Homogeneous Catalysis

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Enantioselective Hydrogenation of α-Substituted Acrylic Acids Catalyzed by Iridium Complexes with Chiral Spiro Aminophosphine Ligands**

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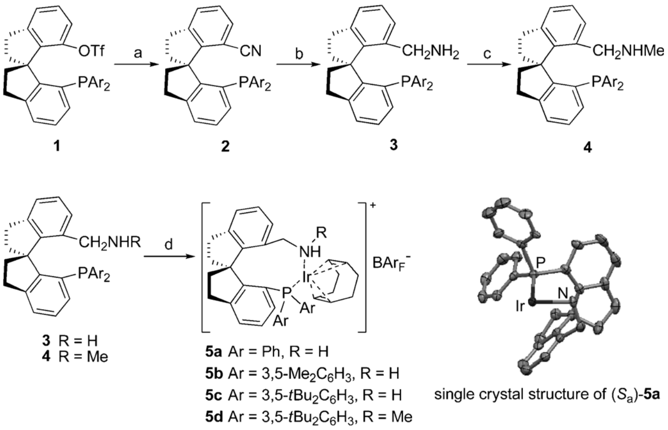
The transition-metal-catalyzed asymmetric hydrogenation reactions attract long-lasting interest from both academic research and industrial production.[1] The development of chiral ligands is the essential impetus for the asymmetric hydrogenation reactions. During the past decades, chiral P,N ligands having both phosphorus and nitrogen atoms as the coordinating groups become popular in the hydrogenation reactions.[2] Generally, molecules with sp^2 nitrogen atoms, such as oxazoline and pyridine, are required for achieving good results for the chiral P,N ligands. Although several phosphine amine ligands containing primary amine moieties have been successfully applied in the highly enantioselective hydrogenation of ketones,[3] to our knowledge, such ligands have not been applied successfully in the asymmetric hydrogenation of olefins. Herein we report the preparation of novel chiral spiro aminophosphine ligands bearing a primary amine moiety **3** (Scheme 1) and their applications in the hydrogenation of α,β-unsaturated carboxylic acids. The iridium complexes **5** derived from the chiral spiro aminophosphine ligands showed unprecedentedly high activity (turnover numbers (TONs) up to 10000; turnover frequencies (TOFs) up to 6000 h^{-1}) and enantioselectivity (94–99% *ee*). The primary amine moiety in the catalysts **5** is the key for obtaining high activity and enantioselectivity.

Chiral spiro aminophosphine ligands **3** and **4** were easily prepared starting from optically pure **1** (Scheme 1).[4] Palladium-catalyzed cyanation of **1** (step a) followed by $LiAlH_4$ reduction (step b) afforded ligands **3** in good yield. Ligands **4**, which have an *N*-methyl group, were prepared from **3** through condensation with ethyl chloroformate and $LiAlH_4$ reduction in one pot (step c). The iridium complexes **5** were prepared by refluxing a mixture of [{Ir(cod)Cl}$_2$], **3** or **4**, and $NaBAr_F$ in dichloromethane for two hours (step d). Complexes **5** were stable enough to be purified by silica gel column chromatography and stored in air without degradation for a few months. The structure of complex (S_a)-**5a** was proved by an X-ray diffraction analysis of a single crystal.[5] According to the crystal structure, (S_a)-**3a** acts as a chelating P,N ligand and creates a rigid chiral pocket around the iridium center.



Scheme 1. Synthesis of chiral spiro aminophosphine ligands and corresponding iridium complexes. Reaction conditions: a) $Zn(CN)_2$, [Pd(PPh$_3$)$_4$], DMF, 84–88%; b) $LiAlH_4$, THF, reflux, 90–94%; c) 1) ClCOOEt, pyridine, THF; 2) $LiAlH_4$, THF, reflux; 60%; d) [{Ir(cod)Cl}$_2$], $NaBAr_F$, CH_2Cl_2, reflux, 76–91%. BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, cod = cyclooctadiene, Tf = trifluoromethanesulfonyl. The hydrogen atoms, cod ligand, and anion (BAr_F^-) were omitted for clarity. Thermal ellipsoids are set at 60% probability. Selected bond lengths [Å] and angles [°]: Ir–N 2.152(4), Ir–P 2.3394(12); N-Ir-P 89.63(13).

The asymmetric hydrogenation of α-substituted acrylic acids **6** (for structures see Table 2) is of highly practical value because the products, optically pure α-substituted propionic acids, include important biologically active compounds. For example, ibuprofen (**7a**) and naproxen (**7f**),[6] two well-known non-steroid anti-inflammatory drugs, can be readily prepared by asymmetric hydrogenation of the corresponding α-aryl acrylic acids. Although chiral ruthenium catalysts usually give high enantioselectivity in the asymmetric hydrogenation of α-substituted acrylic acids, most of these catalysts require high hydrogen pressure (e.g., 100 atm) to achieve complete conversion and high enantioselectivity.[7] The high pressure markedly limits the practical application of the reaction. Rhodium/diphosphine[8] and iridium/phosphine oxazoline[9] catalysts have also been used for the asymmetric hydrogenation of α-aryl acrylic acids; however, these catalysts show unsatisfactory activity, enantioselectivity, or both. Furthermore, the asymmetric hydrogenation of α-alkyl-substituted acrylic acids[10] is highly underdeveloped compared to that of α-aryl-substituted acrylic acids. As part of our

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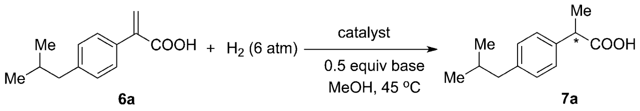
continuing efforts to develop asymmetric hydrogenation of unsaturated carboxylic acids,[11] we tried iridium-catalyzed asymmetric hydrogenation of α-substituted acrylic acids with new chiral spiro aminophosphine ligands **3** or **4**.

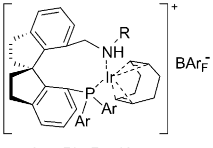
To our delight, the chiral spiro aminophosphine ligands exhibited excellent activity and enantioselectivity for the asymmetric hydrogenation of **6a**. In the presence of 0.1 mol% (ratio substrate/catalyst (S/C) = 1000) of catalyst (S_a)-**5c**, the hydrogenation of **6a** was completed within ten minutes (with a TOF of 6000 h^{-1}) to afford the desired product **7a** with excellent enantioselectivity (98% *ee*; Table 1, entry 3). Iridium catalysts **5** with less bulky *P*-aryl groups showed slightly lower activity and enantioselectivity (Table 1, entries 1 and 2). Although the catalyst (S_a)-**5d**, which has an *N*-methyl group, also showed excellent enantioselectivity, the hydrogenation reaction was not completed after 18 h (Table 1, entry 4). Catalyst (S_a)-**5c** exhibited remarkably high catalytic activity in the asymmetric hydrogenation of **6a**. In the presence of 0.1 mol% of catalyst (S_a)-**5c**, the hydrogenation reaction proceeded at ambient hydrogen pressure (Table 1, entry 5). When the catalyst loading was further reduced to 0.01 mol% (S/C = 10000), the reaction was completed within eight hours at 6 atm hydrogen pressure without significant diminishment of the enantioselectivity (Table 1, entry 6). This result represents the highest level of activity and enantioselectivity of catalysts in the asymmetric hydrogenation of α-substituted acrylic acids. In contrast, (S_a)-**8**, an iridium complex of the ligand SpiroAP[3b] bearing an aromatic amino group, did not catalyze the hydrogenation of **6a** (Table 1, entry 7). The iridium complex (S_a,*S*)-**9** derived from chiral spiro phosphine oxazoline ligands,[12] which exhibit excellent activity and enantioselectivity in the hydrogenation of trisubstituted α,β-unsaturated carboxylic acids,[11c,d] was also less efficient in the present hydrogenation reaction (Table 1, entry 8). Besides Cs_2CO_3, other bases such as Na_2CO_3 and Et_3N were also suitable additives for achieving good results (Table 1, entries 9 and 10); however, the reaction rate decreased dramatically in the absence of base (entry 11). We speculated that the base promoted the formation of the carboxy anion of the substrate, which then chelates to the iridium center of the catalyst more easily than the acid itself, and thus accelerated the hydrogenation reaction.

Table 1: Asymmetric hydrogenation of α-(4-isobutylphenyl)acrylic acid **6a**.[a]

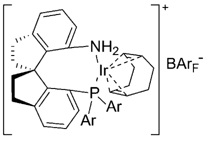


Entry	Catalyst	Base	Time	Conv [%][b]	*ee* [%][c]
1	(S_a)-**5a**	Cs_2CO_3	2 h	100	94 (*R*)
2	(R_a)-**5b**	Cs_2CO_3	1 h	100	96 (*S*)
3	(S_a)-**5c**	Cs_2CO_3	10 min	100	98 (*R*)
4	(S_a)-**5d**	Cs_2CO_3	18 h	44	98 (*R*)
5[d]	(S_a)-**5c**	Cs_2CO_3	4 h	100	99 (*R*)
6[e]	(S_a)-**5c**	Cs_2CO_3	8 h	100	97 (*R*)
7	(S_a)-**8**	Cs_2CO_3	24 h	0	–
8[f]	(S_a,*S*)-**9**	Cs_2CO_3	24 h	36	45 (*R*)
9	(S_a)-**5c**	Na_2CO_3	30 min	100	98 (*R*)
10	(S_a)-**5c**	Et_3N	15 min	100	98 (*R*)
11	(S_a)-**5c**	none	24 h	38	91 (*R*)

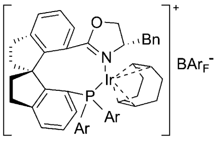
[a] Reaction conditions: 0.5 mmol scale, [substrate] = 0.25 mol L^{-1} in MeOH, S/C = 1000, 0.5 equiv Cs_2CO_3 as additive, P_{H_2} = 6 atm, 45 °C. [b] Determined by ^1H NMR spectroscopy. [c] Determined by chiral GC analysis of the corresponding methyl ester with a Varian CP7502 column (see the Supporting Information for details), absolute configuration was determined by the sign of optical rotation. [d] The reaction was performed under ambient hydrogen pressure. [e] Reaction conditions: 1 mmol scale, [substrate] = 0.25 mol L^{-1} in MeOH, S/C = 10000, 5 equiv NEt_3 as additive, P_{H_2} = 6 atm, 60 °C. [f] S/C = 200.



5a Ar = Ph, R = H
5b Ar = 3,5-$Me_2C_6H_3$, R = H
5c Ar = 3,5-$tBu_2C_6H_3$, R = H
5d Ar = 3,5-$tBu_2C_6H_3$, R = Me



8 Ar = 3,5-$tBu_2C_6H_3$



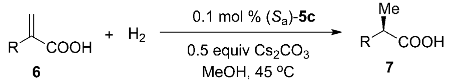
9 Ar = 3,5-$tBu_2C_6H_3$

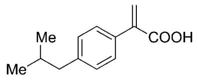
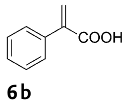
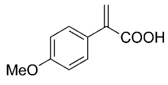
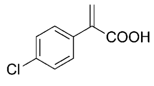
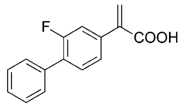
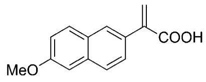
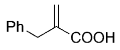
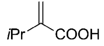
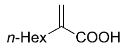
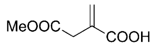
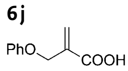
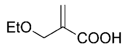
Under the optimal reaction conditions, the hydrogenations of various α-substituted acrylic acids were conducted with 0.1 mol% of catalyst (S_a)-**5c** at 6 atm or ambient hydrogen pressure (Table 2). All the tested acids, regardless of the substituents on the phenyl rings, were rapidly hydrogenated with extremely high enantioselectivity (96–99% ee; Table 2, entries 1–6). Several chiral non-steroid anti-inflammatory drugs, including ibuprofen (**7a**), flurbiprofen (**7e**), and naproxen (**7f**), were prepared with excellent yields and enantioselectivities (Table 2, entries 1, 5, and 6). α-Alkyl acrylic acids were also suitable substrates for this reaction, affording the corresponding saturated acids with high to excellent enantioselectivities (Table 2, entries 7–12). Note that this hydrogenation tolerated a broad range of functional groups. For example, acrylic acids bearing an ester (**6j**), an ether (**6c**, **6f**, **6k**, **6l**), or a halogen substituent (**6d**, **6e**) could be hydrogenated smoothly with 100% conversion and high enantioselectivities. These new catalysts show an advance over known chiral catalysts for the asymmetric hydrogenation of α-substituted acrylic acids owing to high activity, excellent enantioselectivity, and wide substrate scope.

In addition to α-substituted acrylic acids, other typical unsaturated carboxylic acids, such as α-methyl cinnamic acid (**10a**), α-phenyl cinnamic acid (**10b**), tiglic acid (**10c**), α-phenyl butanoic acid (**10d**), and α-benzyloxy cinnamic acid (**10e**) can also be hydrogenated by using catalyst (S_a)-**5c** (Scheme 2), providing the corresponding chiral carboxylic acids in high yield (93–98%) and excellent enantioselectivity (95–99.3% *ee*). These examples demonstrate that the present chiral spiro iridium catalysts derived from aminophosphine ligands **3** have broad applications in the synthesis of chiral carboxylic acids.

It has been reported that the terminal double bond of olefins can isomerize to the more stable internal double bond in iridium-catalyzed hydrogenation reactions.[13] To determine the mode of addition of hydrogen to the double bond of the substrate in the (S_a)-**5c**-catalyzed hydrogenation of α-alkyl-substituted acrylic acids, we conducted deuterium labeling studies (Scheme 3). ^1H NMR spectroscopy analysis of the products of the reactions of **6g** and **6j** with D_2 catalyzed by (S_a)-**5c** under standard reaction conditions showed that the

Table 2: Asymmetric hydrogenation of α-substituted acrylic acids.[a]

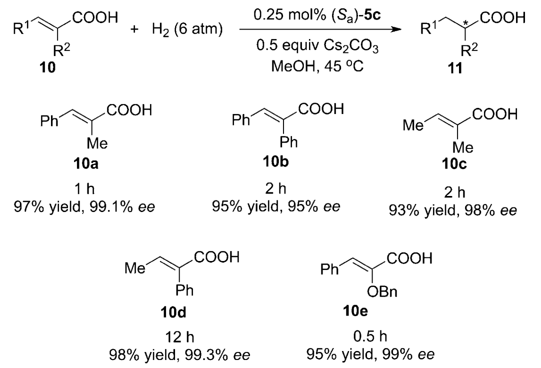


Entry	Substrate	Product	P_{H_2}	Time	Yield [%]	*ee* [%]
1	 **6a**	**7a**	6 atm	10 min	98	98
			ambient	4 h	98	99
2	 **6b**	**7b**	6 atm	15 min	97	98
			ambient	4 h	95	98
3	 **6c**	**7c**	6 atm	15 min	98	98
			ambient	4 h	96	99
4	 **6d**	**7d**	6 atm	30 min	98	97
			ambient	8 h	96	98
5	 **6e**	**7e**	6 atm	15 min	99	96
			ambient	4 h	98	97
6	 **6f**	**7f**	6 atm	15 min	99	97
			ambient	4 h	98	98
7	 **6g**	**7g**	6 atm	15 min	99	98
			ambient	4 h	98	98
8	 **6h**	**7h**	6 atm	25 min	97	96
			ambient[b]	4 h	95	96
9	 **6i**	**7i**	6 atm	30 min	97	94
			ambient[b]	4 h	96	98
10	 **6j**	**7j**	6 atm	15 min	99	95
			ambient	4 h	96	97
11	 **6k**	**7k**	6 atm	15 min	94	96
			ambient	4 h	98	96
12	 **6l**	**7l**	6 atm	15 min	98	95
			ambient	4 h	97	98

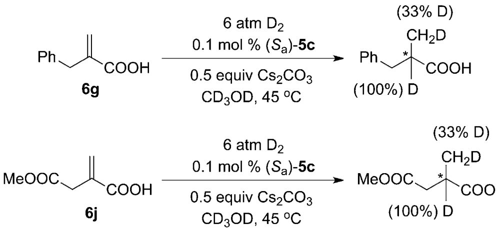
[a] Reaction conditions are the same as those of Table 1, entry 3 (for P_{H_2} = 6 atm) and entry 5 (for P_{H_2} = ambient pressure). See the Supporting Information for detailed analyses of hydrogenation products; [b] S/C = 500.

deuterium atoms were added only to the original double bond of the substrates, which indicated that no double bond isomerization occurred during the reaction.

In summary, we developed new chiral spiro aminophosphine ligands and proved their iridium complexes are highly efficient catalysts for the asymmetric hydrogenation of α-substituted acrylic acids. Different chiral α-substituted carboxylic acids have been synthesized under very mild reaction conditions at low catalyst loadings with high enantioselectivities. The chelating primary amine moiety of the chiral spiro aminophosphine ligands made these catalysts highly efficient for the hydrogenation of α,β-unsaturated carboxylic acids.



Scheme 2. Hydrogenations of α,β-unsaturated carboxylic acids. Reaction conditions: 0.5 mmol scale, [substrate] = 0.25 mol L^{-1} in MeOH, S/C = 400, 0.5 equiv Cs_2CO_3 as additive, P_{H_2} = 6 atm, 45 °C.



Scheme 3. Deuterium labeling studies.

Experimental Section

General hydrogenation procedure: A hydrogenation tube was charged with a stir bar, α-substituted acrylic acids **6** (0.5 mmol), catalyst (S_a)-**5c** (0.9 mg, 0.0005 mmol), Cs_2CO_3 (82 mg, 0.25 mmol) in an argon-filled glovebox. Methanol (2 mL) was injected into the hydrogenation tube by a syringe while stirring. The hydrogenation tube was then put into an autoclave. The autoclave was purged three times with hydrogen. The autoclave was then charged with hydrogen to 6 atm, and the reaction mixture was stirred at 45 °C for a specified time before releasing the hydrogen. The reaction mixture was acidified with 3N HCl and extracted with Et_2O. Evaporation of the solvent afforded the crude product. The conversion of the substrate was determined by ^{1}H NMR spectroscopy. The product was converted into the corresponding ester or amide and the *ee* value was determined by GC, HPLC, or supercritical fluid chromatography (SFC) with a chiral column. The hydrogenation reaction at ambient pressure was performed in a Schlenk tube connected with a hydrogen-filled balloon.

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