Iridium-Catalyzed Hydrogenation

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Enantioselective Iridium-Catalyzed Hydrogenation of β,γ-Unsaturated Carboxylic Acids: An Efficient Approach to Chiral 4-Alkyl-4-aryl Butanoic Acids**

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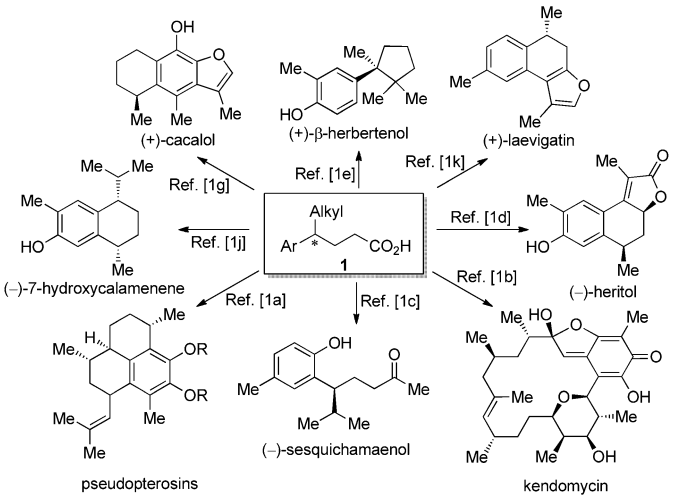
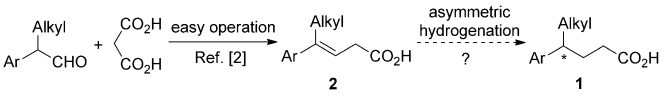
Chiral acids are important intermediates for the construction of biologically active compounds. In particular, optically active 4-alkyl-4-aryl butanoic acids **1** and their derivatives have been widely used in the synthesis of various natural products that have stereogenic centers in the benzylic position (Scheme 1).[1] Although many catalytic enantioselective approaches have been developed for the synthesis of diverse chiral compounds, there is, to the best of our knowledge, no direct method for asymmetric preparation of 4-alkyl-4-aryl butanoic acids **1**.

Optically active 4-alkyl-4-aryl butanoic acids **1** are generally prepared from chiral materials by means of multistep transformations.[1b–e,k] The transition-metal-catalyzed asymmetric hydrovinylation of alkenes,[1a] hydrogenation of α,β-unsaturated carboxylic acids,[1f] isomerization of allylic alcohols,[1j] and some enzymatic catalytic methods[1h,i] have all been used to construct a chiral benzyl center, but a subsequent multistep transformation is required to obtain the target 4-alkyl-4-aryl butanoic acids **1**. Thus, a reliable and efficient catalytic asymmetric method for the preparation of these chiral acids is highly desirable. The transition-metal-catalyzed asymmetric hydrogenation of 4-alkyl-4-aryl-3-butenoic acids **2**, which can be prepared from easily obtained materials,[2] potentially provides an atom-efficient and reliable approach to chiral 4-alkyl-4-aryl butanoic acids **1** (Scheme 2). Various chiral ruthenium, rhodium, and iridium catalysts have been developed for the hydrogenation of a wide range of α,β-unsaturated carboxylic acids.[3] However, only a few examples of catalytic asymmetric hydrogenation of β,γ-unsaturated acids have been reported.[4] The enantioselective hydrogenation of 4-alkyl-4-aryl-3-butenoic acids **2** has not been achieved.[5] Herein we describe a highly enantioselective iridium-catalyzed hydrogenation of **2**. By using a newly developed chiral spiro phosphine–oxazoline ligand bearing an α-naphthylmethyl group on the oxazoline ring, we have prepared various chiral 4-alkyl-4-aryl butanoic acids through the iridium-catalyzed asymmetric hydrogenation reaction with high enantioselectivities (up to 97% *ee*). The concise total syntheses of natural products (*R*)-aristelegone-A, (*R*)-curcumene, and (*R*)-xanthorrhizol were also accomplished with this asymmetric hydrogenation reaction as the key step.

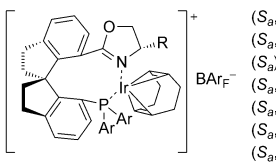


Scheme 1. Applications of optically active 4-alkyl-4-aryl butanoic acids.



Scheme 2. Convenient synthesis of optically active 4-alkyl-4-aryl butanoic acids.

At the outset of this study, (*E*)-4-phenylpent-3-enoic acid was hydrogenated in the presence of 1 mol% chiral spiro iridium complexes **3** (Scheme 3) under 6 atm H_2 pressure at 65 °C. When catalyst (S_a,*S*)-**3a** was used, complete conversion with 60% *ee* was obtained (Table 1, entry 1). A diastereoisomer of (S_a,*S*)-**3a**, complex (R_a,*S*)-**3a**, gave lower conversion



(S_a,*S*)-**3a**, Ar = 3,5-*t*Bu$_2$C$_6$H$_3$, R = Bn
(S_a,*S*)-**3b**, Ar = 3,5-*t*Bu$_2$C$_6$H$_3$, R = *i*Pr
(S_a)-**3c**, Ar = 3,5-*t*Bu$_2$C$_6$H$_3$, R = H
(S_a,*S*)-**3d**, Ar = 3,5-Me$_2$C$_6$H$_3$, R = Bn
(S_a, *S*)-**3e**, Ar = Ph, R = Bn
(S_a,*S*)-**3f**, Ar = 3,5-Me$_2$C$_6$H$_3$, R = α-naphthylmethyl
(S_a,*S*)-**3g**, Ar = 3,5-Me$_2$C$_6$H$_3$, R = β-naphthylmethyl

Scheme 3. Chiral spiro phosphine–oxazoline/iridium complexes. BAr_F^- = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

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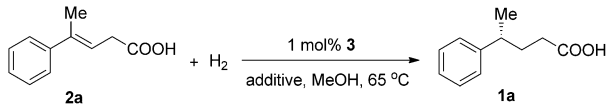
Table 1: Optimization of the reaction conditions.[a]



2a **1a**

Entry	Catalyst	Additive	p_{H_2} [atm]	Conv. [%][b]	*ee* [%][c]
1	(S_a,*S*)-**3a**	NEt_3	6	100	60
2	(R_a,*S*)-**3a**	NEt_3	6	45	rac.
3	(S_a,*S*)-**3b**	NEt_3	6	80	20
4	(S_a)-**3c**	NEt_3	6	85	15
5	(S_a,*S*)-**3d**	NEt_3	6	100	92
6	(S_a,*S*)-**3e**	NEt_3	6	94	85
7	(S_a,*S*)-**3f**	NEt_3	6	100	95
8	(S_a,*S*)-**3g**	NEt_3	6	100	94
9	(S_a,*S*)-**3f**	NEt_3	30	100	90
10	(S_a,*S*)-**3f**	NEt_3	3	100	96
11[d]	(S_a,*S*)-**3f**	NEt_3	3	100	95
12[d,e]	(S_a,*S*)-**3f**	NEt_3	3	98	95
13[d]	(S_a,*S*)-**3f**	iPr_2NEt	3	100	95
14[d]	(S_a,*S*)-**3f**	Et_2NH	3	100	95
15[d]	(S_a,*S*)-**3f**	Cs_2CO_3	3	21	–

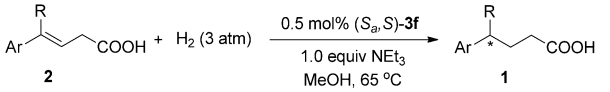
[a] Reaction conditions: 0.5 mmol scale, [substrate] = 0.25 mol L^{-1}, 1.0 equiv additive, 12 h. [b] Determined by NMR spectroscopy. [c] Determined by chiral-phase HPLC or supercritical fluid chromatography (SFC) analysis of the corresponding anilide. [d] Using 0.5 mol% catalyst. [e] Using 0.5 equiv NEt_3.

and racemic product (entry 2). This result demonstrated that the chiralities in (R_a,*S*)-**3a** were unmatched in their ability to induce enantioselectivity in the hydrogenation reaction. The effect of the oxazoline ring substituent of the ligand on the enantioselectivity of the reaction was studied. Changing the substituent from benzyl to isopropyl [(S_a,*S*)-**3b**] or H [(S_a)-**3c**] decreased both conversion and enantioselectivity (entries 3 and 4). The substituents on the phosphorous of the ligand strongly affected the enantioselectivity (entries 1, 5, and 6): catalyst (S_a,*S*)-**3d**, with 3,5-dimethylphenyl substituents on the phosphorous, exhibited the best chiral induction (92% *ee*, entry 5). To further improve the enantioselectivity, we synthesized two new ligands with an α-naphthylmethyl or a β-naphthylmethyl group on the oxazoline ring, and the corresponding catalysts (S_a,*S*)-**3f** and (S_a,*S*)-**3g** were prepared by means of a previously reported method.[6] Both (S_a,*S*)-**3f** and (S_a,*S*)-**3g** showed higher enantioselectivities in the hydrogenation reaction than did (S_a,*S*)-**3d** (entries 7 and 8).

The reaction conditions were optimized with catalyst (S_a,*S*)-**3f**. Experiments on hydrogen pressure showed that the reaction gave higher enantioselectivity under lower hydrogen pressure (Table 1, entry 10 vs. entries 7 and 9), which is similar to our previous observations in the hydrogenation of α,β-unsaturated carboxylic acids.[3j] The catalyst loading can be reduced to 0.5 mol% without diminishing the reactivity and enantioselectivity (entry 11). Reducing the basic additive NEt_3 to 0.5 equiv slightly decreased the conversion under standard reaction conditions (entry 12). Aside from NEt_3, other organic bases, such as iPr_2NEt and $NHEt_2$, were also suitable additives for the hydrogenation reaction, affording identical results to NEt_3 (entries 13 and 14). On the other hand, the use of the inorganic base Cs_2CO_3 drastically decreased the reactivity of the catalyst; only 21% conversion was obtained under the standard reaction conditions (entry 15).

With the optimal reaction conditions determined, various 4-alkyl-4-aryl-3-butenoic acids **2** were hydrogenated. The substituent on the phenyl ring of the substrate had a negligible influence on the enantioselectivity, and all of the tested substrates afforded essentially the same enantioselectivity (92–96% ee; Table 2, entries 2–10). The reactivity of (*E*)-4-(naphthalen-2-yl)pent-3-enoic acid (**2k**) was similar to that of **2a**, and an enantioselectivity of 97% *ee* was obtained

Table 2: Asymmetric hydrogenation of 4-alkyl-4-aryl-3-butenoic acids.[a]



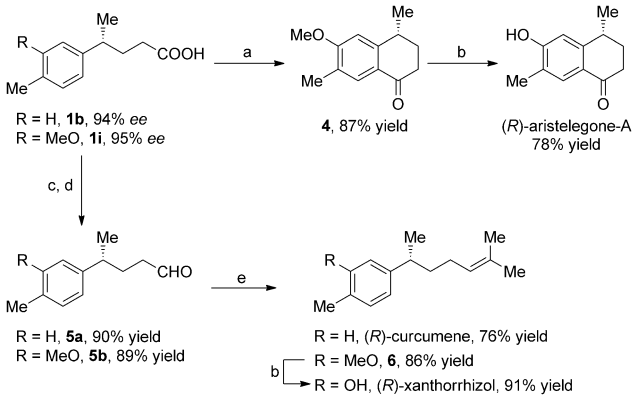
2 **1**

Entry	Ar: R (**2**)	Product	Yield [%]	*ee* [%]
1	C_6H_5: Me (**2a**)	**1a**	97	95
2[b]	4-MeC_6H_4: Me (**2b**)	**1b**	97 (98)	94 (93)
3	4-$MeOC_6H_4$: Me (**2c**)	**1c**	96	94
4	4-FC_6H_4: Me (**2d**)	**1d**	96	96
5	3-BrC_6H_4: Me (**2e**)	**1e**	98	95
6	3-MeC_6H_4: Me (**2f**)	**1f**	96	92
7	3-$MeOC_6H_4$: Me (**2g**)	**1g**	97	95
8	3,4-$Me_2C_6H_3$: Me (**2h**)	**1h**	98	95
9	3-MeO-4-MeC_6H_3: Me (**2i**)	**1i**	97	95
10[c]	3,4-$(OCH_2O)C_6H_3$: Me (**2j**)	**1j**	98	95
11	2-naphthyl: Me (**2k**)	**1k**	98	97
12[c]	2-thiophenyl: Me (**2l**)	**1l**	96	90
13	4-$MeOC_6H_4$: Et (**2m**)	**1m**	96	92
14[c]	4-$MeOC_6H_4$: *i*Pr (**2n**)	**1n**	97	88

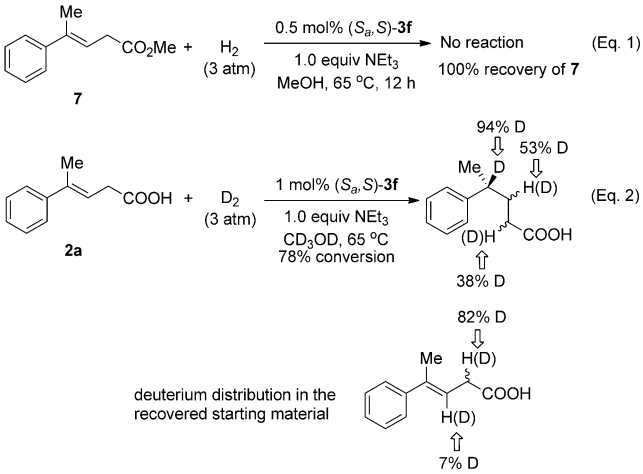
[a] The reaction conditions and analysis were the same as those in Table 1, entry 11. Full conversions were obtained in all cases. [b] The data in parentheses were obtained at 1.52 g scale. [c] Using 1 mol% catalyst.

(entry 11). The Ar group of **2** can also be a heterocycle. For example, the hydrogenation of (*E*)-4-(thiophen-2-yl)pent-3-enoic acid (**2l**) ran smoothly and afforded the desired product with 90% *ee* in the presence of 1 mol% catalyst (entry 12). Changing the R group of the acid **2** from methyl to ethyl (**2m**) slightly reduced the enantioselectivity (entry 13). However, when R was a bulky isopropyl (**2n**), 1 mol% of the catalyst was required for complete conversion, and the *ee* decreased to 88% (entry 14). This asymmetric hydrogenation reaction could easily be carried out on a gram scale, which is a benefit for practical applications. For instance, (*E*)-4-*p*-tolylpent-3-enoic acid (**2b**) was hydrogenated smoothly on a 1.52 g scale under the standard hydrogenation conditions to produce the desired product without compromise of either yield or enantioselectivity (entry 2).

To further demonstrate the utility of the hydrogenation reaction, three natural sesquiterpenes, (*R*)-aristelegone-A, (*R*)-curcumene, and (*R*)-xanthorrhizol were conveniently synthesized from the products of the asymmetric hydrogenation (Scheme 4). With the hydrogenation product **1i** as starting material, (*R*)-aristelegone-A,[7] was obtained through a Brønsted acid catalyzed Friedel–Crafts acylation and a subsequent demethylation with $Et_2NCH_2CH_2SNa$ in 68% overall yield (steps a and b). Note that the present procedure



Scheme 4. Synthetic applications of hydrogenation products. Reaction conditions: a) trifluoroacetic acid, trifluoroacetic anhydride, 0 °C; b) $Et_2NCH_2CH_2SNa$, DMF, reflux; c) CH_3I, K_2CO_3, DMF, RT; d) diisobutylaluminum hydride, CH_2Cl_2, −78 °C; e) $(CH_3)_2CH{=}PPh_3$, THF, −15 °C.



Scheme 5. Substrate and mechanistic studies.

is a novel and general route for the construction of tetralones with a chiral benzyl center, a core structure for diverse natural products.[1a,d,f,g,k] The (*R*)-curcumene[8] and (*R*)-xanthorrizol,[9,10] were synthesized from the hydrogenation products **1b** and **1i** respectively. The chiral acids were first transformed into the corresponding aldehydes **5** by means of esterification and a subsequent reduction (steps c and d). A Wittig reaction was then performed to introduce the alkene moiety, giving (*R*)-curcumene in 76% yield (step e). Finally, (*R*)-xanthorrizol was obtained by cleavage of the methyl group of **6**. Thus, the concise total syntheses of (*R*)-curcumene and (*R*)-xanthorrizol were accomplished in three steps (from **1b**, 68% overall yield) and four steps (from **1i**, 70% overall yield), respectively.

To improve our understanding of the mechanism of the hydrogenation reaction, we performed additional experiments. As iridium complexes of phosphine–oxazoline ligands are also well-known catalysts for the hydrogenation of unfunctionalized olefins, work pioneered by the Pfaltz group,[11] it would be interesting to know whether the carboxy group in β,γ-unsaturated acids **2** is necessary for the hydrogenation reaction. The fact that the methyl ester of acid **2a**, (*E*)-methyl 4-phenylpent-3-enoate (**7**), is inert in the hydrogenation under the standard reaction conditions indicates that the functional carboxy group of the substrates **2** is crucial for the reaction; it may act as an anchor to coordinate with iridium and make the hydrogenation possible [Scheme 5, Eq. (1)]. A deuterium-labeling study was also performed [Scheme 5, Eq. (2)]. The essentially identical deuterium distribution (1.1:1) at the β- and γ-positions of the hydrogenation product demonstrated that olefin migration did not take place during the hydrogenation. A significant α-deuterium substitution was observed in both product and recovered starting material, which can be attributed to H/D exchange under basic conditions.

In conclusion, a highly enantioselective iridium-catalyzed hydrogenation of 4-alkyl-4-aryl-3-butenoic acids was accomplished. The reaction provides a direct enantioselective method for the preparation of chiral 4-alkyl-4-aryl butanoic acids. The concise syntheses of (*R*)-aristelegone-A, (*R*)-curcumene, and (*R*)-xanthorrhizol, starting from chiral 4-alkyl-4-aryl butanoic acids, show a high potential for the wide application of this new catalytic asymmetric reaction in organic synthesis.

Experimental Section

General hydrogenation procedure: Substrate **2** (0.5 mmol), catalyst (*S*a,*S*)-**3f** (4.6 mg, 0.0025 mmol), NEt_3 (51 mg, 0.5 mmol), and MeOH (2 mL) were added to a hydrogenation tube containing a stir bar. The hydrogenation tube was then put into an autoclave. The autoclave was sealed and the atmosphere was purged five times with hydrogen. The autoclave was then charged with hydrogen to 3 atm, and the reaction mixture was subsequently stirred at 65 °C for 12 h. After venting the autoclave, the reaction solution was treated with 5% NaOH (10 mL) and extracted with Et_2O (10 mL). The aqueous layer was then treated with 3 M HCl (pH 1) before being again extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with a saturated solution of NaCl, dried over $MgSO_4$, and evaporated in vacuo to produce the hydrogenation product. The product (0.5 mmol) was reacted with aniline (50 μL, 0.55 mmol) in the presence of *N*,*N*-dimethylaminopyridine (DMAP, 4 mg, 0.033 mmol) and dicyclohexylcarbodiimide (DCC, 110 mg, 0.53 mmol) in 1 mL THF for 2 h. The reaction mixture was filtered through celite and the filtrate was diluted with Et_2O (10 mL), washed with 3 M HCl (10 mL) and saturated $NaHCO_3$ (10 mL), and then dried over $MgSO_4$. After flash chromatography on silica gel with petroleum ether/ethyl acetate (4:1), the desired amide was obtained and analyzed by supercritical fluid chromatography (SFC) or HPLC to determined *ee* value.

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