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Highly Enantioselective Iridium-Catalyzed Hydrogenation of α,β-Unsaturated Esters

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Abstract: α,β-Unsaturated esters have been employed as substrates in iridium-catalyzed asymmetric hydrogenation. Full conversions and good to excellent enantioselectivities (up to 99% *ee*) were obtained for a broad range of substrates with both aromatic- and aliphatic substituents on the prochiral carbon. The hydrogenated products are highly useful as building blocks in the synthesis of a variety of natural products and pharmaceuticals.

Keywords: asymmetric catalysis · chirality · hydrogenation · iridium · α,β-unsaturated esters

Introduction

Catalytic asymmetric synthesis is an important field of research in the fine chemical industry and the pharmaceutical sciences because it allows many of the diverse structures required in these areas to be produced both efficiently and selectively.[1] Currently, many types of stereogenic centers and frameworks can be produced with high enantioselectivity, but original methodologies and new chiral molecules are still sought. Chiral carboxylic acid derivatives bearing tertiary stereogenic centers, and in particular chiral tertiary benzylic aliphatic centers, are ubiquitous in natural products, agrochemicals, fragrances (e.g., (+)-Florhydral), and pharmaceuticals (such as the ACAT inhibitor R-106578 and APTIVUS; Figure 1).[2] Moreover, because carbonyl groups are readily elaborated to other moieties, carboxylic acid derivatives are versatile chiral building blocks. For example, the bisabolane sesquiterpenes, such as (+)-Dehydrocurcumene, (+)-Curcumene, (+)-Tumerone, (+)-Nuciferol, (+)-Nuciferal, and (+)-Erogorgiaene (see later, Figure 3), which have multiple natural sources and exhibit biological features ranging from olfactive to antibabesial properties, can all be accessed from (3*S*)-ethyl 3-(*p*-tolyl)butanoate.

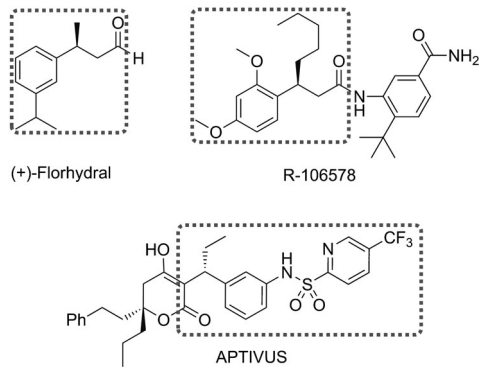

Figure 1. Structures of (+)-Florhydral, R-1067578, and APTIVUS.

There are many methods for approaching α- and β-chiral carboxylic acid derivatives; however, these often suffer limitations. Cu- and Rh-catalyzed asymmetric 1,4-reductions of α,β-unsaturated carbonyl compounds enable the construction of tertiary stereogenic carbon centers, but require very moisture-sensitive hydrosilane derivatives as efficient hydride-donors.[3] The Co-catalyzed asymmetric conjugate reduction of α,β-unsaturated carbonyls by using a combination of borohydride reagents has been studied.[4] Metal (Pd, Rh and Cu)-catalyzed asymmetric 1,4-additions of organometallic (Grignard or organozinc) or nonmetallic (organoboron) reagents to α,β-unsaturated carbonyl compounds are versatile procedures for the synthesis of chiral β-substituted carbonyl compounds.[5] The chemoenzymatic method, that is, the lipase-catalyzed kinetic resolution of esters, has also been attempted, but required long reaction times and produced low yields.[6] Asymmetric alkylations using chiral auxiliaries, such as *N*-acyl oxazolidinones and atropisomeric anilides, have also been studied and give good results; however, the chiral auxiliaries must be installed and removed, adding steps to the synthesis.[7] Thus, the development of synthetic routes to α- and β-chiral carboxylic acid derivatives are still desirable and ongoing.

In contrast to the methods mentioned above, the catalytic asymmetric hydrogenation of prochiral olefins offers perfect atom economy, high turnover numbers and high reaction rates under mild conditions, making it one of the most straightforward metal-catalyzed approaches to chiral compounds.[8] The Rh- and Ru-catalyzed asymmetric hydrogenations of olefins have long histories, but generally rely on a metal-coordinating group close to the double bond to pro-

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duce high enantioselectivity.[9] In contrast to Rh and Ru catalysts, Crabtree's achiral complex, [(cod)Ir(Pyridine)-(PCy_3)]$^+$ $[PF_6]^-$, (COD = 1,4-cyclooctadiene), is highly active for the hydrogenation of unfunctionalized alkenes.[10] Since Pfaltz and co-workers made the first chiral mimic of Crabtree's catalyst, which was highly active and enantioselective for the reduction of olefins,[11] many types of chiral iridium catalysts have been developed.[12] As Ir-based catalysts perform better with substrates containing only weakly, or even without coordination groups, they complement Rh- and Ru complexes, making transition-metal-catalyzed asymmetric hydrogenation an even stronger methodology.[13] Recent work has focused on expanding the substrate scope[14] and exploring the synthetic application[15] of these enantioselective reactions.

In the present study, we demonstrate the highly enantioselective iridium-catalyzed asymmetric hydrogenation of a broad range of substrates containing (*E*)- or (*Z*)-β,β-disubstituted α,β-unsaturated esters or (*E*)-α,β-disubstituted unsaturated esters. These reactions yield important chiral building blocks that can be applied in the syntheses of natural products and pharmaceuticals.

Results and Discussion

Asymmetric hydrogenation of (*E*)- and (*Z*)-β,β-disubstituted α,β-unsaturated esters: (*E*)-Ethyl β-methylcinnamate **1** is a common substrate in iridium-catalyzed asymmetric hydrogenation, and has been reduced with high enantioselectivity.[16] However, almost no other substrates of this class have been studied. Moreover, β,β-dialkyl α,β-unsaturated esters have been very challenging substrates in the asymmetric hydrogenation with iridium-N,P complexes. Only one dialkyl ester, (*E*)-ethyl 3-methyl-5-phenylpent-2-enoate, has been reduced with modest to good enantioselectivity.[17]

The iridium catalyst bearing the thiazole-phosphine ligand **A** (Figure 2), which is based on a bicyclic backbone, is very

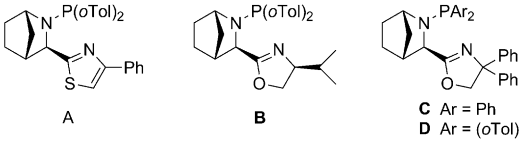
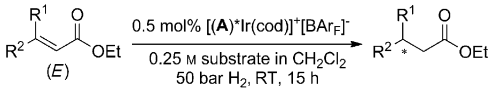
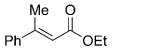
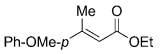
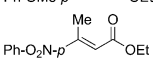
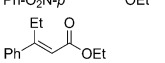
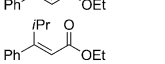
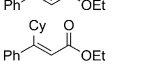
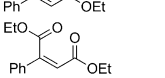
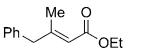
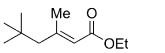
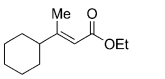


Figure 2. The chiral ligands used in this study.

efficient in the asymmetric hydrogenation of ester **1** (>99% conversion and 98% enantiomeric excess (*ee*)).[18] We thus investigated the scope of the asymmetric α,β-unsaturated ester reduction with [(**A**)*Ir(cod)]$^+$[BAr_F]$^-$ (BAr_F = tetrakis-(3,5-bis(trifluoromethyl)phenyl) borate) by using a wide range of (*E*)-β,β-disubstituted α,β-unsaturated esters. (*E*)-Ethyl β-alkylcinnamates were first evaluated (Table 1). Aryl moieties with electron-donating and electron-withdrawing groups were studied. Introducing a strongly electron-donating group (-OMe) on the *para* position of the phenyl ring effected neither the reactivity nor the selectivity (Table 1, entry 2). The *para*-nitro-substituted substrate **3** was fully converted to its corresponding saturated ester with excellent enantioselectivity (97% *ee*; see Table 1, entry 3), and the nitro group was retained. Increasing the size of alkyl group on the β position effected neither the reactivity nor the selectivity; substrates **4**, **5**, and **6**, bearing ethyl, isopropyl, and cyclohexyl groups, respectively, were all hydrogenated in >99% conversion and >99% *ee* (Table 1, entries 4–6). To broaden the synthetic utility of this reaction, substrate **7** (which has an ethyl ester group on the β position) was hydrogenated. Full conversion and an excellent *ee* (95%) were obtained. The corresponding product has two ester groups and can therefore be further modified to access diverse chiral precursors.[19]

Table 1. Asymmetric hydrogenation of (*E*)-β,β-disubstituted α,β-unsaturated esters.[a]



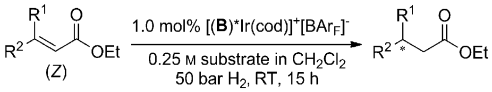
Entry	Substrate		*ee*[b] [%]
1		**1**	98 (*R*)-(−)
2		**2**	98 (*R*)-(−)
3		**3**	97 (−)
4		**4**	>99 (*R*)-(−)
5		**5**	>99 (*S*)-(−)
6		**6**	>99 (−)
7		**7**	95 (−)
8		**8**	93 (+)
9		**9**	87 (+)
10		**10**	87 (*R*)-(−)

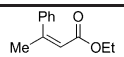
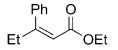
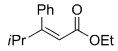
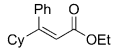
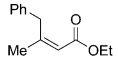
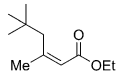
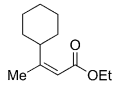
[a] Conversion (determined by ^{1}H NMR spectroscopy) was >99% in all cases. [b] Determined by chiral chromatography (see Supporting Information for details).

Contrary to (*E*)-β,β-disubstituted α,β-unsaturated esters, members of the (*Z*)-configured cohort have proven very hard to hydrogenate with excellent *ee* by using N,P-chelated iridium catalysts.[20] We found the hydrogenation of substrate **11** by [(**A**)*Ir(cod)]$^+$[BAr_F]$^-$ to be no exception, as an

ee value of 90% was obtained for the reaction. However, surprisingly we found that an iridium catalyst containing the bicycle-supported oxazoline-phosphine ligand **B** (Figure 2), which has been employed in the asymmetric hydrogenation of aryl imines[21] (with up to 92% *ee*) as well as of di- and trisubstituted enol phosphinates[22] (with up to 99% *ee*), was very enantioselective (98% *ee*) for the hydrogenation of (*Z*)-ethyl β-methylcinnamate **11** (Table 2, entry 1). As the hydrogenation of **11** was slower than that of the corresponding (*E*)-configured ester **1**, 1 mol% of catalyst was required to ensure full conversion. Keeping the excellent enantioselectivity in view, we reduced a series of (*Z*)-β,β-disubstituted α,β-unsaturated esters with $[(\mathbf{B})^*Ir(cod)]^+[BAr_F]^-$. Substrates bearing aryl moieties (Table 2, entries 1–4) were reduced highly selectively (up to 99% *ee*), performing slightly better than the dialkyl cohort (*ee* values of 85–93%; Table 2, entries 5–7). These observations echoed those from the hydrogenation of (*E*)-esters. Enantioselectivity increased with increasing bulk on the prostereogenic center of the (*Z*)-dialkyl esters; this was contrary to the trend observed when using (*E*)-dialkyl esters (cf., Table 1, entries 8–10 and Table 2, entries 5–7).

Table 2. Hydrogenation of (*Z*)-β,β-disubstituted α,β-unsaturated esters.[a]



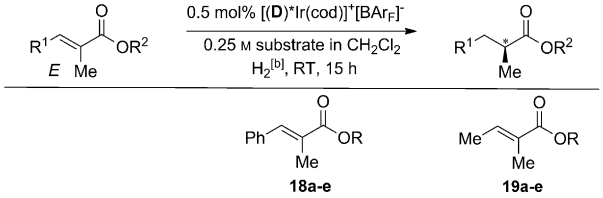
Entry	Substrate		*ee*[b] [%]
1		**11**	98 (*S*)-(+)
2		**12**	98 (*S*)-(+)
3		**13**	>99 (*R*)-(+)
4		**14**	>99 (+)
5		**15**	85 (−)
6		**16**	87 (−)
7		**17**	93 (*S*)-(+)

[a] Conversion (determined by ^{1}H NMR spectroscopy) was >99% in all cases. [b] Determined by chiral chromatography (see the Supporting Information for details).

However, neither α-alkoxy α,β-unsaturated esters nor β,γ-unsaturated carboxylic esters could be hydrogenated with the same catalyst.[24b,c] α,β-Disubstituted unsaturated esters have long been challenging substrates in asymmetric hydrogenation when iridium-N,P complexes have been used as catalysts. In 2010, Pfaltz and co-workers applied pyridylphosphinite-ligated iridium catalysts in the reduction of α-methylcinnamates,[17b] and reported enantioselectivities of up to 99%. Although only three substrates, which differed only in the ester moiety, were hydrogenated, these enantioselectivities were unprecedented in the iridium-catalyzed asymmetric hydrogenation α-methylcinnamates.

Previously, an iridium catalyst based on the bicycle-supported oxazoline-phosphine ligand **C** (Figure 2) had given the best result among the catalysts developed in our group in the reduction of ethyl α-methylcinnamate **18a**; however, only 90% *ee* was obtained in that case.[25] The phosphorus atom in ligand **C** has two phenyl groups; however, in some cases, we have found that replacing a diphenylphosphine with a bis(*ortho*-tolyl)phosphine increased the stereodiscrimination of our catalysts.[26] Indeed, the modified catalyst $[(\mathbf{D})^*Ir(cod)]^+[BAr_F]^-$, with a -P(*o*Tol)$_2$ phosphine moiety, gave improved enantioselectivity (95% *ee*) in the hydrogenation of **18a**, and still gave 99% conversion. We therefore used $[(\mathbf{D})^*Ir(cod)]^+[BAr_F]^-$ to study the asymmetric hydrogenation of α-substituted cinnamates and β-substituted methacrylates (Table 3).

Table 3. Hydrogenation of α-methylcinnamates and β-methylmethacrylates with varied O-alkyl groups.[a]



Entry	R	Substrate	*ee*[c] [%]	Substrate	*ee*[c] [%]
1	Et	**18a**	95	**19a**	97
2	Bn	**18b**	97	**19b**	99
3	*i*Pr	**18c**	93	**19c**	93
4	(+)-1-Phenylethyl	**18d**	99	**19d**	91
5	(±)-1-Phenylethyl	**18e**	99	**19e**	93

[a] Conversion (determined by ^{1}H NMR spectroscopy) was >99% in all cases. [b] 50 bar H_2 was used for **18a–e** and 20 bar H_2 was used for **19a–e**. [c] Determined by chiral chromatography (see the Supporting Information for details).

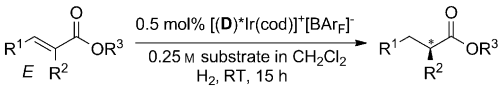
Asymmetric hydrogenation of (*E*)-α,β-disubstituted unsaturated carboxylates: α,β-Disubstituted unsaturated carboxylic acids have been hydrogenated with high enantioselectivities by using various Ru,[23a] Rh,[23b] and Pd[23c] catalysts with phosphorus-containing ligands. Recently, Zhou and co-workers reported the very enantioselective hydrogenation of α-alkyl[24a] and α-alkoxy[24b] α,β-unsaturated carboxylic acids as well as of β,γ-unsaturated carboxylic acids[24c] with Ir-SIPHOX (SIPHOX = spiro phosphine-oxazoline) complexes.

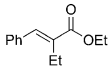
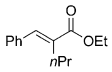
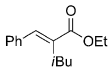
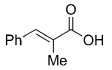
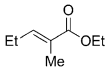
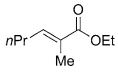
At first, we evaluated α-methylcinnamates and β-methylmethacrylates with different O-alkyl groups, because the steric demands of ester groups often have an impact on the reactivities and enantioselectivities of transition-metal-catalyzed asymmetric hydrogenation reactions.[27] Here, full conversions were observed in all cases but the enantioselectivities varied. The benzyl esters were hydrogenated to give products with the highest enantioselectively (97% *ee* for the cinnamate and >99% *ee* for the methacrylate; Table 3,

entry 2). The ethyl esters were reduced to give products with a slightly lower *ee* value (Table 3, entry 1), and the larger, isopropyl esters with even lower *ee* value (Table 3, entry 3), although the product was still obtained with >90% *ee*. Comparing the hydrogenations of substrates **18d** and **19d** with chiral ester moieties, and their racemic forms **18e** and **19e**, allowed us to study the effect of a pre-existing stereogenic center in the ester groups of the substrates (Table 3, entries 4 and 5). There was no influence on α-methylcinnamates; the (+) and racemic forms were hydrogenated with identical *ee* values. Very little influence was observed for the β-methylmethacrylates, as the *ee* values differed by only 2% between the optically pure and racemic forms.

We also studied the influence of substituents in the α position of ethyl cinnamates (Table 4). Substrates **20** and **21**, with α-ethyl and α-*n*-propyl groups, respectively, were both hydrogenated in full conversion and 96% *ee* (Table 4, entries 1 and 2). Substrate **22**, which has a bulkier isobutyl group in the α position, was reduced in 90% *ee* (Table 4, entry 3). α-Methylcinnamic acid, **23**, could also be fully hydrogenated with an excellent *ee* of 99% (Table 4, entry 4). Unlike the hydrogenation described by Zhou and co-workers,[24a] this reaction did not require Et_3N as an additive to reach full conversion. In the hydrogenation of ethyl methacrylates, the enantioselectivity slightly decreased when the length of the chain in the β position increased from ethyl to *n*-propyl (Table 4, entries 5 and 6).

Table 4. Hydrogenation of α,β-disubstituted unsaturated carboxylates.[a]



Entry	Substrate		*ee*[b] [%]
1[c]		**20**	96 (*S*)-(+)
2[c]		**21**	96 (*S*)-(+)
3[c,d]		**22**	90 (*S*)-(+)
4[c]		**23**	99 (*S*)-(+)
5[e]		**24**	96 (*S*)-(+)
6[e]		**25**	93 (*S*)-(+)
7[e]		**26**	96 (*R*)-(−)
8[c]		**27**	99 (*R*)-(−)

[a] Conversion (determined by ^1H NMR spectroscopy) was >99% in all cases. [b] Determined by chiral chromatography (see the Supporting Information for details). [c] H_2 (50 bar) was used. [d] The *E*/*Z* ratio was 10:1 for this substrate. [e] H_2 (20 bar) was used.

The exocyclic α,β-unsaturated lactone can be considered as a special α,β-unsaturated ester in which the α-substituent and the O-alkyl moiety are one and the same group. The six-membered-ring lactones **26** and **27**, with methyl and phenyl groups, respectively, on the exo double bond, were hydrogenated with excellent *ee* values and in full conversion (Table 4, entries 7 and 8). Zhang and co-workers have reported the asymmetric hydrogenation of substrate **27** with an iridium catalyst; however, only 71% *ee* was obtained.[28]

DFT calculations performed by Andersson and co-workers have predicted that a trisubstituted olefin will bind to an iridium atom that bears a chiral N,P-bidentate ligand in the same equatorial plane as the ligand, *cis* to the chelating nitrogen, and that the vinylic proton of the olefin will be oriented toward the bulk of the substituent on the chelating nitrogen-containing heterocycle (Figure 3).[29] They also noted

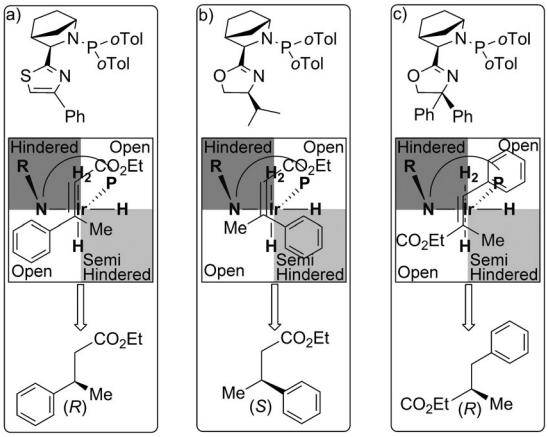
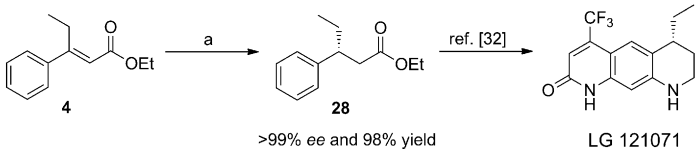


Figure 3. Predicted enantiocontrol in the asymmetric hydrogenation of α,β-unsaturated esters.

that the absolute configuration of the major product formed in the asymmetric hydrogenation of a trisubstituted olefin by this type of catalyst can be predicted by determining if the ligand N terminus has greater steric bulk above or below the N-Ir-P plane.[30] As the absolute configurations of most of the products formed in this study have been reported, we were able to test the utility of the model shown in Figure 3 in predicting the sense of selectivity in our hydrogenations of α,β-unsaturated esters. All three of ligands **A**, **B**, and **D** bind to iridium with the steric bulk at N lying above the N-Ir-P plane when the N atom is drawn on the left of the complex (as in Figure 3). Thus, drawing the Ir-bound substrates with their vinylic-H atoms in the hindered quadrant leads to the prediction that (*E*)-ethyl β-methylcinnamate **1** will be hydrogenated to its corresponding *R* product (Figure 3a), whereas (*Z*)-ethyl β-methylcinnamate **11** will form the corresponding *S* product (Figure 3b). Both results are observed experimentally (Table 1, entry 1 and Table 2, entry 1). In fact, the model rationalized the absolute configurations of all the products of (*E*)- and (*Z*)-β,β-disubstituted α,β-unsaturated esters for which assignments were available.

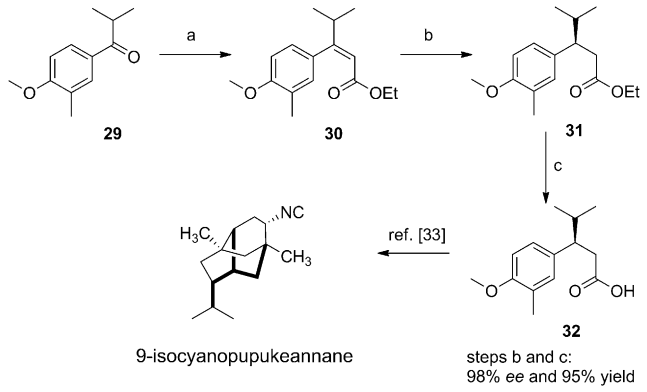
According to this selectivity model, (*E*)-ethyl α-methylcinnamate **18a** should be hydrogenated to the corresponding *R* product (Figure 3c); however, the experimental result was the opposite, as the *S* product was formed (Table 3, entry 1). Calculations on the former system allowed this effect to be attributed to the polarity of the double bond; when **18a** binds to iridium in the sterically most favored configuration (i.e., shown in Figure 3c), hydrogenation must occur by a hydride transfer to the electron-rich terminus of the olefin.[31] The electronic penalty is greater than the steric one for binding the opposite face of the olefin to Ir, so **18a** is hydrogenated to the enantiomer opposite to that predicted by the model. This effect may also direct the hydrogenation of all α,β-disubstituted unsaturated carboxylates present in Tables 3 and 4 through $[(\mathbf{D})^*\mathrm{Ir(cod)}]^+[\mathrm{BAr_F}]^-$.

To demonstrate the utility of this highly efficient catalytic asymmetric hydrogenation, we prepared key intermediates for the total synthesis of several natural products and bioactive compounds. The first orally active, nonsteroidal androgen receptor modulator, LG 121071, has been generated from (*R*)-ethyl 3-phenylpentanoate (**28**) by using a Cu-catalyzed asymmetric conjugate reduction (86% *ee*).[32] We have established that the hydrogenation of α,β-unsaturated ester **4** gives direct access to **28** with >99% *ee* and in 98% yield of the isolated product (Scheme 1).



Scheme 1. Catalytic enantioselective synthesis of LG 121071 starting material **28**. a) $[(\mathbf{A})^*\mathrm{Ir(cod)}]^+[\mathrm{BAr_F}]^-$, CH_2Cl_2, 50 bar H_2, RT.

Carboxylic acid **32** was used as the key intermediate in Brown and Corey's enantioselective synthesis of 9-isocyanopupukeannane.[33] Through the iridium-catalyzed asymmetric hydrogenation of substrate **30** and subsequent conversion of the ester to an acid, we synthesized **32** in 98% *ee* and with 95% yield of the isolated product (Scheme 2).



Scheme 2. Enantioselective synthesis of 9-isocyanopupukeanane intermediate **31**. a) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0°C to reflux; b) $[(\mathbf{B})^*\mathrm{Ir(cod)}]^+[\mathrm{BAr_F}]^-$, CH_2Cl_2, 50 bar H_2, RT; c) NaOH (aq. 1 M), MeOH, RT.

Shishido et al. have used (*R*)-3-(2,5-dimethoxy-4-methylphenyl) butanoic acid (**36**) in an enantioselective total synthesis of the strongly allelopathic (−)-Heliannuol A.[34] They started from the lipase-mediated transesterification of a prochiral diol to create a chiral monoacetate (78% *ee*), which was elaborated in five steps to give **36**. Recently, the same group has also employed **36** as the key intermediate in the total synthesis of (+)-Heliannuol D, which has phytotoxic allelopathic activity.[35] They shortened the synthetic route to **36** to two steps by using a diastereoselective conjugate addition; however, a chiral auxiliary had to be introduced to promote the diastereoselective reaction and then removed afterwards to give the free acid. We reached the key intermediate carboxylic acid **36** from **34** via **35** with 92% *ee* and in 96% yield of the isolated product (Scheme 3). Reduction of ester **35** with $LiAlH_4$ provided the corresponding alcohol **37** (93% isolated product yield from **34**), which is another key intermediate in the syntheses of Helibisabonol A,[36] (which also exhibits allelopathic activity), and (−)-Curcuhydroquinone,[6a] which has been isolated from the Caribbean gorgonian *Pseudopterogorgia rigida* and has shown antibacterial activity against *Staphylococcus aureus* and the marine pathogen *Vibro anguillarum*.

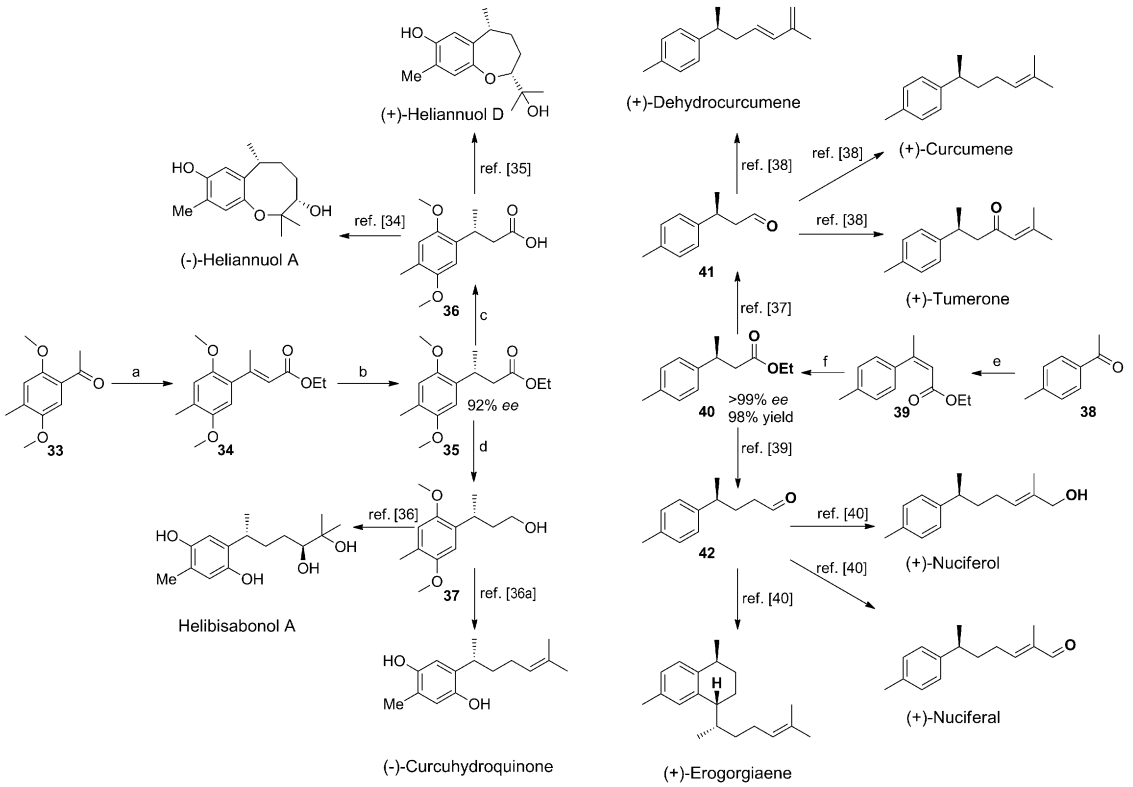
The asymmetric hydrogenation of (*Z*)-ethyl 3-(*p*-tolyl)-but-2-enoate **39** gave (*S*)-ethyl 3-(*p*-tolyl)butanoate **40** as a single enantiomer in 98% yield (Scheme 3). This can be transformed to (*S*)-3-(*p*-tolyl)butanal **41**,[37] which has been used in the total syntheses of (+)-Dehydrocurcumene, (+)-Curcumene, and (+)-Tumerone.[38] Ester **40** could also be converted to 4-(*p*-tolyl)pentanal **42**,[39] a precursor in the syntheses of (+)-Nuciferol, (+)-Nuciferal, and (+)-Erogorgiaene.[40]

Conclusion

In summary, we have used an iridium-catalyzed asymmetric hydrogenation to convert α,β-unsaturated esters to their corresponding saturated chiral products. Notably, good to excellent enantioselectivities were obtained in the hydrogenations of (*E*)-β,β-dialkyl and (*Z*)-β,β-disubstituted α,β-unsaturated esters and (*E*)-α,β-disubstituted unsaturated esters, which are very challenging substrates in N,P-ligated-iridium-catalyzed asymmetric hydrogenation. Furthermore, the saturated chiral esters have been used in synthetic transformations as well as in the formal syntheses of natural products.

Experimental Section

General procedure: A vial was charged with the substrate (0.25 M) and the Ir complex (0.0025–0.005 M). Dry CH_2Cl_2 was added (2 mL) and the vial was placed in a high-pressure hydrogenation apparatus. The reactor was purged three times with Ar, then filled with H_2 to a pressure of 20 or 50 bar. The reaction was stirred at room temperature for 15 h before the H_2 pressure was released and the solvent was removed in vacuum. The crude product was filtered through a short plug of silica. Conversions



Scheme 3. Use of iridium-catalyzed asymmetric hydrogenation of α,β-unsaturated esters to produce chiral intermediates for total syntheses. a) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0 °C to reflux; b) $[(\mathbf{A})^*Ir(cod)]^+[BAr_F]^-$, CH_2Cl_2, 50 bar H_2, RT; c) NaOH (aq. 1 M), MeOH, RT (steps b and c, 96% yield); d) LAH, THF, −30 °C (steps b and d, 93% yield); e) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0 °C to reflux; f) $[(\mathbf{B})^*Ir(cod)]^+[BAr_F]^-$, CH_2Cl_2, 50 bar H_2, RT.

were determined by ^1H NMR spectroscopy and *ee* values were determined using chiral GC or HPLC.

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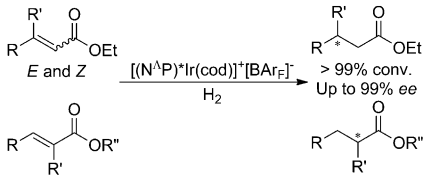
Asymmetric hydrogenation: A variety of α,β-unsaturated esters were hydrogenated with high enantioselectivities (see scheme). The hydrogenated products have been used in synthetic transformations as well as in formal total syntheses.



Hydrogenation

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Highly Enantioselective Iridium-Catalyzed Hydrogenation of α,β-Unsaturated Esters