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Highly Enantioselective Hydrogenation of α-Arylmethylene Cycloalkanones Catalyzed by Iridium Complexes of Chiral Spiro Aminophosphine Ligands

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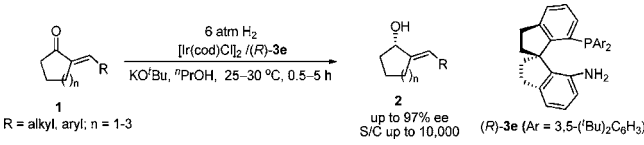
Chiral allylic alcohols are important and versatile intermediates in organic synthesis because they can be readily converted into a variety of biologically active molecules, such as pharmaceuticals and natural products.[1] The transition-metal-catalyzed asymmetric hydrogenation of the carbonyl group of α,β-unsaturated ketones is a direct method to produce chiral allylic alcohols.[2] The Ir-complexes of phosphine ligands were the first catalysts used for asymmetric hydrogenation of α,β-unsaturated ketones but yield the corresponding chiral allylic alcohols with low ee values.[3] High enantioselectivity (up to 98% ee) in the hydrogenation of α,β-unsaturated ketones was obtained by Noyori et al. using Ru-BINAP/diamine catalysts in 1995.[4] Since then, the catalysts used in the asymmetric hydrogenation of α,β-unsaturated ketones to chiral allylic alcohols have been dominated by Ru-diphosphine/diamine complexes, and various acyclic and *endo*-cyclic α,β-unsaturated ketones have been hydrogenated with good to excellent enantioselectivities.[5] However, the asymmetric hydrogenation of *exo*-cyclic α,β-unsaturated ketones is still a challenge,[6] despite the fact that the corresponding hydrogenation products, *exo*-cyclic allylic alcohols, serve as key intermediates for the synthesis of chiral drugs (e.g., the trinem antibiotic sanfetrinem)[6c] and natural products (e.g., slaframine).[6d] Thus, the development of highly efficient methods for the asymmetric synthesis of *exo*-cyclic allylic alcohols is highly desirable.

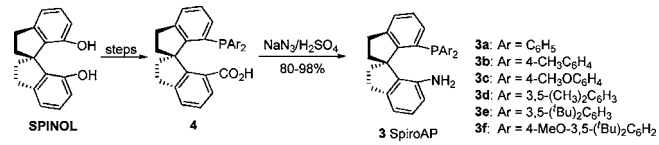
Scheme 1. Asymmetric Hydrogenation of *exo*-Cyclic α,β-Unsaturated Ketones



Recently, we demonstrated that Ru-SDPs/diamine catalysts are highly efficient for the asymmetric hydrogenation of ketones and aldehydes,[7] providing chiral alcohols with excellent enantioselectivities. When we attempted to apply these catalysts for the hydrogenation of *exo*-cyclic (*E*)-α,β-unsaturated ketone **1a** (R = Ph, *n* = 2), we obtained allylic alcohol **2a** in low yield with moderate ee.[8] To develop efficient methods for the preparation of enantiomer-enriched *exo*-cyclic allylic alcohols, we investigated iridium catalysts and found that the Ir-complex of spiro aminophosphine ligand (*R*)-**3e** is a highly efficient catalyst for the hydrogenation of (*E*)-α-arylmethene cycloalkanones **1** (Scheme 1). In this Communication, we report the first highly enantioselective hydrogenation of (*E*)-α-arylmethene cycloalkanones by using chiral Ir-complexes of spiro aminophosphine ligands **3** and its application in the synthesis of the key intermediate of the active form of the anti-inflammatory loxoprofen **7**.

Chiral spiro aminophosphine (abbreviated as SpiroAP) ligands **3** were prepared from optically pure 1,1′-spirobiindane-7,7′-diol[9] via bisarylphosphino-7′-carboxy-1,1′-spirobiindanes **4**, which was the key intermediate in our previous synthesis of spiro phosphine-oxazoline ligands.[10] The acids **4** were easily converted to spiro aminophosphine ligands **3a**−**f** in excellent yields (80−98%) using a Schmidt reaction (Scheme 2).

Scheme 2. Synthesis of Chiral Spiro Aminophosphine Ligands **3**



In the study of Ir-catalyzed asymmetric hydrogenation of α-arylmethylene cycloalkanones **1**, we initially chose (*E*)-α-benzylidene cyclohexanone (**1a**) as a model substrate and performed the hydrogenation in 1-propanol containing KO^{t}Bu under 6 atm of H_2 with the catalyst Ir-(*R*)-**3** generated *in situ* from 0.05 mol % $[Ir(COD)Cl]_2$ and 0.12 mol % ligand (*R*)-**3**. A comparison of ligands showed that the ligand (*R*)-**3e**, which has bulky 3,5-di-*tert*-butylphenyl groups on the P-atom, gave the highest activity and enantioselectivity. The reaction was completed within 0.5 h and provided the hydrogenation product (*S*)-**2a** at a yield of 98% with 97% ee (Table 1, entry 5). The ligand (*R*)-**3f** with 3,5-di-*tert*-butyl-4-methoxyphenyl groups on the P-atom gave a comparable yield and enantioselectivity (entry 6), while the other ligands yielded (*S*)-**2a** in only small amounts with moderate ee values (entries 1−4). The addition of a strong base, such as KO^{t}Bu and KOH, was required to obtain high activity and enantioselectivity. No reaction was observed in the absence of hydrogen gas, which indicated that hydrogenation instead of transfer hydrogenation occurred in the reaction. Solvent experiments showed that both ^{n}PrOH and EtOH were good solvents for this reaction, but MeOH and ^{i}PrOH were inferior, offering lower yields and ee values (entries 9 and 11). The ratio of Ir/L was also investigated, and the results showed that one

Table 1. Asymmetric Hydrogenation of **1a** Catalyzed by Ir-(*R*)-**3**[a]

entry	ligand	base	solvent	conv. (%)[b]	yield (%)[c]	ee (%)[d]
1	(*R*)-**3a**	KO^{t}Bu	^{n}PrOH	24	23	53
2	(*R*)-**3b**	KO^{t}Bu	^{n}PrOH	36	34	68
3	(*R*)-**3c**	KO^{t}Bu	^{n}PrOH	45	39	71
4	(*R*)-**3d**	KO^{t}Bu	^{n}PrOH	20	18	61
5	(*R*)-**3e**	KO^{t}Bu	^{n}PrOH	100	98	97
6	(*R*)-**3f**	KO^{t}Bu	^{n}PrOH	95	87	94
7	(*R*)-**3e**	KOH	^{n}PrOH	100	95	96
8	(*R*)-**3e**	K_2CO_3	^{n}PrOH	100	92	90
9	(*R*)-**3e**	KO^{t}Bu	MeOH	100	86	89
10	(*R*)-**3e**	KO^{t}Bu	EtOH	100	93	97
11	(*R*)-**3e**	KO^{t}Bu	^{i}PrOH	100	71	93
12[e]	(*R*)-**3e**	KO^{t}Bu	^{n}PrOH	100	97	96
13[f]	(*R*)-**3e**	KO^{t}Bu	^{n}PrOH	100	91	93

[a] Reaction conditions: 3.0 mmol scale, [subst] = 1.5 M, 0.05 mol % $[Ir(COD)Cl]_2$, 0.12 mol % (*R*)-**3**, [Base] = 0.04 M, 6 atm of H_2, 2.0 mL of solvent, rt, 0.5 h. [b] Determined by ^{1}H NMR. [c] Isolated yield. [d] Determined by HPLC. [e] Ir/L = 1:2. [f] S/C = 10 000, 50 atm of H_2, 30 °C, 4 h.

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equivalent ligand is enough to achieve high activity and enantioselectivity, indicating that the active catalyst contains only one aminophosphine ligand (entries 5 and 12). The Ir-(*R*)-**3e** catalyst had a very high activity such that the reaction could be performed with as low as 0.01 mol % of catalyst loading.

As summarized in Table 2, a number of (*E*)-α-arylmethylene cyclohexanones **1** can be hydrogenated to the chiral *β*-arylmethylene cyclohexanols **2** in high yields with excellent enantioselectivities (entries 1−10). Either the electron-donating or electron-withdrawing substituent on the phenyl ring of the substrate had little effect on both the reactivity and enantioselectivity of the reaction. When the substrate with a five-membered ring (**1k**−**m**) or a seven-membered ring (**1n**) was subjected to the hydrogenation, the corresponding *β*-arylmethylene cyclic alcohols were obtained at 97−98% yields with 93−96% enantiomeric excesses (entries 11−14). The (*E*)-α-alkylmethylene cyclohexanone **1o** (R = Me) could also be hydrogenated to the desired allylic alcohol **2o** with 91% ee, albeit with a lower reaction rate and yield (entry 15).

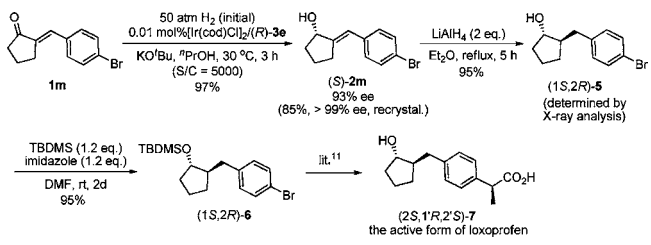
Table 2. Asymmetric Hydrogenation of **1** Catalyzed by Ir-(*R*)-**3e**[a]

entry	R	*n*	product	time (h)	yield (%)[b]	ee (%)[c]
1	C_6H_5	2	**2a**	0.5	98	97 (*S*)
2	4-MeC_6H_4	2	**2b**	0.5	99	95
3	4-MeOC_6H_4	2	**2c**	0.5	99	96
4	4-ClC_6H_4	2	**2d**	0.5	97	94
5	4-BrC_6H_4	2	**2e**	0.5	98	94
6	3-MeOC_6H_4	2	**2f**	0.5	98	95
7	2-MeOC_6H_4	2	**2g**	0.5	99	95
8	2-Furyl	2	**2h**	1.0	95	92
9	1-naphthyl	2	**2i**	1.0	95	89
10	2-naphthyl	2	**2j**	0.5	98	93
11	C_6H_5	1	**2k**	0.5	98	96
12	4-MeOC_6H_4	1	**2l**	0.5	99	95
13	4-BrC_6H_4	1	**2m**	0.5	98	94 (*S*)
14	C_6H_5	3	**2n**	0.5	97	93
15	Me	2	**2o**	5.0	66	91

[a] Reaction conditions are the same as those in Table 1, entry 5. [b] Isolated yield. [c] Determined by GC or HPLC.

To demonstrate the utility of this asymmetric hydrogenation, we studied the synthesis of (1*S*,2*R*)-**6**, a key intermediate in the preparation of the active form of the anti-inflammatory loxoprofen **7** (Scheme 3). Recently, Kobayashi et al. reported the synthesis of (1*S*,2*R*)-**6** with an 85% yield by a five-step procedure, starting from optically pure (1*R*,4*S*)-4-hydroxycyclopent-2-enyl acetate, in the total synthesis of the active form of loxoprofen **7**.[11] We performed the hydrogenation of (*E*)-2-(4-bromobenzylidene)cyclopentanone (**1m**) with 0.02 mol % Ir-(*R*)-**3e** as catalyst (S/C = 5000) under the standard conditions and obtained allylic alcohol (*S*)-**2m** at a yield of 97% with 93% ee. The ee value of (*S*)-**2m** was further improved to 99% by recrystallization from ethyl acetate/petroleum ether. The reduction of (*S*)-**2m** with $LiAlH_4$ yielded alcohol (1*S*,2*R*)-**5** at 95%, and its absolute configuration was determined by X-ray structure analysis (see Supporting Information). The hydroxyl group of (1*S*,2*R*)-**5** was protected with *tert*-butyldimethylsilyl chloride to yield (1*S*,2*R*)-**6** at 95%. Thus, (1*S*,2*R*)-**6** was prepared with a yield of 77% in three steps from an achiral starting material.

Scheme 3. Enantioselective Synthesis of (1*S*,2*R*)-**6**



In conclusion, the highly efficient asymmetric hydrogenation of α-arylmethylene cycloalkanones was realized by using Ir-complexes of chiral spiro aminophosphine ligands. This new reaction provides a practical approach to the synthesis of *exo*-cyclic allylic alcohols and *β*-arylmethyl cyclic alcohols, including the key intermediate of the active form of loxoprofen.

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Supporting Information Available: Experimental procedures, the characterizations of chiral ligands and products, and the analysis of ee values of hydrogenation products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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