Asymmetric Catalysis

DOI: 10.1002/anie.201402034

Asymmetric Hydrogenation of Maleic Acid Diesters and Anhydrides**

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Abstract: *Asymmetric hydrogenation of maleic and fumaric acid derivatives with iridium catalysts based on N,P ligands provides an efficient route to chiral enantioenriched succinates. A new catalyst derived from a 2,6-difluorophenyl-substituted pyridine-phosphinite ligand was developed and enables the conversion of a wide range of 2-alkyl and 2-arylmaleic acid diesters into the corresponding succinates in high enantiomeric purity. Mixtures of cis/trans substrates can be hydrogenated in an enantioconvergent fashion with high enantioselectivity, and further enhances the scope of this transformation. The products are valuable chiral building blocks with a structural motif found in many bioactive compounds, such as metalloproteinase inhibitors.*

Iridium complexes derived from chiral heterobidentate ligands have considerably enhanced the scope of asymmetric hydrogenation.[1] Compared to rhodium and ruthenium catalysts, which require a coordinating group near the C=C bond, iridium catalysts have been successfully used for the asymmetric hydrogenation of a much wider range of functionalized and unfunctionalized olefins. Nevertheless, there are still important substrates classes, for which suitable chiral catalysts are lacking.

Although highly enantioselective hydrogenations of α,β-unsaturated carboxylic acids, esters, amides, and ketones have been reported,[2,3] prochiral fumaric and maleic acid derivatives remain a challenging substrate class.[4] The enantioselective hydrogenation of substrates of this type would provide access to synthetically valuable 2-substituted succinic acid derivatives, which are versatile chiral building blocks and are found in a variety of biologically active molecules (Figure 1).[5–8] Examples are the matrix metalloproteinase (MMP) inhibitors **1** and **2**, the caspase 1 inhibitor **3**, and mitiglinide **4** (a drug used to treat type 2 diabetes). Thus, efficient methods for the enantioselective synthesis of substituted succinic acids and related compounds are of great interest.

So far enantiomerically enriched 2-substituted succinic acid derivatives have been synthesized by rhodium-catalyzed asymmetric hydrogenation of the corresponding itaconic acid precursors (Scheme 1 a),[9] 1,4-addition of arylboronic acids to fumaric acid di-*tert*-butyl diester or maleimides (Scheme 1 b),[10] or by organocatalytic parallel kinetic resolution of monosubstituted succinic anhydrides (Scheme 1 c).[11] While the latter method is limited to a maximum yield of 50%, the hydrogenation of itaconic acid derivatives becomes difficult when the C=C bond is tetrasubstituted, as would be required for the synthesis of compounds such as **2** or **3**. Moreover, 2-aryl-succinic acid derivatives are not accessible in this way, whereas the rhodium-catalyzed 1,4-addition is limited to arylboronic acids. Herein we report an efficient alternative approach to this class of products based on iridium-catalyzed asymmetric hydrogenation of prochiral maleic and fumaric acid derivatives.

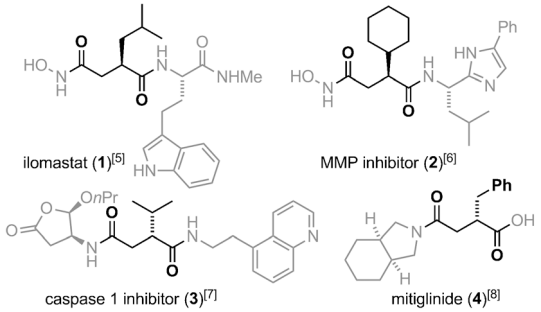
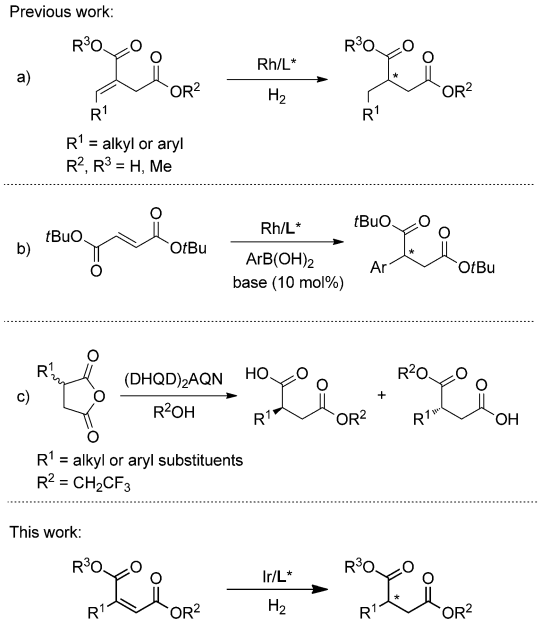


Figure 1. Structures of biologically active compounds containing a 2-substituted succinic acid moiety.



Scheme 1. Enantioselective routes to chiral 2-substituted succinic acid derivatives.

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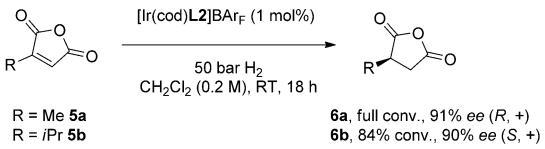
[**] We are thankful to R. Liffert for catalyst synthesis and Dr. Paolo Tosatti for helpful discussions and help with the preparation of this manuscript. Support by the Swiss National Science Foundation is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201402034.

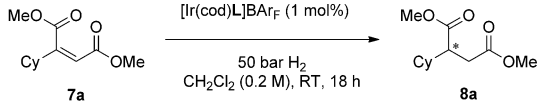


Scheme 2. Iridium-catalyzed asymmetric hydrogenation of maleic anhydrides. See Table 1 for ligand structure. BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

We first studied the hydrogenation of the maleic anhydrides **5a** and **5b** (Scheme 2). In an initial screening using 12 chiral iridium complexes and **5a** as a test substrate, the complex derived from the NeoPHOX ligand **L2** emerged as the best catalyst (see the Supporting Information). With this catalyst **5a** and **5b** could be converted into the corresponding succinic anhydrides **6a** and **6b** in good yield and high enantioselectivity. However, the poor solubility of other maleic anhydrides in dichloromethane prompted us to examine the corresponding diesters, which are more soluble and easily prepared in one step from dimethyl acetylenedicarboxylate.[12]

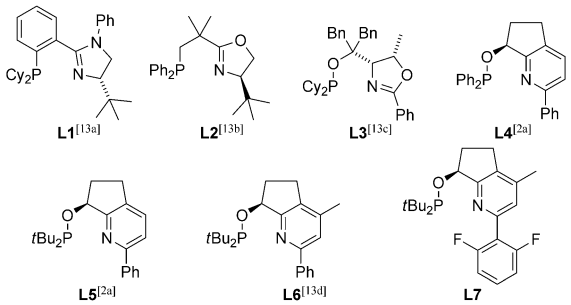
We first examined the asymmetric hydrogenation of dimethyl 2-cyclohexylmaleate (**7a**) using a selection of catalysts, based on N,P ligands (**L1**–**L7**), under standard reaction conditions (Table 1). The catalyst derived from **L2**, which had performed best with **5a** and **5b**, showed high enantioselectivity but poor reactivity, thus resulting in low conversion. Similar *ee* values but much higher conversions

Table 1: Ligand screening for the asymmetric hydrogenation of 2-cyclohexyl dimethyl maleate (**7a**).[a]



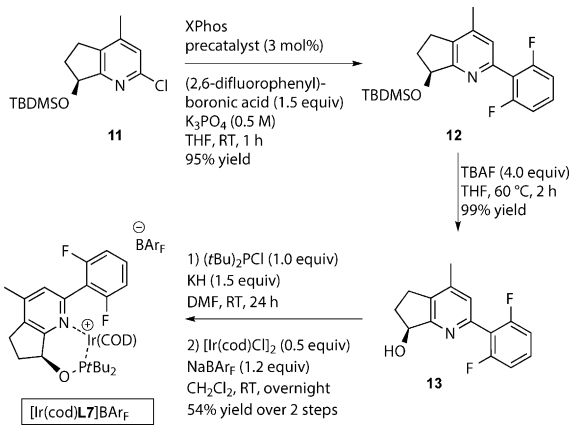
Entry	L	Conversion [%][b]	*ee* [%][c]
1	**L1**	63	19 (−)
2	**L2**	26	90 (+)
3	**L3**	86	77 (−)
4	**L4**	41	77 (+)
5	**L5**	96	92 (+)
6	**L6**	98	96 (+)
7	**L7**	>99	99 (+)

[a] Reaction conditions: substrate (0.1 mmol), catalyst (1 mol%), CH_2Cl_2 (0.5 mL, 0.2 M). [b] Conversions were determined by GC analysis. [c] Enantioselectivities were determined by GC analysis using a chiral stationary phase.



were achieved with the catalyst prepared from the pyridine-phosphinite **L5**. Apparently, the tBu_2P group has a positive effect on both the enantioselectivity and reactivity compared to the Ph_2P group in the analogous ligand **L4**. Further variation of the ligand structure finally led to a virtually perfect catalyst based on the pyridine-phosphinite **L7**, which afforded the desired product **8a** with full conversion and 99% *ee*. The 2,6-difluorophenyl group in this new ligand was introduced to examine the effect of an electron-withdrawing substituent at this position and to prevent insertion of the iridium atom into an adjacent aromatic C–H bond, a process which is facile for 2-phenylpyridines and can lead to catalyst deactivation.[14]

The synthesis of this catalyst is summarized in Scheme 3. The key step is a Suzuki–Miyaura cross-coupling of the chloropyridine precursor **11**[2b] with commercially available (2,6-difluorophenyl)boronic acid using a procedure from

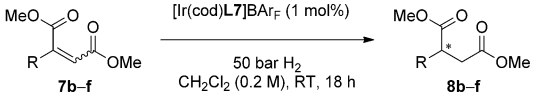


Scheme 3. Synthesis of the ligand **L7** and the corresponding [Ir**L7**-(cod)]BAr_F complex (for procedures, see the Supporting Information).

Buchwald and co-workers.[15] The reaction proceeded under mild reaction conditions to afford the (2,6-difluorophenyl)-pyridine **12** in excellent yield. Deprotection of the alcohol, followed by nucleophilic substitution with di-*tert*-butylphosphoryl chloride, and subsequent complexation afforded the complex [Ir(cod)**L7**]BAr_F in good overall yield.

To evaluate the scope of this catalyst for the hydrogenation of maleic and fumaric acid esters, we examined a series of 2-alkyl-substituted derivatives as substrates (Table 2). Remarkably, the reactivity and enantioselectivity of the catalyst proved to be rather insensitive to the steric properties of the substrate. The *ee* values obtained from methyl-, *n*-alkyl-, branched alkyl-, and even *tert*-butyl-substituted maleate were all within a narrow range of 95–99%. Surprisingly, the fumarate derivative (*E*)-**7b** afforded the same enantiomer of **8b** with virtually the same *ee* value as the corresponding maleate (*Z*)-**7b** (entries 1 and 2). This result contrasts with the general experience that hydrogenation of the *cis* and the *trans* isomer of a trisubstitued alkene leads to opposite enantiomers with iridium catalysts of this type.[1c] Accordingly, *cis*/*trans* mixtures can be hydrogenated in an enantioconvergent fashion to give the corresponding succinic

Table 2: Asymmetric hydrogenation of the alkyl-substituted dimethyl maleates and fumarates **7b–f**.[a]



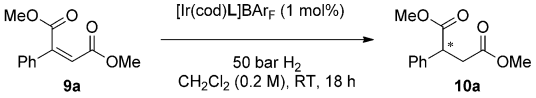
Entry	R	Conversion [%][b]	*ee* [%][c]
1	(*Z*)-**7b** (R = Me)	> 99	97 (*R*, +)
2	(*E*)-**7b** (R = Me)	> 99	98 (*R*, +)
3	(*E*/*Z*)-**7b** (R = Me)[d]	> 99	98 (*R*, +)
4	(*Z*)-**7c** (R = *n*Bu)	97	96 (+)
5	(*Z*)-**7d** (R = *i*Bu)	> 99	95 (+)
6	(*Z*)-**7e** (R = *i*Pr)	> 99	99 (*S*, +)
7	(*Z*)-**7f** (R = *t*Bu)	99	98 (*S*, +)

[a] Reaction conditions: see Table 1. [b] Conversions were determined by GC analysis. [c] Enantioselectivities were determined by GC analysis using a chiral stationary phase. [d] A 1.5:1 mixture of (*Z*)-**7b** and (*E*)-**7b** was used.

acid derivative with excellent enantioselectivity (entry 3), thus making this transformation very attractive, especially for substrates which are not easily obtained as pure *E* or *Z* isomers.

We next examined 2-aryl-substituted dimethyl maleates as substrates. In the hydrogenation of 2-phenylmaleate (**9a**), the catalyst derived from **L7** again showed the best performance, thus affording the phenylsuccinate **10a** with 96% *ee* and 95% conversion (Table 3). The ThrePHOX complex [Ir-

Table 3: Ligand screening for the asymmetric hydrogenation of dimethyl 2-phenylmaleate (**9a**).[a]



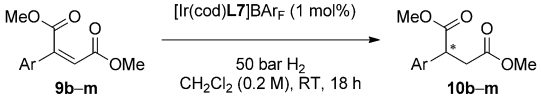
Entry	L	Conversion [%][b]	*ee* [%][c]
1	**L3**	> 99	79 (*R*, −)
2	**L5**	16	92 (*S*, +)
3	**L6**	14	89 (*S*, +)
4	**L7**	95	96 (*S*, +)

[a] Reaction conditions: see Table 1. [b] Conversions were determined by GC analysis. [c] Enantioselectivities were determined by GC analysis using a chiral stationary phase.

(cod)**L3**]BAr_F exhibited somewhat higher reactivity, but gave distinctly lower *ee* values. The complexes based on the ligands **L5** and **L6** induced good enantioselectivities, but conversions were below 20%.

Screening of a series of 2-arylmaleates with [Ir(cod)**L7**]BAr_F as the catalyst showed that both electron-rich and electron-poor aryl groups were well tolerated (Table 4, entries 5–12). A wide range of substrates with a *meta* or *para* substituent on the aryl group was hydrogenated with high enantioselectivies of 91–97% *ee*. While hydrogenation of the *para*-substituted substrates **9b**, **9e**, **9f**, **9h**, **9i**, and **9j** went to completion under standard reaction conditions, the *meta*-methylphenyl derivative **9c** required a higher catalyst loading

Table 4: Asymmetric hydrogenation of the aryl- and heteroaryl-substituted dimethyl maleates **9b–m**.[a]



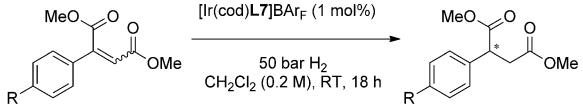
Entry	Ar	Conversion [%][b]	*ee* [%][c]
1	4-MeC_6H_4 (**9b**)	> 99	97 (+)
2	3-MeC_6H_4 (**9c**)	52	95 (+)
3[d]	3-MeC_6H_4 (**9c**)	> 99	96 (+)
4	2-MeC_6H_4 (**9d**)	2	n.d.
5	4-OMeC_6H_4 (**9e**)	> 99	97 (+)
6	4-FC_6H_4 (**9f**)	> 99	96 (+)
7	3-FC_6H_4 (**9g**)	99	95 (+)
8	4-ClC_6H_4 (**9h**)	> 99	92 (+)
9	4-$CF_3C_6H_4$ (**9i**)	> 99	91 (+)
10	4-$C_6H_4C_6H_4$ (**9j**)	> 99	97 (+)
11	4-TMSC_6H_4 (**9k**)	30	n.d.[e]
12[d]	4-TMSC_6H_4 (**9k**)	> 99	96 (+)
13	4-SMeC_6H_4 (**9l**)	0	–
14	3-thiophenyl (**9m**)	88	84 (+)

[a] Reaction conditions: see Table 1. [b] Conversions were determined by GC analysis. [c] Enantioselectivities were determined by GC or HPLC analysis using a chiral stationary phase. [d] 2 mol% of catalyst were used. [e] The *ee* value could not be determined because of overlapping peaks of unreacted **9k** and one of the enantiomers of the product in the HPLC analysis. n.d. = not determined.

of 2 mol% for full conversion (entries 2 and 3). A trimethylsilyl group in the *para* position also reduced the reactivity, but by increasing the catalyst loading to 2 mol% complete conversion to the product was achieved (entries 11 and 12). An *ortho*-methyl or a *para*-methylthio group, in contrast, were not tolerated (entries 4 and 13). The 3-thiophenyl derivative **9m** showed somewhat lower reactivity than the corresponding **9a**, but still could be hydrogenated with 88% conversion and 84% *ee* (entry 14). Overall, a diverse set of highly enantioenriched succinates with an aromatic substituent in the 2-position is available in this way.

We also examined the hydrogenation of *cis*/*trans* mixtures of 2-aryl-substituted fumarates and maleates (Table 5). In contrast to the hydrogenation of the 2-methyl-substituted analogues (Table 2, entries 2 and 3), the enantioselectivities were lower than those obtained with the pure *Z* isomers.

Table 5: Asymmetric hydrogenation of mixtures of fumarates and maleates.[a]



Entry	R	*E*/*Z*	Conv. [%][b]	*ee* [%][c]
1	(*E*/*Z*)-**9a** (R = H)	1:1.2	> 99	87 (*S*, +)
2	(*E*/*Z*)-**9b** (R = Me)	1:3.4	> 99	93 (+)
3	(*E*/*Z*)-**9i** (R = CF_3)	1:1.1	95	89 (+)
4	(*E*/*Z*)-**9j** (R = Ph)	1:1.2	> 99	88 (+)

[a] Reaction conditions: See Table 1. [b] Conversions were determined by GC analysis. [c] Enantioselectivities were determined by GC or HPLC analysis using a chiral stationary phase.

However the *ee* values were still between 87–93%, meaning that pure *cis*- and *trans*-configured substrates are not required in this case for achieving high enantiomeric ratios.

In summary, asymmetric hydrogenation of maleic and fumaric acid derivatives opens up an attractive alternative route to chiral enantioenriched succinates. The new catalyst [Ir(cod)**L7**]BAr_F, derived from a 2,6-difluorophenyl-substituted pyridine-phosphinite ligand, enables the conversion of a wide range of 2-alkyl and 2-arylmaleic acid diesters into the corresponding succinates in high enantiomeric purity. Our finding that *cis*/*trans* mixtures of substrates can be hydrogenated in an enantioconvergent fashion with high enantioselectivity further enhances the scope this transformation. The products which are available by this route are valuable chiral building blocks with a structural motif found in many bioactive compounds such as metalloproteinase inhibitors.

Received: February 3, 2014
Published online: April 7, 2014

Keywords: asymmetric catalysis · hydrogenation · iridium · N,P ligands · synthetic methods

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