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# Iridium-Catalyzed Enantioselective Hydrogenation of α,β-Unsaturated Carboxylic Acids

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Transition-metal-catalyzed asymmetric hydrogenation of prochiral double bonds represents one of the most efficient and atom-economic methods for preparing chiral compounds and has drawn increasing attention in both academic research and industrial production.[1] In this research field, the search for new catalysts with high activity and enantioselectivity is the key issue and also an enduring challenge. Catalytic enantioselective hydrogenation of α,β-unsaturated carboxylic acids is a straightforward method for the synthesis of chiral carboxylic acids, which are important intermediates for the construction of biologically active compounds.[2] In the past decades, various Ru catalysts with chiral diphosphine ligands[3] and Rh catalysts with chiral phosphorus or nitrogen-containing ligands[4] have been developed for the hydrogenation of different α,β-unsaturated carboxylic acids in high enantioselectivities. However, the efficiency of the Ru and Rh catalysts is highly substrate-dependent. For most reported catalysts, a high catalyst loading, drastic reaction conditions, or long reaction time are needed for achieving satisfactory results. Thus, more efficient chiral catalysts are highly desirable in this useful reaction.

The chiral Ir catalysts, which are very efficient in the hydrogenations of unfunctionalized olefins, imines, and heteroaromatic compounds,[5] have long been neglected in the hydrogenation of unsaturated carboxylic acids. To the best of our knowledge, only one example of Ir-catalyzed asymmetric hydrogenation of unsaturated carboxylic acids has been reported so far. By using Pfaltz's Ir-PHOX catalyst, Scrivanti and co-workers[6] achieved the asymmetric hydrogenation of 2-phenethylacrylic acid. However, the high catalyst loading (4.0 mol %) and moderate enantioselectivity (<81% ee) showed that this Ir catalyst competes poorly against Ru catalysts. Recently, we developed a novel class of chiral spiro iridium/phosphine-oxazoline complexes (Ir-SIPHOX, Scheme 1, **1a**−**c**), which proved to be efficient catalysts for the asymmetric hydrogenation of *N*-arylketimines under ambient pressure.[7] The high stability, ease of handling, and ready tunability of the Ir-SIPHOX catalysts prompted us to extend the scope of their reactions. Herein, we report the application of Ir-SIPHOX catalysts in asymmetric hydrogenation of α,β-unsaturated carboxylic acids to produce α-substituted chiral carboxylic acids in exceptionally high enantioselectivity (up to 99.4% ee) and reactivity (TON up to 10 000).

The α-methylcinnamic acid (**2a**) was chosen as a model substrate to estimate the catalytic activity of catalysts **1**. The hydrogenation reaction was performed with 0.25 mol % of catalyst ($S/C = 400$) in MeOH under 6 atm of $H_2$ at room temperature for 24 h. With catalyst ($S_a$,*S*)-**1a**, the hydrogenation product α-methylhydrocinnamic acid (**3a**) was obtained in 82% ee, but with only 15% conversion (Table 1, entry 1). Notably, the reaction can not occur with catalyst ($R_a$,*S*)-**1a**, demonstrating that the chiralities on the spirobiindane backbone and oxazoline ring in this catalyst are mismatched (entry 2). The catalysts ($S_a$,*S*)-**1b** and ($S_a$,*S*)-**1c** gave almost the same results as those with catalyst ($S_a$,*S*)-**1a** (entries 3 and 4). We then synthesized the catalysts **1d**−**h** bearing bulky 3,5-di-*tert*-butylphenyl groups on the P atom and tested them in the hydrogenation of **2a**. Gratifyingly, the catalyst ($S_a$,*S*)-**1d** remarkably increased both conversion (58%) and enantioselectivity (99% ee) of the reaction (entry 5).[8]

***Scheme 1***

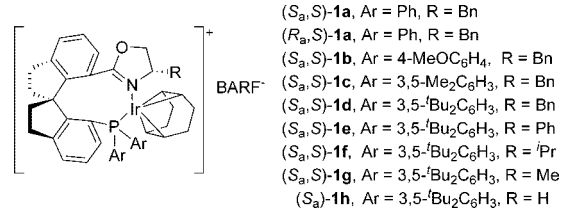
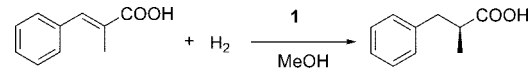



***Table 1.*** Asymmetric Hydrogenation of α-Methylcinnamic Acid[a]




**2a** **3a**

| entry | catalyst | additive | time (h) | conv (%)[b] | yield (%)[c] | ee (%)[d] |
|---|---|---|---|---|---|---|
| 1 | ($S_a$,*S*)-**1a** | none | 24 | 15 | − | 82 |
| 2 | ($R_a$,*S*)-**1a** | none | 24 | NR[e] | − | − |
| 3 | ($S_a$,*S*)-**1b** | none | 24 | 16 | − | 85 |
| 4 | ($S_a$,*S*)-**1c** | none | 24 | 29 | − | 76 |
| 5 | ($S_a$,*S*)-**1d** | none | 24 | 58 | − | >99 |
| 6 | ($S_a$,*S*)-**1d** | 0.5 equiv of $NEt_3$ | 0.5 | 100 | 99 | >99 |
| 7 | ($S_a$,*S*)-**1e** | 0.5 equiv of $NEt_3$ | 1 | 100 | 99 | 96 |
| 8 | ($S_a$,*S*)-**1f** | 0.5 equiv of $NEt_3$ | 2 | 100 | 98 | >99 |
| 9 | ($S_a$,*S*)-**1g** | 0.5 equiv of $NEt_3$ | 3 | 100 | 99 | >99 |
| 10 | ($S_a$)-**1h** | 0.5 equiv of $NEt_3$ | 8 | 100 | 97 | >99 |
| 11[f] | ($S_a$,*S*)-**1d** | 0.5 equiv of $NEt_3$ | 4 | 100 | 98 | >99 |

[a] Reaction conditions: 0.5 mmol scale, [substrate] = 0.25 mol $L^{-1}$ in MeOH, $S/C = 400$, $P_{H_2} = 6$ atm, room temperature. [b] Determined by $^1$H NMR. [c] Isolated yield. [d] Determined by chiral HPLC analysis of the corresponding anilide. [e] No reaction. [f] $P_{H_2} = 1$ atm.

To improve the reaction rate and conversion, we then examined the effect of adding $NEt_3$, which was often used to increase both reaction rate and enantioselectivity in asymmetric hydrogenation reactions.[9] Satisfyingly, the addition of 0.5 equiv $NEt_3$ significantly improved the reaction rate, giving quantitative conversion within 30 min without losing enantioselectivity (Table 1, entry 6).[10] Under the conditions with $NEt_3$, the catalysts ($S_a$,*S*)-**1e**−**h** gave results similar to those of ($S_a$,*S*)-**1d**, showing that the substituent on the oxazoline ring of the catalyst had a negligible influence on the conversion and enantioselectivity of the reaction, albeit a slightly longer reaction time was needed in the reaction with catalyst ($S_a$,*S*)-**1h** (entry 10). In the presence of $NEt_3$, the catalyst ($S_a$,*S*)-**1d** was even able to hydrogenate α-methylcinnamic acid under ambient hydrogen pressure (entry 11).

A variety of α-methylcinnamic acid derivatives **2** could be hydrogenated by catalyst ($S_a$,*S*)-**1d** with excellent enantioselectivities (>96% ee) regardless of the electronic properties of the substituents on the phenyl ring of the substrates (Table 2). The hydrogenations were very fast and gave full conversions within 1 h with few exceptions. This result represents the highest enantioselectivity and



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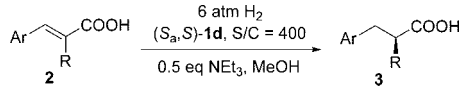
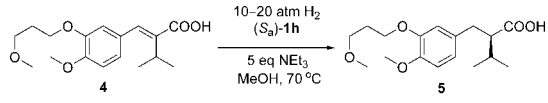
***Table 2.*** Asymmetric Hydrogenation of Cinnamic Acid Derivatives[a]




| entry | Ar | R | time | yield (%) | ee (%) | TOF ($h^{-1}$) |
|---|---|---|---|---|---|---|
| 1 | Ph (**2a**) | Me | 30 min | 99 | 99.2 (*S*) | 800 |
| 2 | 2-$MeC_6H_4$ (**2b**) | Me | 40 min | 97 | 99 | 600 |
| 3 | 3-$MeC_6H_4$ (**2c**) | Me | 40 min | 98 | 99 | 600 |
| 4 | 4-$MeC_6H_4$ (**2d**) | Me | 40 min | 98 | 99 | 600 |
| 5 | 2-$OMeC_6H_4$ (**2e**) | Me | 35 min | 98 | 99 | 686 |
| 6 | 3-$OMeC_6H_4$ (**2f**) | Me | 35 min | 99 | 98 | 686 |
| 7 | 4-$OMeC_6H_4$ (**2g**) | Me | 35 min | 97 | 99 | 686 |
| 8 | 2-$ClC_6H_4$ (**2h**) | Me | 10 h | 97 | 96 | 40 |
| 9 | 3-$ClC_6H_4$ (**2i**) | Me | 30 min | 98 | 99 | 800 |
| 10 | 4-$ClC_6H_4$ (**2j**) | Me | 30 min | 97 | 98 (*S*) | 800 |
| 11 | 3-$BrC_6H_4$ (**2k**) | Me | 30 min | 97 | 99 | 800 |
| 12 | 4-$BrC_6H_4$ (**2l**) | Me | 30 min | 97 | 98 (*S*) | 800 |
| 13 | 4-$CF_3C_6H_4$ (**2m**) | Me | 1 h | 98 | 97 | 400 |
| 14 | 2-naphthyl (**2n**) | Me | 8 h | 96 | 99 | 50 |
| 15 | furan-2-yl (**2o**) | Me | 18 h | 98 | 98 | 22 |
| 16 | Ph (**2p**) | $^i$Pr | 3 h | 97 | 99 | 133 |
| 17[b] | Ph (**2q**) | Ph | 5 h | 95 | 94 | 20 |

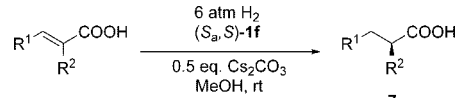
[a] Reaction conditions and analysis are the same as those of Table 1, entry 6. Full conversions were obtained for all cases. [b] *S/C* = 100.

***Scheme 2***




S/C = 6,000, 7 h, 100% conv., 96% yield, 98% ee.
S/C = 10,000, 18 h, 97% conv., 95% yield, 95% ee.

***Table 3.*** Asymmetric Hydrogenation of Tiglic Acid Derivatives[a]




| entry | $R^1$ | $R^2$ | *S/C* | time (h) | yield (%) | ee (%) |
|---|---|---|---|---|---|---|
| 1 | Me | Me (**6a**) | 400 | 0.5 | 92 | 99.1 (*S*) |
| 2 | Et | Me (**6b**) | 200 | 18 | 93 | 98 (*S*) |
| 3 | $^n$Pr | Me (**6c**) | 200 | 18 | 89 | 99 (*S*) |
| 4 | $^i$Bu | Me (**6d**) | 100 | 18 | 97 | 90 |
| 5 | $^n$Pr | Et (**6e**) | 100 | 18 | 89 | 99.4 (*S*) |
| 6 | Me | $^n$Pr (**6f**) | 200 | 18 | 92 | 98 (*R*) |

[a] Reaction conditions are the same as those of Table 1, entry 6, unless otherwise indicated. Full conversions were obtained for all cases.

efficiency in the asymmetric hydrogenation of α-methylcinnamic acid derivatives.[3,4]

To demonstrate the potential of this highly efficient catalytic asymmetric reaction, we carried out the hydrogenation of α-isopropylcinnamic acid derivative **4** to prepare the acid (*R*)-**5**, which is the key intermediate for the synthesis of the new blood-pressure-lowering drug Aliskiren.[11] The compound **4** was successfully hydrogenated by catalyst ($S_a$)-**1h**, which had no substituent on the oxazoline ring and gave the best performance in this reaction. The carboxylic acid (*R*)-**5** was attained in high yield with 98% and 95% ee at catalyst loadings of 0.017 mol % (*S/C* = 6000) and 0.01 mol % (*S/C* = 10 000), respectively (Scheme 2). This primary result was superior to those reported previously.[4e,11c,d]

Further studies revealed that the iridium complexes **1** were also suitable catalysts for the hydrogenation of tiglic acid and its derivatives **6**. In this reaction, the ($S_a$,*S*)-**1f** with an isopropyl group on the oxazoline ring was the most efficent catalyst and $Cs_2CO_3$ was the most suitable additive for achieving the best result.[12] Under the optimal conditions, different tiglic acid derivatives were hydrogenated to produce the corresponding saturated acids in excellent enantioselectivities (Table 3). A higher catalyst loading was needed when a bulky group was introduced into either the α-position or β-position of tiglic acid.

In summary, the first highly enantioselective Ir-catalyzed hydrogenation of α,β-unsaturated carboxylic acids was developed by using SIPHOX ligands. The extremely high activity, enantioselectivity, broad substrate scope, and mild reaction conditions demonstrated that the Ir-SIPHOX were excellent catalysts for the synthesis of enantiopure carboxylic acids.

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**Supporting Information Available:** Details of experimental procedures, the synthesis and analysis data of catalysts, and the analysis data of ee values of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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