supporting Information). Methanol was found to be the best choice for the asymmetric hydrogenation. In addition to *t*BuOK, other bases, such as *t*BuONa, KOH, NaOH, and K_2CO_3, could be used in the reaction (see Supporting Information). When the hydrogen pressure was lowered from 10 atm to 1 atm, 100% conversion was obtained within 4.5 h, without any loss of enantioselectivity (entry 14). Catalyst (*R*)-**5k** was extremely active. When the hydrogenation of **8a** was carried out at a catalyst loading of 0.001 mol% (S/C = 100000), full conversion and an enantioselectivity of 95% *ee* were obtained, although high hydrogen pressure (50 atm) and a long reaction time (20 h) were needed

(entry 15). When the catalyst loading was further reduced to 0.0002 mol% (S/C = 500000), the conversion was 71% (turnover number = 355000), and (*R*)-**9b** was obtained with 93% *ee* (entry 16). These results demonstrate that (*R*)-**5k** is one of the most active chiral catalysts reported to date for the asymmetric hydrogenation of β-alkyl-β-ketoesters.[8]

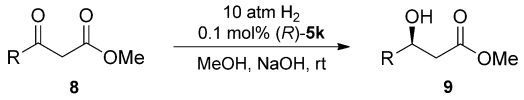
A wide range of β-alkyl-β-ketoester substrates (**8a**–**m**) could be hydrogenated under the optimal reaction conditions (Table 2). Catalyst (*R*)-**5k** showed high yields (91–98%) and excellent enantioselectivities (95–99.9% *ee*) for all the tested substrates, regardless of the electronic and steric properties of the alkyl group (entries 1–13). Hydrogenation product (*R*)-**9e**, which has a long chain (R = $C_{11}H_{23}$), and product (*R*)-**9i**, which has a trifluorobenzyl group, are critical intermediates in the syntheses of the chiral antiobesity drug orlistat[11] and the antidiabetes drug sitagliptin,[12] respectively. Catalyst (*R*)-**5k** tolerated various functional groups, including a double bond (**8j**), an ether (**8k**), and an amide (**8l**), in the substrate, affording chiral β-hydroxyesters (*R*)-**9j**, (*R*)-**9k**, and (*S*)-**9l**, which are key intermediates in the syntheses of natural products brefeldin A[13] and dolabelides[14] and the chiral drug carnitine,[15] respectively, in high yields with excellent enantioselectivities (entries 10–12). (*R*)-**5k** also catalyzed the hydrogenation of β-aryl-β-ketoester **8n** to afford **9n** with high enantioselectivity (95% *ee*, entry 14).

In addition, (*R*)-**5k** also efficiently catalyzed the asymmetric hydrogenation of β-alkyl-β-ketoamides. For example, hydrogenation of *N*,*N*-dimethyl-3-oxobutanamide (**8o**) catalyzed by (*R*)-**5k** yielded chiral (*S*)-3-hydroxy-*N*,*N*-dimethylbutanamide ((*S*)-**9o**) in 91% yield with 90% *ee* within 0.5 h (Scheme 4). Because (*S*)-**9i** is a key intermediate in the synthesis of sitagliptin, we hydrogenated **8i** on a gram scale using 0.002 mol% of catalyst (S/C = 50000) under an initial hydrogen pressure of 50 atm at room temperature; the reaction afforded desired product (*S*)-**9i** in 99% yield with 99% *ee* (Scheme 4). This result is superior to that reported by Merck using an (*S*)-BINAPRuCl$_2$-triethylamine complex as a catalyst (94% *ee* at S/C = 1000).[12]



Scheme 4. Asymmetric hydrogenation of β-alkyl-β-ketoamide **8o** and synthesis of (*S*)-**9i**.

Table 2: Asymmetric hydrogenation of β-alkyl-β-ketoesters **8** with (*R*)-**5k**.[a]



Entry	R	8	*t* [h]	9	Yield [%][b]	*ee* [%][c]
1	Me	**8a**	0.5	**9a**	92	95 (*R*)
2	Et	**8b**	0.5	**9b**	91	98 (*R*)
3	*n*Pr	**8c**	4	**9c**	94	98 (*R*)
4	*n*Bu	**8d**	2	**9d**	92	98 (*R*)
5	$C_{11}H_{23}$	**8e**	2	**9e**	98	98 (*R*)
6	*i*Pr	**8f**	2	**9f**	93	98 (*S*)
7	*t*Bu	**8g**	3	**9g**	96	99.9 (*S*)
8	Bn	**8h**	2	**9h**	96	98 (*R*)
9	2,4,5-$F_3C_6H_2CH_2$	**8i**	2	**9i**	98	99 (*R*)
10	$Me_2C{=}CH(CH_2)_2$	**8j**	2	**9j**	96	99 (*R*)
11	$BnO(CH_2)_2$	**8k**	2	**9k**	95	98 (*R*)
12	$CbzNHCH_2$	**8l**	4	**9l**	97	98 (*S*)
13	CF_3	**8m**	0.5	**9m**	92	99.9 (*S*)
14	C_6H_5	**8n**	4	**9n**	93	95 (*S*)

[a] Reaction conditions were the same as those listed in Table 1, entry 18. [b] Yield of isolated product. [c] Determined by GC or HPLC on a chiral stationary phase (see the Supporting Information).

In conclusion, previously unreported chiral spiro P-N-S ligands and their iridium complexes were prepared. These new complexes proved to be highly efficient catalysts for the asymmetric hydrogenation of β-alkyl-β-ketoesters, affording chiral β-alkyl-β-hydroxyesters with excellent enantioselectivities (95–99.9% *ee*) and turnover numbers of up to 355000.

Keywords: asymmetric catalysis · hydrogenation · iridium · ketoesters · spiro ligands

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