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Asymmetric Hydrogenation of α,β-Unsaturated Carboxylic Esters with Chiral Iridium N,P Ligand Complexes

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Abstract: Enantioselective conjugate reduction of a wide range of α,β-unsaturated carboxylic esters was achieved using chiral Ir N,P complexes as hydrogenation catalysts. Depending on the substitution pattern of the substrate, different ligands perform best. α,β-Unsaturated carboxylic esters substituted at the α position are less problematic substrates than originally anticipated and in some cases α-substituted substrates actually reacted with higher enantioselectivity than their β-substituted analogues. The resulting saturated esters with a stereogenic center in the α or β position were obtained in high enantiomeric purity.

Keywords: asymmetric catalysis · hydrogenation · iridium · N,P ligands · unsaturated esters

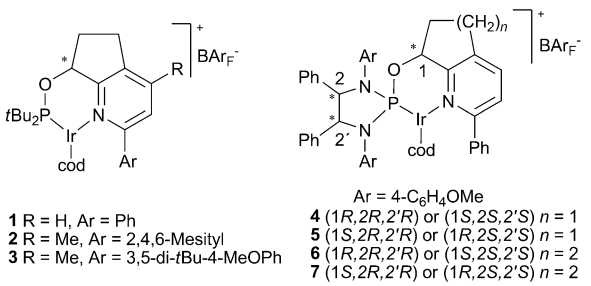
Introduction

Enantioselective conjugate reduction of α,β-unsaturated carboxylic acids and esters is an important transformation leading to synthetically useful products, which can be further elaborated by reactions at the carboxyl or ester group. Moreover, many natural and synthetic bioactive carboxylic acid derivatives are known that possess a tertiary stereogenic center in the α or β position.[1] A variety of chiral metal catalysts and reducing agents such as hydrosilanes, sodium borohydride, or dihydrogen have been used for conjugate reductions. For the asymmetric hydrogenation of α,β-unsaturated carboxylic acids ruthenium–binap complexes have established themselves as efficient, widely applicable catalysts,[2] but they do not react with the corresponding esters. More recently, very high enantioselectivities and turnover numbers have been achieved in the hydrogenation of α-substituted unsaturated carboxylic acids with iridium catalysts based on spirocyclic phosphine–oxazoline ligands.[3]

In many synthetic applications the use of esters rather than carboxylic acids is preferred because polar free acids are in general more difficult to handle. High enantioselectivities in the conjugate reduction of α,β-unsaturated carboxylic esters have been achieved with cobalt catalysts using sodium borohydride as a reductant[4] and in hydrosilane-based reductions using Cu–diphosphine[5] or Rh–bisoxazoline pincer complexes as catalysts.[6] For catalytic hydrogenation using dihydrogen as the reductant, Ir complexes with chiral N,P ligands have emerged as catalysts of choice for this substrate class.[7] Rh– and Ru–diphosphine catalysts have been used as well, but in general their application range is restricted to additionally functionalized esters such as dehydroamino acid derivatives.[7d] Although high enantioselectivities have been reported for a diverse array of Ir catalysts based on N,P and C,N ligands, only a limited number of substrates has been investigated so far, with most studies focusing on simple α- or β-substituted cinnamic esters.

Here, we report the results of a systematic evaluation of Ir complexes with chiral N,P ligands in the asymmetric hydrogenation of a wide range of α,β-unsaturated carboxylic esters, which demonstrates the scope of Ir catalysts for this transformation. Our study focused on pyridine-derived ligand complexes **1**–**7**, based on promising results that we had recently obtained with catalysts of this type (Figure 1).[8]

In previous work, which featured a modular approach to iridium pyridyl–phosphinite catalysts,[8,9] we demonstrated that small changes made to the catalyst led to large differences in enantioselectivity.[8] Replacing the *ortho*-phenyl group in ligand **1** by sterically more demanding aryl groups, such as mesityl or 3,5-di-*tert*-butyl-4-methoxyphenyl (ligands **2**



1 R = H, Ar = Ph
2 R = Me, Ar = 2,4,6-Mesityl
3 R = Me, Ar = 3,5-di-*t*Bu-4-MeOPh

Ar = 4-C$_6$H$_4$OMe
4 (1*R*,2*R*,2′*R*) or (1*S*,2*S*,2′*S*) n = 1
5 (1*S*,2*R*,2′*R*) or (1*R*,2*S*,2′*S*) n = 1
6 (1*R*,2*R*,2′*R*) or (1*S*,2*S*,2′*S*) n = 2
7 (1*S*,2*R*,2′*R*) or (1*R*,2*S*,2′*S*) n = 2

Figure 1. Chiral iridium N,P precatalysts **1**–**7**.

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and **3**), gave appreciable increases in enantioselectivity for difficult substrates. The importance of the substituent at the *ortho* position of the pyridine ring is in accordance with Andersson's model for the enantioselectivity-determining step (Figure 2)[10] because it is this substituent that is closest to

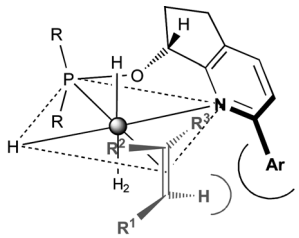


Figure 2. Andersson's model for the enantioselectivity-determining step.[10]

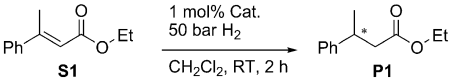
the coordinated substrate. Although the substituents at the phosphorus atom are too remote for direct steric interaction with the substrate, they too can influence the enantioselectivity through electronic effects as well as steric effects by interaction with axial ligands and the carbocyclic ring. Such effects are expected to be most pronounced for sterically demanding phosphine units such as bis(*N*-arylamino)phosphine, which we had used before as a phosphinite replacement for oxazoline-based N,P ligands.[11] This led us to use this modification with the pyridyl alcohol scaffold of **1** to create a set of diastereomeric complexes **4**–**7**, which we then evaluated as catalysts for the asymmetric hydrogenation of α,β-unsaturated carboxylic esters. A first successful application of these complexes was recently reported for two hydrogenation steps in the synthesis of platensimycin.[12]

Results and Discussion

Hydrogenation of the β-methyl-substituted ester **S1** indicated that replacement of the phenyl group in the parent complex **1** by more sterically demanding aryl groups resulted in a loss of enantioselectivity. However, with the exception of **7**, all other catalysts still gave enantioselectivities above 90% enantiomeric excess (*ee*; Table 1). The configuration of the product **P1** produced by catalysts **4**–**7** was found to depend on the configuration of the stereogenic center next to the pyridine ring. Only a small difference in enantioselectivity was observed between the diastereomeric complexes **4** and **5**, indicating that the additional chiral diaminophosphine unit makes little contribution to the enantioselectivity. However, a more pronounced contribution to the enantioselectivity was observed with the less reactive diastereomeric iridium complexes **6** and **7**, amounting to a 0.4 kcal mol^{-1} lower activation energy of the enantioselectivity-determining step for the (1*S*,2*R*,2′*R*) catalyst **7** at 298 K.

A completely different selectivity order of catalysts **1**–**7** was observed for the α-methyl cinnamic esters **S2**–**4**. These substrates are less reactive than **S1** and, in general, require

Table 1. Enantioselective hydrogenation of (*E*)-β-methylcinnamic acid ethyl ester **S1**.

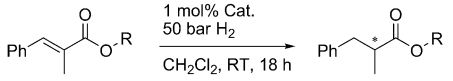


Entry	Catalyst	$\Delta\Delta G^{+}$ [kcal mol^{-1}]	*ee* [%] **P1**
1	**1** (*S*)	>3.09	>99 (*S*)[a]
2	**2** (*S*)	2.68	98 (*S*)
3	**3** (*R*)	1.94	93 (*R*)
4	**4** (1*R*,2*R*,2′*R*)	1.94	93 (*R*)
5	**5** (1*S*,2*R*,2′*R*)	2.14	95 (*S*)
6	**6** (1*R*,2*R*,2′*R*)	1.86	92 (*R*) (94)[b]
7	**7** (1*S*,2*R*,2′*R*)	1.43	84 (*S*) (95)[b]

[a] Catalyst (*S*)-**1** produced **P1** in >99% *ee* with $[\alpha]_D^{20}$ (c=0.91, $CHCl_3$), consistent with the values in the literature for the *S* enantiomer. [b] Conversions less than complete are listed next to the *ee* value in brackets.

longer reaction times. Initial hydrogenation studies indicated a complicated selectivity trend (Table 2). Complexes derived from ligands **2** and **3** with sterically more demanding *ortho*-aryl substituents induced distinctly higher enantioselectivities than the parent complex **1**. Complex **2** provided by far the best results with *ee* values of 97 to >99% (Table 2, entry 2). Among the bis(*N*-arylamino)phosphine derivatives **4**–**7** the (1*R*,2*R*,2′*R*)-isomer **4** was the most selective catalyst across the range of esters **S2**–**4**, with a marked improvement over the parent complex **1**, whereas catalysts **5**–**7** gave unsatisfactory results in terms of *ee* value and conversion.

Table 2. Enantioselective hydrogenation of (*E*)-α-methylcinnamic acid esters **S2**–**4**.



S2 R = Et
S3 R = Me
S4 R = *i*Pr

P2 R = Et
P3 R = Me
P4 R = *i*Pr

Entry	Catalyst	*ee* [%] **P2**[a]	*ee* [%] **P3**[a]	*ee* [%] **P4**[a]
1	**1** (*S*)	46 (*R*)	69 (*R*)	70 (*R*)
2	**2** (*S*)	97 (*R*)	97 (*R*)[b]	>99 (*R*)
3	**3** (*R*)	76 (*S*)	95 (*S*)	93 (*S*)
4	**4** (1*R*,2*R*,2′*R*)	87 (*R*)	77 (*R*)	75 (*R*)
5	**5** (1*S*,2*R*,2′*R*)	76 (*S*) (93)	60 (*S*) (92)	48 (*S*) (90)
6	**6** (1*R*,2*R*,2′*R*)	76 (*R*) (23)	70 (*R*) (20)	58 (*R*) (10)
7	**7** (1*S*,2*R*,2′*R*)	43 (*S*) (13)	47 (*S*) (14)	39 (*S*) (9)

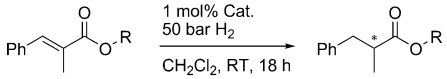
[a] All conversions less than complete are listed next to the *ee* value in brackets. [b] Catalyst (*S*)-**2** produced **P2** in 97% *ee* with $[\alpha]_D^{20}$ (c=0.17, $CHCl_3$), consistent with the values in literature for the *R* enantiomer.

Although the configuration induced by complexes **4**–**7** is controlled by the stereogenic center next to the pyridine ring, as in the hydrogenation of the β-methyl cinnamic ester **S1**, the sense of chiral induction is opposite to that observed for catalysts **1**–**3**. This discrepancy in product configuration indicates a divergence in coordination modes of the alkene in the active catalysts between pyridyl phosphinites **1**–**3** and the diazaphospholane analogues **4**–**7**.

The configuration induced by catalysts **1–3** is opposite to that predicted by Andersson's model[10] considering only steric interactions (Figure 2). However, based on their computational studies Andersson et al. noted that α-substituted esters are special substrates, because the sterically favored transition state involves hydride transfer to the α-C atom of the ester, which is electronically disfavored. So they concluded that the α-methylcinnamic ester **S2** reacts through a sterically favored but electronically disfavored alignment and that the lower enantioselectivity they observed for this substrate compared with the β-methyl isomer is due to this steric–electronic mismatch. In our case, catalysts **1–3** seem to prefer a sterically disfavored but electronically favored orientation, whereas catalysts **4–7** show the same behavior as Andersson's catalysts. What is surprising is that catalysts **2** and **3** induce such high enantioselectivities that are almost the same or, in the case of **3**, even higher compared with those recorded for the β-methyl-substituted ester **S1**. The perception that α-substituted α,β-unsaturated esters are more difficult substrates than the β-methyl-substituted analogues apparently does not apply to all catalysts.

For catalyst **2** a positive effect on the enantioselectivity with increasing steric demand of the ester group was evident. Consequently, substrates **S5** and **S6** were evaluated to further investigate the influence of the ester group (Table 3). The products **P5** and **P6** were formed with excellent selectivity with (*S*)-**2** giving the *R*-configured products **S5** in 96% *ee* and **S6** in 97% *ee*. Evidently, primary and secondary alkyl ester groups are well tolerated. However, as found later for a different carboxylic acid derivative **S12** (Table 6), a *tert*-butyl ester group slows down the reaction considerably resulting in incomplete conversion for catalysts **2–4**. Apparently, there is a limit to the size of the functional groups that can be accommodated by these sterically encumbered catalysts.

Table 3. Enantioselective hydrogenation of (*E*)-α-methylcinnamic esters **S5** and **S6**.



S5 R = *n*Hept
S6 R = *i*Bu

P5 R = *n*Hept
P6 R = *i*Bu

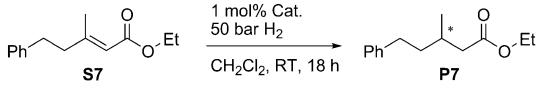
Entry	Catalyst	*ee* [%] **P5**[a]	*ee* [%] **P6**[a]
1	**1** (*S*)	78 (*R*)	75 (*R*)
2	**2** (*S*)	96 (*R*)	97 (*R*)
3	**3** (*R*)	74 (*S*)	89 (*S*)

[a] Full conversion was obtained for all entries.

Many catalysts that perform well with substrates that have aromatic substituents on the C=C bond fail to give appreciable levels of enantioselectivity when the aryl group is replaced with an alkyl group. Therefore, we extended our study to the β-alkyl substituted 1,4-unsaturated ester **S7** and α-substituted analogues **S8** and **S9** to identify the most suitable catalysts for these more demanding substrates.

Ester **S7** was efficiently reduced by iridium catalysts **1–5** but conversion was incomplete with the less reactive six-membered ring analogues **6** and **7** (Table 4). Excellent enantioselectivity was obtained with catalyst (*S*)-**2** producing (*R*)-**P7** in 94% *ee*. Iridium complex (1*R,2R,2′R*)-**4** was also highly selective to give (*S*)-**P7** in 93% *ee*, whereas the diastereomer (1*S,2R,2′R*)-**5** led to the *R* isomer with 88% *ee*, indicating that the product configuration is controlled by the stereogenic center in the carbocyclic ring, as observed before for cinnamic acid esters.

Table 4. Enantioselective hydrogenation of (*E*)-ethyl β-methyl-5-phenylpent-2-enoate **S7**.



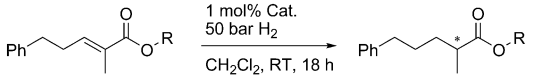
S7 **P7**

Entry	Catalyst	*ee* [%] **P7**[a]
1	**1** (*S*)	86 (*R*)
2	**2** (*S*)	94 (*R*)[b]
3	**3** (*R*)	40 (*S*)
4	**4** (1*R,2R,2′R*)	93 (*S*)
5	**5** (1*S,2R,2′R*)	88 (*R*)
6	**6** (1*R,2R,2′R*)	86 (*S*) (95)
7	**7** (1*S,2R,2′R*)	67 (*R*) (95)

[a] All conversions less than complete are listed next to the *ee* value in brackets. [b] Catalyst (*S*)-**2** produced **P7** in 94% *ee* with $[\alpha]_D^{20}$ ($c=0.71$, $CHCl_3$), consistent with the values in literature for the *R* enantiomer.

For the α-substituted esters, complexes **2** and **4** were again the most enantioselective catalysts (Table 5). The highest *ee* value of 96% was obtained in the hydrogenation of ethyl ester **S8** with catalyst **2**. In line with the results recorded for α- and β-methyl cinnamates **S1** and **S3**, the enantioselectivity was higher than for the corresponding β-methyl analogue (96 vs. 94% *ee*). Catalysts **1** and **3** were poorly suited for this type of substrate giving low enantioselectivities for substrates **S8** and **S9**.

Table 5. Enantioselective hydrogenation of (*E*)-α-methyl-5-phenylpent-2-enoic esters **S8** and **S9**.



S8 R = Et
S9 R = *i*Pr

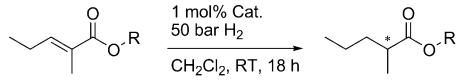
P8 R = Et
P9 R = *i*Pr

Entry	Catalyst	*ee* [%] **P8**[a]	*ee* [%] **P9**[a]
1	**1** (S)	11 (+)	16 (−)
2	**2** (*S*)	96 (−)	93 (−)
3	**3** (R)	64 (+)	51 (+)
4	**4** (1*R,2R,2′R*)	91 (−)	93 (−)
5	**5** (1*S,2R,2′R*)	68 (+) (86)	81 (+)
6	**6** (1*R,2R,2′R*)	89 (−)	79 (−) (96)
7	**7** (1*S,2R,2′R*)	33 (+) (67)	60 (+) (89)

[a] Conversions less than complete are listed next to the *ee* value in brackets.

Hydrogenation of purely aliphatic esters **S10–12** proved to be more difficult (Table 6). With the ethyl ester **S10**, only

Table 6. Enantioselective hydrogenation of (*E*)-α-methylpent-2-enoic esters **S10**–**12**.



S10 R = Et
S11 R = *i*Pr
S12 R = *t*Bu

P10 R = Et
P11 R = *i*Pr
P12 R = *t*Bu

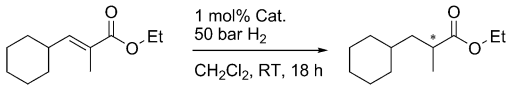
Entry	Catalyst	*ee* [%] **P10**[a]	*ee* [%] **P11**[a]	*ee* [%] **P12**[a]
1	**1** (*S*)	3 (−)	27 (−)	–
2	**2** (*S*)	71 (−)	91 (−)	87 (−) (34)
3	**3** (*R*)	42 (+)	82 (+)	n.d. (1)
4	**4** (1*R*,2*R*,2′*R*)	84 (−)	88 (−)	74 (−) (70)
5	**5** (1*S*,2*R*,2′*R*)	76 (+)	–	–

[a] Conversions less than complete are listed next to the *ee* value in brackets.

catalyst **4** reacted with appreciable enantioselectivity (84% *ee*). Catalyst **2** that gave 96% *ee* in the hydrogenation of the 4-phenyl-substituted analogue **S8**, induced only 71% *ee*. Obviously, the remote phenyl group in substrates **S8** and **S9** has a surprisingly strong effect, possibly by interaction of the π-system with the catalyst.

Complex (*S*)-**2** hydrogenated the isopropyl ester **S11** to produce (−)-**P11** with 91% *ee*, in close agreement with the selectivity for the analogous distal phenyl-substituted **S9**. Catalyst **4** was similarly selective yielding **P11** with 88% *ee*. The *tert*-butyl ester **S12** was much less reactive than the corresponding ethyl and isopropyl esters, resulting in incomplete conversion. In the hydrogenation of substrate **S13** these catalysts showed very low enantioselectivity, with the exception of complex **6** that led to product **P13** with 68% *ee* but incomplete conversion (Table 7).

Table 7. Enantioselective hydrogenation of (*E*)-ethyl 3-cyclohexyl-2-methylacrylate **S13**.



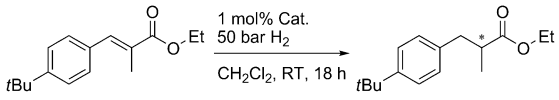
S13 **P13**

Entry	Catalyst	Conv. [%] **P13**	*ee* [%] **P13**
1	**2** (*S*)	100	45 (+)
2	**3** (*R*)	100	13 (−)
3	**4** (1*R*,2*R*,2′*R*)	100	32 (+)
4	**5** (1*S*,2*R*,2′*R*)	100	16 (−)
5	**6** (1*R*,2*R*,2′*R*)	80	68 (+)
6	**7** (1*S*,2*R*,2′*R*)	42	9 (+)

Substrate **S14** proved to be unexpectedly difficult to reduce and full conversion could not be reached with 1 mol% catalyst loading using standard conditions (Table 8). Why the remote *tert*-butyl group has such a pronounced effect is unclear. Nevertheless, catalyst **2** produced **P14** in an excellent 94% *ee* and 91% conversion.

Next, the substituent at the α position next to the ester group was varied. Incorporation of a phenyl group at this position gave substrates **S15** and **S16**. These bulky esters

Table 8. Enantioselective hydrogenation of (*E*)-ethyl 3-(4-*tert*-butylphenyl)-2-methylacrylate **S14**.

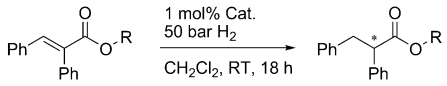


S14 **P14**

Entry	Catalyst	Conv. [%] **P14**	*ee* [%] **P14**
1	**1** (*S*)	90	71 (*R*)
2	**2** (*S*)	91	94 (*R*)
3	**3** (*R*)	63	64 (*S*)
4	**4** (1*R*,2*R*,2′*R*)	23	22 (*R*)

proved very difficult to reduce at 1 mol% catalyst loading and full conversion was not achieved for any of the attempted hydrogenations (Table 9). However, useful levels of con-

Table 9. Enantioselective hydrogenation of (*E*)-2,3-diphenylacrylate esters **S15** and**16**.



S15 R = Et
S16 R = *i*Pr

P15 R = Et
P16 R = *i*Pr

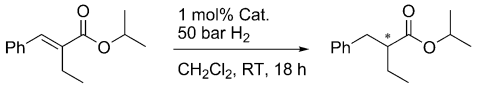
Entry	Catalyst	Conv. [%] **P15**	*ee* [%] **P15**	Conv. [%] **P16**	*ee* [%] **P16**
1	**1** (*S*)	41	89 (*S*)	80	97 (+)
2	**2** (*S*)	8	67 (*R*)	7	42 (−)
3	**3** (*R*)	90	57 (*R*)	86	82 (−)
4	**4** (1*R*,2*R*,2′*R*)	2	n.d.	–	–

version and enantioselectivity were obtained with catalyst (*S*)-**1**, which gave the *R*-configured product **P16** in 97% *ee* and 80% conversion. The more sterically encumbered complexes **2** and **4** showed almost no reaction, which is not surprising considering the severe steric shielding of the C=C bond by the two phenyl groups.

The α-ethyl-substituted ester **S17** proved to be a more problematic substrate than the α-methyl analogue **S4** (Table 10). Catalyst **3** performed best in this case with the *R* complex giving product (+)-**P17** in 88% *ee* and full conversion.

Hydrogenation of the lactone **S18** was very sensitive to the reaction conditions (Table 11). Hydrogenations stopped at conversions of less than 10% and indicated higher enan-

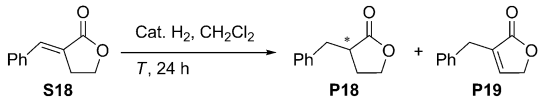
Table 10. Enantioselective hydrogenation of (*E*)-isopropyl 2-benzylidenebutanoate **S17**.



S17 **P17**

Entry	Catalyst	Conv. [%] **P17**	*ee* [%] **P17**
1	**1** (*S*)	36	n.d.
2	**2** (*S*)	89	78 (−)
3	**3** (*R*)	100	88 (+)

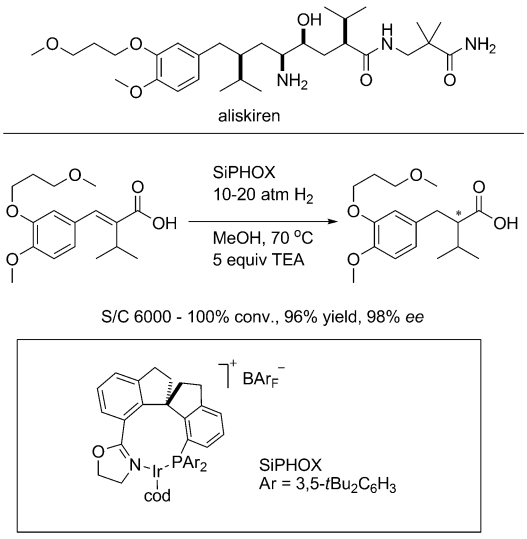
Table 11. Enantioselective hydrogenation of (*E*)-3-benzylidenedihydrofuran-2(3H)-one **S18**.



Entry	Catalyst	Catalyst loading [mol%]	*T* [°C]	P [bar]	Conv. [%]	**P19** iso [%]	*ee* [%]
1	**1** (*S*)	1	RT	100	80	5	84 (−)
2	**1** (*S*)	1	RT	3	0	0	0
3	**1** (*S*)	2	RT	3	0	0	0
4	**1** (*S*)	3	RT	3	15	0	70 (−)
5	**2** (*S*)	1	RT	100	26	1	23 (+)
6	**3** (*R*)	1	RT	100	98	1	86 (+)
7	**3** (*R*)	1	80	55	100	0	70 (+)
8	**3** (*R*)	1	0	90	2	0	n. d.
9	**3** (*R*)	2	0	90	94	0	89 (+)
10	**4** (1*R*,2*R*,2′*R*)	1	RT	100	26	23	70 (+)
11	**4** (1*R*,2*R*,2′*R*)	2	RT	100	93	6	70 (+)

tioselectivity with catalyst **1**, however, as the reaction proceeded a steady loss of *ee* value was observed. Isomerized lactone **P19** was detected by GC-MS and ^{1}H NMR spectroscopy and quantified by GC, indicating that the observed decrease in *ee* value could be due a competing isomerization–hydrogenation sequence via **P19**. Lower temperature and 2 mol% catalyst loading of iridium complex **3** gave **P18** in 89% *ee* and 94% conversion at 90 bar of hydrogen pressure; higher temperature gave better conversion but at a loss of enantioselectivity.

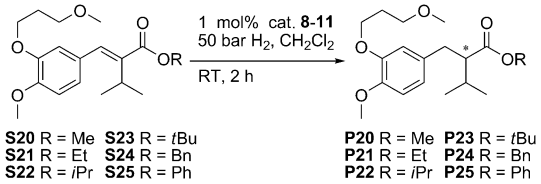
An important α,β-unsaturated acid intermediate used in the synthesis of the renin inhibitor aliskiren was reduced with high efficiency and enantioselectivity by the group of Zhou with an Ir-SiPHOX catalyst, a rigid large ring chelate complex incorporating the coordinating units of PHOX (Scheme 1).[3] Since the enantioselective reduction of analogous esters had not been reported yet, we decided to investigate the hydrogenation of substrates **S20–25**, which would allow for alternative synthetic approaches to aliskiren.

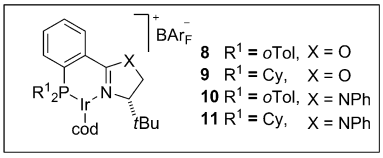


Scheme 1. Ir–SiPHOX-catalyzed asymmetric hydrogenation of an aliskiren precursor developed by Zhou et al.[3]

Unfortunately, complexes **1–7** reacted with poor enantioselectivity and conversion with esters **S20–25**. However, in an extensive screening of different N,P complexes, the phosphino–oxazoline (PHOX) as well as phosphino–imidazoline (PHIM) complexes emerged as more promising catalysts. The best results were obtained with catalysts **8–11** (Table 12). Increasing the steric hindrance of the ester group

Table 12. Asymmetric hydrogenation of aliskiren intermediate esters **S20–25**.[a]





Entry	Substrate	R	**8** *ee* [%]	**9** *ee* [%]	**10** *ee* [%]	**11** *ee* [%]
1	**S20**	Me	65 (+)	70 (+)	80 (+)[b]	60 (+)[c]
2	**S21**	Et	83 (+)	87 (+)	90 (+)	74 (+)
3	**S22**	*i*Pr	92 (+)	92 (+)	97 (+)	92 (+)
4	**S23**	*t*Bu	99 (+)[d]	99 (+)[e]	99 (+)[f]	95 (+)[f]
5	**S24**	Bn	81 (+)	85 (+)	90 (+)	77 (+)
6	**S25**	Ph	78 (+)	72 (+)[g]	91 (+)[h]	88 (+)

[a] Full conversion was obtained unless otherwise noted. [b] 67% conversion. [c] 96% conversion. [d] 24% sat. carboxylic acid was formed. [e] 31% sat. carboxylic acid was formed. [f] 13% sat. carboxylic acid was formed. [g] 93% conversion. [h] 81% conversion.

clearly had a beneficial effect on the overall enantioselectivity for complexes **8–11** with the exception of the phenyl ester **S25**. The sterically demanding PHIM complex **10** performed consistently in the good to excellent enantioselectivity range for the different esters. Clearly the highest enantioselectivities were achieved with this catalyst in the hydrogenation of the isopropyl and *tert*-butyl ester. Complexes **8**, **9**, and **11** also gave very high levels of *ee* value with the *tert*-butyl ester **S23**, however, formation of variable amounts of the corresponding saturated carboxylic acid as a side product was a recurrent problem, which we attribute to the Brønsted acidity of Ir hydrides formed as intermediates in the catalytic cycle.[14]

Conclusion

The high enantioselectivities obtained in the hydrogenation of various α,β-unsaturated carboxylic esters with aryl or alkyl substituents at the C=C bond show that iridium com-

plexes derived from chiral N,P ligands are efficient catalysts for this transformation. As expected none of the complexes that we evaluated emerged as a universal catalyst. Depending on the substitution pattern of the substrate, different ligands perform best. For instance, iridium complex **2** outperforms the less sterically demanding complex **1** by a considerable degree of enantioselectivity for a variety of substrates but not all, which highlights the advantage of a modular approach to the synthesis of catalysts and the need for screening groups of catalysts with tuneable steric and electronic properties. Our results also show that α,β-unsaturated carboxylic esters substituted at the α position are less problematic substrates than originally anticipated based on previous studies. In some cases α-substituted substrates actually reacted with higher enantioselectivity than their β-substituted analogues. Pyridine-based N,P complexes proved to be excellent catalysts for sterically accessible unsaturated esters, whereas for the sterically more demanding aliskiren precursors **S20**–**S22** with an isopropyl substituent in the α position, phosphinooxazoline and phosphinoimidazoline complexes emerged as superior catalysts.

Experimental Section

Typical catalyst synthesis: (*R*)-2-Mesityl-4-methyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-7-ol (50 mg, 189 μmol) was added to a dry Young tube that was evacuated and backfilled with argon three times. Potassium hydride (11 mg, 281 μmol) was added followed by di-*tert*-butylchlorophosphine (34 mg, 189 μmol) and DMF (450 μL). The reaction mixture was stirred for 48 h and the solvent evaporated at high vacuum using a hot water bath (60 °C) to afford a red foam that was redissolved in dry THF (500 μL). The resulting suspension was filtered using a syringe and a micron filter inside a glove box and the filtrate (including 2×500 μL washings with THF) was collected into a vial containing a solution of [Ir(cod)$_2$]BArF (BArF = tetrakis[bis-3,5-(trifluoromethyl)phenyl]borate; 240 mg, 189 μmol) in THF (1 mL). The resulting dark red solution was stirred for 6 h and adsorbed onto silica gel. Column chromatography (SiO_2, 2×10 cm hexane/diethyl ether (1:1)) followed by elution of the product with CH_2Cl_2 afforded a dark red solid that was dissolved in CH_2Cl_2 (1 mL) and layered with hexane (4 mL). The biphasic mixture was stored in a refrigerator for 48 h to yield catalyst **2** as dark red crystals (120 mg, 76.2 μmol, 40 %). For analytical data, see ref. [8].

Typical procedure for Ir-catalyzed hydrogenation: Catalyst **1** (24.0 mg, 15.8 μmol, 1.0 mol %) was added to a solution of (*E*)-ethyl 3-phenylbut-2-enonate (**S1**, 300 mg, 1.58 mmol) in dry CH_2Cl_2 (7.9 mL). The reaction vial was equipped with a magnetic stirrer bar and placed in an autoclave that was pressurized to 50 bar with H_2. The reaction mixture was stirred at 800 rpm for 2 h and, after this time, hydrogen was released and the solvent removed under reduced pressure. The mixture was filtered through a plug of silica gel (1×8 cm) using a mixture of pentane/diethyl ether (1:1, 50 mL). After evaporation of the solvent, the analytically pure hydrogenation product **P1** (292 mg, 1.52 mmol, 96 %) was obtained as a colorless liquid. Catalyst screening was performed on a 0.1 mmol scale. For analytical data, see ref. [4b]. For separation conditions, see ref. [7i].

For complete experimental procedures and analytic data see the Supporting Information.

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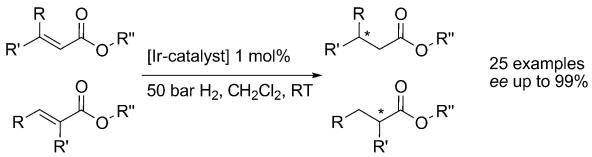
Asymmetric Synthesis

*D. H. Woodmansee, M.-A. Müller, L. Tröndlin, E. Hörmann, A. Pfaltz** ..... ▮▮▮▮–▮▮▮▮

Asymmetric Hydrogenation of α,β-Unsaturated Carboxylic Esters with Chiral Iridium N,P Ligand Complexes



Enantioselective conjugate reduction of a wide range of α,β-unsaturated carboxylic esters was achieved using chiral Ir N,P complexes as hydrogenation catalysts. The resulting saturated esters with a stereogenic center in the α or β position were obtained in high enantiomeric purity (see scheme).