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Iridium-Catalyzed Enantioselective Hydrogenation of α,β-Unsaturated Carboxylic Acids with Tetrasubstituted Olefins

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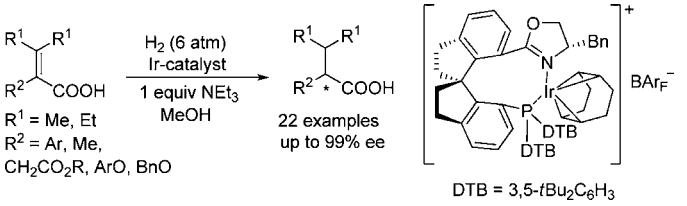
ABSTRACT



A highly efficient asymmetric hydrogenation of α,β-unsaturated carboxylic acids with tetrasubstituted olefin catalyzed by chiral spiro iridium complexes has been developed for the preparation of chiral α-substituted carboxylic acids in excellent enantioselectivities (up to 99% ee).

Transition-metal-catalyzed asymmetric hydrogenation of prochiral unsaturated carboxylic acids represents one of the most efficient and atom-economic methods for preparation of chiral carboxylic acids. In the past decades, remarkable progress has been achieved in the asymmetric hydrogenation of unsaturated carboxylic acids with di-[1] or trisubstituted[2] olefins by using chiral rhodium, ruthenium, and iridium catalysts. The asymmetric hydrogenation of α,β-unsaturated carboxylic acids with highly hindered tetrasubstituted olefins also draws intense attention, because its products, chiral carboxylic acids **2** and their derivatives are core structures of many pharmaceuticals,[3] natural products,[4] and organocatalysts[5] (Figure 1). However, in contrast to the successful hydrogenation of the unsaturated carboxylic acids with di- and trisubstituted olefins,

(1) (a) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174. (b) Pai, C.-C.; Lin, C.-W.; Lin, C.-C.; Chen, C.-C.; Chan, A. S. C.; Wong, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 11513. (c) Sun, X.; Zhou, L.; Wang, C.-J.; Zhang, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 2623. (d) Zhu, S.-F.; Yu, Y.-B.; Li, S.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8872. (e) Song, S.; Zhu, S.-F.; Yu, Y.-B.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 1556.

(2) (a) Maligres, P. E.; Krska, S. W.; Humphrey, G. R. *Org. Lett.* **2004**, *6*, 3147. (b) Hoen, R.; Boogers, J. A. F.; Bernsmann, H.; Minnaard, A. J.; Meetsma, A.; Tiemersma-Wegman, T. D.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4209. (c) Tellers, D. M.; McWilliams, J. C.; Humphrey, G.; Journet, M.; DiMichele, L.; Hinksmon, J.; McKeown, A. E.; Rosner, T.; Sun, Y.; Tillyer, R. D. *J. Am. Chem. Soc.* **2006**, *128*, 17063. (d) Chen, W.; McCormack, P. J.; Mohammed, K.; Mbafor, W.; Roberts, S. M.; Whittall, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4141. (e) Li, S.; Zhu, S.-F.; Zhang, C.-M.; Song, S.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2008**, *130*, 8584. (f) Li, S.; Zhu, S.-F.; Xie, J.-H.; Song, S.; Zhang, C.-M.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2010**, *132*, 1172. (g) Song, S.; Zhu, S.-F.; Yang, S.; Li, S.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 2708. (h) Li, Y.; Dong, K.; Wang, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 6748.

(3) (a) Hatzemann, A.; Fruchtmann, R.; Mohrs, K. H.; Raddatz, S.; MüllerPeddinghuas, R. *Biochem. Pharmacol.* **1993**, *45*, 101. (b) Crameri, Y.; Foricher, J.; Hengartner, U.; Jenny, Ch.; Kienzle, F.; Ramuz, H.; Scalone, M.; Schlageter, M.; Schmid, R.; Wang, S. *Chimia* **1997**, *51*, 303. (c) Yamamoto, H. *CHEMTECH* **1985**, 482.

(4) (a) Chen, H.; Bai, J.; Fang, Z.-F.; Yu, S.-S.; Ma, S.-G.; Xu, S.; Li, Y.; Qu, J.; Ren, J.-H.; Li, L.; Si, Y.-K.; Chen, X.-G. *J. Nat. Prod.* **2011**, *74*, 2438. (b) Benincori, T.; Bruno, S.; Celentano, G.; Pilati, T.; Ponti, A.; Rizzo, S.; Sada, M.; Sannicolò, F. *Helv. Chim. Acta* **2005**, *88*, 1776.

(5) (a) Fujita, M.; Yoshida, Y.; Miyata, K.; Wakisaka, A.; Sugimura, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7068. (b) Fujita, M.; Wakita, M.; Sugimura, T. *Chem. Commun.* **2011**, *47*, 3983.

(6) (a) Khumsubdee, S.; Burgess, K. *ACS Catal.* **2013**, *3*, 237. (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (c) Woodmansee, D. H.; Pfaltz, A. *Chem. Commun.* **2011**, 7912. (d) Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem.—Eur. J.* **2010**, *16*, 14232. (e) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402–1411. (f) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272. (g) Uemura, T.; Zhang, X.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1996**, *61*, 5510. For the hydrogenations of other tetrasubstituted olefins, see: (h) Schrems, M. G.; Neumann, E.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8274. (i) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570. (j) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. (k) Dobbs, D. A.; Vanhessche, K. P. M.; Brazi, E.; Rautenstrauch, V.; Lenoir, J.-Y.; Genêt, J.-P.; Wiles, J.; Bergens, S. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1992.

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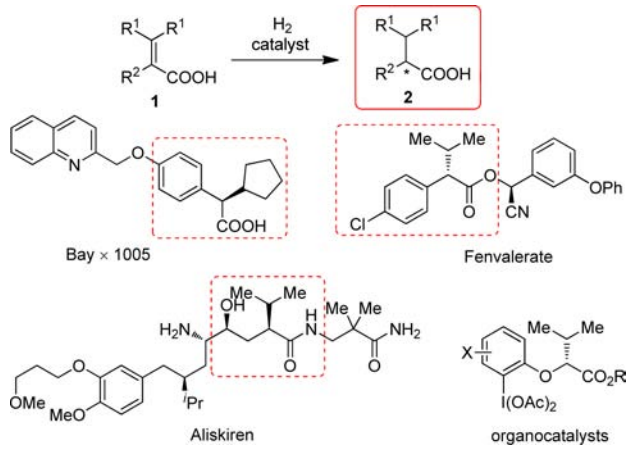


Figure 1. The asymmetric hydrogenation reactions of unsaturated carboxylic acids with tetrasubstituted olefins and the potential applications.

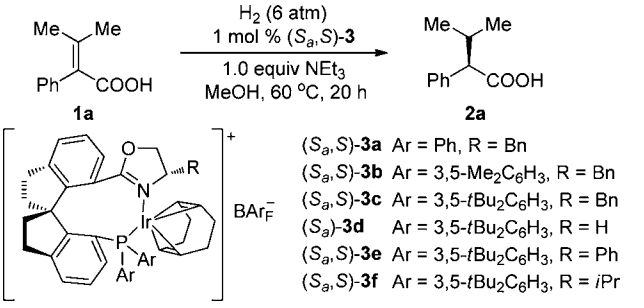
the asymmetric hydrogenation of unsaturated carboxylic acids with tetrasubstituted olefins has achieved limited success.[6] A few rhodium and ruthenium-catalyzed hydrogenations of trisubstituted acrylic acids afforded over 90% ee.[7] Herein, we reported an iridium-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acids bearing a tetrasubstituted olefin with high enantioselectivities (up to 99% ee) under mild reaction conditions.

The hydrogenation of α-phenyl-β,β-dimethyl acrylic acid **1a** was initially studied with chiral spiro iridium catalysts **3** (Table 1).[8] The catalyst (S_a,*S*)-**3a** bearing phenyl groups on the phosphorus atom and a benzyl group on the oxazoline ring afforded carboxylic acid **2a** in 45% conversion with 66% ee (entry 1). The substituents on the *P*-phenyl rings of the ligand strongly affected the enantioselectivity of the reaction (entries 1−3). Catalyst (S_a,*S*)-**3c** bearing bulky 3,5-di-*tert*-butylphenyl groups on the phosphorus atom increased both reactivity (100% conversion) and enantioselectivity (94% ee) (entry 3). The catalysts bearing other substituents on the oxazoline ring showed lower enantioselectivity or reactivity (entries 4−6). The basic additive Cs_2CO_3 can also promote the hydrogenation reaction, however affording slightly lower enantioselectivity comparing to NEt_3 (entry 7 vs entry 3).

Under the optimal reaction conditions, a variety of α-aryl-β,β-dimethyl acrylic acids **1a**−**1h** were hydrogenated (Table 2). The substituents on the phenyl ring of the substrates have a weak influence on the reaction, and all the tested substrates afforded high enantioselectivities (90−97% ee; entries 1−8). The hydrogenation products **2b** and **2c** are the key intermediates of chiral drugs Mibefradil[7b] and Fenvalerate,[3c] respectively. In addition to α-aryl-β,β-dimethyl acrylic acids, trimethyl acrylic acid **1i** was also a suitable substrate for the hydrogenation (93% yield, 97% ee, entry 9).

The iridium-catalyzed asymmetric hydrogenation reaction has good toleration with functional groups.

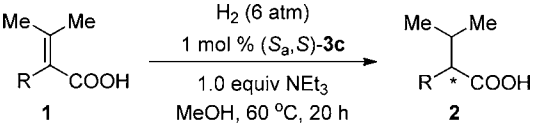
Table 1. Enantioselective Iridium-Catalyzed Hydrogenation of α-Phenyl-β,β-dimethyl Acrylic Acid: Optimization of the Reaction Conditions[a]



entry	catalyst	conv (%)[b]	ee (%)[c]
1	(S_a,*S*)-**3a**	45	66
2	(S_a,*S*)-**3b**	47	73
3	(S_a,*S*)-**3c**	100	94
4	(S_a)-**3d**	100	74
5	(S_a,*S*)-**3e**	65	68
6	(S_a,*S*)-**3f**	100	91
7[d]	(S_a,*S*)-**3c**	100	92

[a] Reaction conditions: 0.25 mmol **1a**, [substrate] = 0.125 mol/L, substrate/catalyst = 100:1, H_2 (6 atm), 1.0 equiv NEt_3 as additive. The absolute configuration of the product is *R*, which was determined by comparing the optical rotation with literature data.[7a] BAr_F^- = tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate. [b] Determined by ^1H NMR. [c] Determined by chiral HPLC analysis of the corresponding anilide. [d] Using 1.0 equiv of Cs_2CO_3 as additive.

Table 2. Enantioselective Iridium-Catalyzed Hydrogenation of α-Aryl and α-Methyl-β,β-dimethyl Acrylic Acids[a]



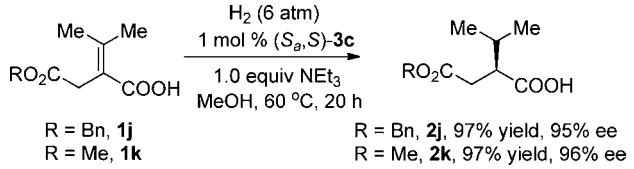
entry	R	product	yield (%)	ee (%)
1	Ph (**1a**)	**2a**	98	94 (*R*)
2	4-FC_6H_4 (**1b**)	**2b**	97	94 (*R*)
3[b]	4-ClC_6H_4 (**1c**)	**2c**	94	93 (*R*)
4	4-$MeOC_6H_4$ (**1d**)	**2d**	98	93 (*R*)
5[b]	3-MeC_6H_4 (**1e**)	**2e**	98	92 (−)
6[b]	3-BrC_6H_4 (**1f**)	**2f**	97	90 (−)
7[b]	3-$CF_3C_6H_4$ (**1g**)	**2g**	96	95 (−)
8[b]	2-naphthyl (**1h**)	**2h**	99	97 (*R*)
9	Me (**1i**)	**2i**	93	97 (*S*)

[a] The reaction conditions and analysis are identical to those in Table 1, entry 3. Full conversions were obtained in all cases. [b] Using 2 mol % (S_a,*S*)-**3c**.

(7) (a) Hayashi, T.; Kawamura, N.; Ito, Y. *J. Am. Chem. Soc.* **1987**, *109*, 7876. (b) Crameri, Y.; Foricher, J.; Scalone, M.; Schmid, R. *Tetrahedron: Asymmetry* **1997**, *8*, 3617. (c) Arena, G.; Barreca, G.; Carcone, L.; Cini, E.; Marras, G.; Nedden, H. G.; Rasparini, M.; Roseblade, S.; Russo, A.; Taddei, M.; Zanotti-Gerosa, A. *Adv. Synth. Catal.* **2013**, *355*, 1449.

(8) Zhu, S.-F.; Xie, J.-B.; Zhang, Y.-Z.; Li, S.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2006**, *128*, 12886.

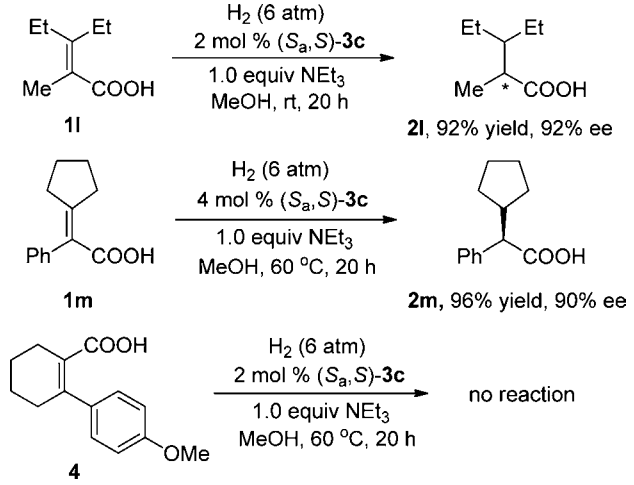
Scheme 1. Enantioselective Iridium-Catalyzed Hydrogenation of β,β-Dimethyl Itaconic Acid Derivatives



The hydrogenation of β,β-dimethyl itaconic acid derivatives **1j** and **1k**, which have an ester group at side chain, underwent smoothly and afforded the corresponding products **2j** and **2k**, respectively, in high yields and high enantioselectivities (95 and 96% ee, respectively) by using catalyst (S_a,*S*)-**3c** (Scheme 1). Chiral carboxylic acid **2j** is an important building block of chiral drugs such as Aliskiren.[9]

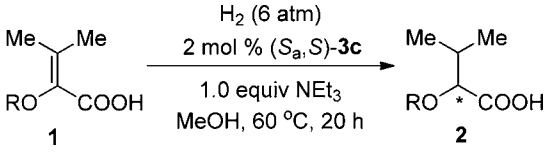
The hydrogenation of α-methyl-β,β-diethyl acrylic acid (**1l**) and 2-cyclopentylidene-2-phenylacetic acid (**1m**) were also performed under the standard reaction conditions (Scheme 2). By using catalyst (S_a,*S*)-**3c**, the hydrogenation of **1l** provided chiral carboxylic acid **2l** in 92% yield with 92% ee at room temperature. However, the substrate **1m** was less reactive, which needs 4 mol % catalyst for full conversion. The hydrogenation product **2m** is the basic skeleton of lipoxygenase inhibitor Bay × 1005.[3a] Unsaturated carboxylic acid **4** bearing a tetrasubstituted endocyclic olefin cannot be hydrogenated under standard reacition conditions.[10]

Scheme 2. Enantioselective Iridium-Catalyzed Hydrogenation of Trisubstituted Acrylic Acids



The chiral α-aryloxy isopentyl carboxylic acids are the key structure of many organocatalysts[5] and biologically active molecules.[11] The asymmetric hydrogenation of α-aryloxy-β,β-dimethyl acrylic acids afforded a direct route to chiral α-aryloxy isopentyl carboxylic acids.[2a] We investigated the asymmetric hydrogenation of α-aryloxy-β,β-dimethyl acrylic acids by using catalysts **3** (Table 3). The (S_a,*S*)-**3c** was found to be an efficient catalyst for the hydrogenation of substrates **1n**–**1u** (entries 1–8). The hydrogenation reactions were performed in MeOH under 6 atm of H_2 at 60 °C with 1.0 equiv of NEt_3 as additive and afforded the corresponding chiral carboxylic acids (**2n**–**2u**) in high yields (96–99%) and excellent enantioselectivities (93–98% ee). The *ortho*-substituted substrates **1s** and **1t** need higher reaction temperature (80 °C) for full conversion

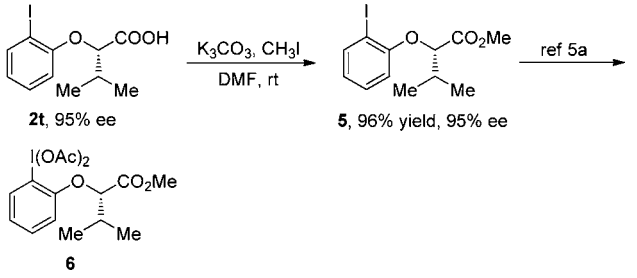
Table 3. Enantioselective Iridium-Catalyzed Hydrogenation of α-Aryloxy-β,β-dimethyl Acrylic Acids[a]



entry	R (**1**)	product	yield (%)	ee (%)
1	Ph (**1n**)	**2n**	98	93 (*S*)
2	4-MeC_6H_4 (**1o**)	**2o**	99	97 (–)
3	4-ClC_6H_4 (**1p**)	**2p**	96	95 (–)
4	4-$MeOC_6H_4$ (**1q**)	**2q**	96	95 (–)
5	3-MeC_6H_4 (**1r**)	**2r**	98	98 (–)
6[b]	2-MeC_6H_4 (**1s**)	**2s**	97	97 (–)
7[b]	2-IC_6H_4 (**1t**)	**2t**	98	95 (*S*)
8	2-Naphthyl (**1u**)	**2u**	98	96 (–)
9	Benzyl (**1v**)	**2v**	95	99 (*S*)

[a] The reaction conditions and analysis are identical to those in Table 1, entry 3. Full conversions were obtained in all cases. [b] Performed at 80 °C.

Scheme 3. Asymmetric Synthesis of Hypervalent Iodine **6**



(9) (a) Hanessian, S.; Claridge, S.; Johnstone, S. *J. Org. Chem.* **2002**, *67*, 4261. (b) Galatsis, P.; Caprathe, B.; Gilmore, J.; Thomas, A.; Linn, K.; Sheehan, S.; Harter, W.; Kostlan, C.; Lunney, E.; Stankovic, C.; Rubin, J.; Brady, K.; Allen, H.; Talanian, R. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5184. (c) Taddei, M.; Russo, A.; Cini, E.; Riva, R.; Rasparini, M.; Carcone, L.; Banfi, L.; Vitale, R.; Roseblade, S.; Zanotti-Gerosa, A. C. WO patent 151442, 2011.

(10) Catalyst (S_a,*S*)-**3c** showed excellent enantioselectivities in the hydrogenation of α,β-unsaturated carboxylic acids bearing a trisubstituted endocyclic olefin, see: Song, S.; Zhu, S.-F.; Pu, L.-Y.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 6072.

(11) (a) Liu, W.; Liu, K.; Wood, H. B.; McCann, M. E.; Doebber, T. W.; Chang, C. H.; Akiyama, T. E.; Einstein, M.; Berger, J. P.; Meinke, P. T. *J. Med. Chem.* **2009**, *52*, 4443. (b) Edmondson, S. D.; Mastracchio, A.; Beconi, M.; Colwell, L. F., Jr; Habulihaz, B.; He, H.; Kumar, S.; Leiting, B.; Lyons, K. A.; Mao, A.; Marsilio, F.; Patel, R. A.; Wu, J. K.; Zhu, L.; Thornberry, N. A.; Weber, A. E.; Parmee, E. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5151.

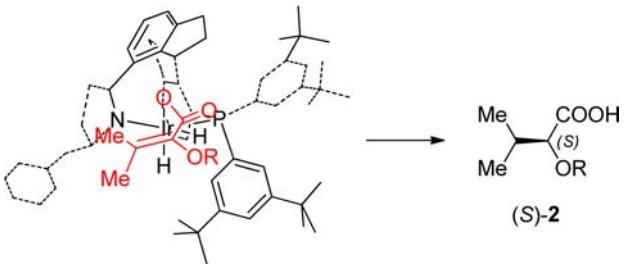


Figure 2. Proposed coordination model of substrate **1** with catalyst (S_a,*S*)-**3c**.

(entries 6 and 7). The hydrogenation of α-alkyloxy substrate **1v** also underwent the hydrogenation smoothly with 99% ee (entry 9). As shown in Scheme 3, the hydrogenation product **2t** with an *ortho*-iodophenoxy group could be easily converted to the chiral hypervalent iodine catalyst **6**,[5a] which further demonstrated the potential application of this hydrogenation reaction.

On the basis of the crystal structure of (S_a,*S*)-**3c**[2f] and the absolute configuration of the hydrogenation products, a chiral induction model was proposed in Figure 2. The α-aryloxy or α-alkyloxy-*β*,*β*-dimethyl acrylic acids **1** prefer to coordinate to catalyst (S_a,*S*)-**3c** with *Re*-face and thus afford hydrogenation products **2** with *S* configuration, which is consistent with the experimental results.

In conclusion, the highly enantioselective hydrogenation of α,*β*-unsaturated carboxylic acids with tetrasubstituted olefins has been realized by using chiral spiro iridium catalysts. The reaction provides a direct catalytic approach to chiral carboxylic acids having an α-aryl, α-alkyl, α-aryloxy or α-alkyloxy substituent.

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Supporting Information Available. Experimental procedures, characterization data, HPLC and SFC spectra for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.