Asymmetric Catalysis

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Iridium-Catalyzed Asymmetric Hydrogenation of Unfunctionalized Tetrasubstituted Olefins**

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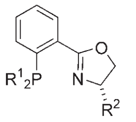
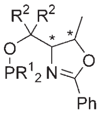
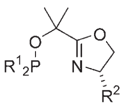
Iridium complexes with chiral N,P ligands have emerged as a new class of highly efficient catalysts for asymmetric hydrogenation with an application range that is largely complementary to rhodium and ruthenium diphosphane complexes.[1–3] They have been used successfully for the hydrogenation of a wide range of functionalized and unfunctionalized di- and trisubstituted olefins. Unlike Rh and Ru diphosphane complexes, they do not require the presence of a coordinating group near the C=C bond, so even purely alkyl-substituted olefins can be hydrogenated with high enantioselectivity.[3] However, to date no practical catalysts are known for the asymmetric hydrogenation of unfunctionalized tetrasubstituted olefins. Although Buchwald and co-workers have obtained high enantioselectivities in the hydrogenation of tetrasubstituted aryl alkenes using a chiral zirconocene complex,[4] high catalyst loadings, long reaction times, and high sensitivity of the catalyst have prevented widespread use of this method. Ir catalysts based on chiral phosphanyl oxazoline (phox) ligands **1**,[5] on the other hand, showed high activity in the hydrogenation of tetrasubstituted aryl alkenes such as **5**, but enantiomeric excesses were at best moderate (Table 1).[1a,6]



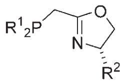
(*S*)-**1a**: R^1=Ph; R^2=*i*Pr
(*S*)-**1b**: R^1=*o*-Tol; R^2=*t*Bu



(*R*,*R*)-**2a**: R^1=Ph; R^2=Bn
(*S*,*S*)-**2b**: R^1=Cy; R^2=Bn

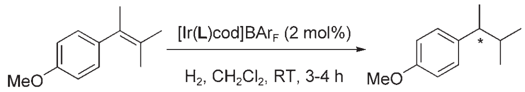


(*S*)-**3a**: R^1=Ph; R^2=*i*Pr
(*S*)-**3b**: R^1=*o*-Tol; R^2=*t*Bu



4a: R^1=Cy; R^2=*i*Pr
4b: R^1=Cy; R^2=*t*Bu
4c: R^1=Cy; R^2=CH_2*t*Bu
4d: R^1=Cy; R^2=Ph
4e: R^1=Cy; R^2=Bn
4f: R^1=*t*Bu; R^2=*i*Pr
4g: R^1=*t*Bu; R^2=*t*Bu
4h: R^1=*t*Bu; R^2=CH_2*t*Bu
4i: R^1=*t*Bu; R^2=Ph
4j: R^1=*t*Bu; R^2=Bn
4k: R^1=Ph; R^2=*i*Pr
4l: R^1=Ph; R^2=*t*Bu
4m: R^1=Ph; R^2=CH_2*t*Bu
4n: R^1=Ph; R^2=Ph
4o: R^1=Ph; R^2=Bn
4p: R^1=*o*-Tol; R^2=*i*Pr
4q: R^1=*o*-Tol; R^2=Bn

Table 1: Ir-catalyzed hydrogenation of **5**.[a]



5 **6**

Ligand L	*p* [bar]	Conversion [%][b]	*ee* [%][d]
1a	50	>99	79 (−)
1b	50	65	2 (+)
2a	50	55	5 (−)
2b	50	95	82 (−)
3a	50	95	14 (−)
3b	50	83	14 (+)
(*S*)-**4a**	50	>99	88 (−)
(*S*)-**4b**	50	>99	80 (−)
(*S*)-**4c**	50	>99	92 (−)
(*S*)-**4d**	50	>99	92 (−)
	5	>99[c]	96 (−)
	1	99	97 (−)
(*S*)-**4e**	50	>99	71 (−)
(*S*)-**4f**	50	>99	74 (−)
(*S*)-**4g**	50	>99	27 (−)
(*S*)-**4h**	50	>99	85 (−)
(*S*)-**4i**	50	>99	84 (−)
(*S*)-**4j**	50	>99	62 (−)
(*S*)-**4k**	50	>99	40 (−)
	10	>99	58 (−)
	5	>99[c]	69 (−)
(*S*)-**4l**	50	>99	30 (−)
(*S*)-**4m**	50	60	62 (−)
(*R*)-**4n**	50	>99	73 (+)
(*S*)-**4o**	50	86	48 (−)
(*S*)-**4p**	50	>99	42 (−)
(*S*)-**4q**	50	>99	79 (−)

[a] See above equation and the Supporting Information for conditions; BAr$_F$ = 3,5-di(trifluoromethyl)phenyl)borate. [b] Conversion was determined by GC. [c] *t* = 8 h. [d] Determined by GC on a chiral column.

We have recently found that Ir complexes based on the structurally simple and readily accessible phosphanyl oxazolines **4** are much better suited for such reactions.[7] A subsequent study with a wide range of ligands **4** and phosphinite oxazoline ligands of types **2** and **3** revealed that **5** and other tetrasubstituted olefins can be hydrogenated with high enantioselectivity at remarkably low catalyst loadings. Herein, we report the results of this study, which has led to highly efficient and practical Ir catalysts for the asymmetric hydrogenation of tetrasubstituted unfunctionalized olefins.

Although the phosphanylmethyloxazoline **4k** was reported by Sprinz and Helmchen[8] many years ago, ligands of this type have not, to date, received much attention.[9] Using a modified synthetic route starting from two sets of secondary phosphanes and chloromethyloxazoline com-

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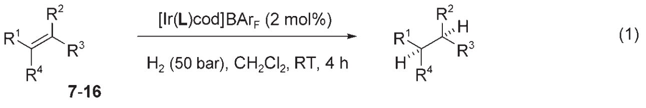
pounds derived from chloroacetyl chloride and amino alcohols,[10] we readily prepared a library of ligands **4a–q** (Cy = cyclohexyl, Bn = benzyl, *o*-Tol = *ortho*-tolyl). Among these 17 ligands, derivatives **4c** and **4d** gave *ee* values above 90% in the hydrogenation of substrate **5** (Table 1). With ligand **1b** and with phosphinites **2a**, **3a**, and **3b**, which had all been successfully used for the hydrogenation of trisubstituted olefins,[1a] the reaction was slower and led to nearly racemic product. Ligand **1a**, which gives only moderate to low enantioselectivities with trisubstituted olefins, clearly outperforms the sterically more demanding derivative **1b**. Obviously, the optimum ligand structures for tri- and tetrasubstituted olefins differ strongly. Interestingly, ligand **2b** with cyclohexyl groups at the P atom led to 95% conversion and a respectable 82% *ee*, whereas the analogous Ph_2P-substituted derivative **2a** gave only 55% conversion and 5% *ee*. In general, ligands with dialkylphosphanyl substituents seem to be better suited for this substrate than diarylphosphanyl oxazolines. Ligand **4d** showed the best overall performance for this substrate. Surprisingly, the enantiomeric excess increased from 92% at 50 bar to 97% when the pressure was lowered to 1 bar, while the reaction was still sufficiently fast to allow essentially full conversion under standard conditions.

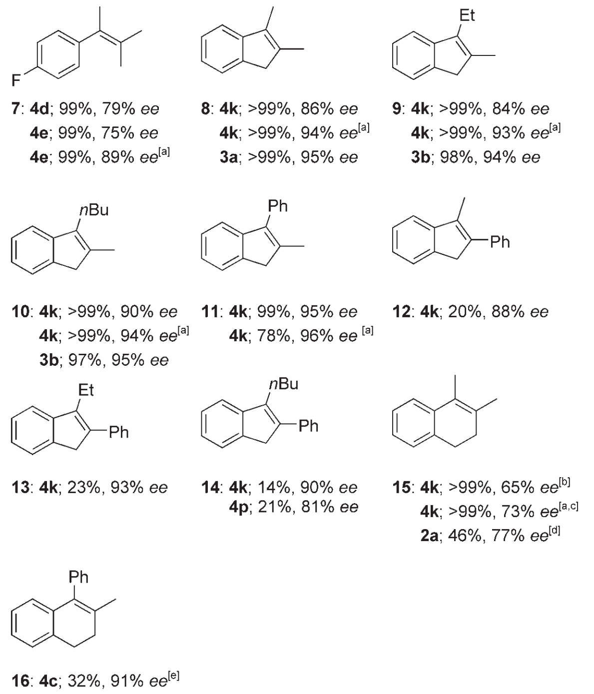
The analogous *para*-fluorophenyl-substituted alkene **7** turned out to be a more difficult substrate. The maximum enantiomeric excess at 50 bar was 79% using ligand **4d**, whereas at 5 bar up to 89% *ee* could be obtained with ligand **4e** (Scheme 1). We next tested a series of cyclic olefins **8–16**[4] (Scheme 1). The 2,3-disubstituted indenes **8–11** readily reacted, yielding high enantioselectivities under the conditions given in Equation (1). Among the phosphanylmethyloxazolines **4a–q**, ligand **4k** gave the best results for this class of substrates with 95% *ee* for indene **11**. However, the previously developed phosphinite oxazolines **3a** and **3b**[11] also proved to be efficient ligands, which outperformed ligand **4k** in the hydrogenation of **8–10**. Indenes **12–14** reacted with similarly high enantioselectivities using Ir-**4k**, but conversions were low. Importantly, no isomerization at the benzylic position was observed with Ir-**4**, so the relative configuration of the products was exclusively *cis*.[14]



(1)

As observed with substrate **5**, we obtained higher *ee* values at lower hydrogen pressures in the hydrogenation of olefins **8–11** using Ir-**4k**. For olefin **8** the enantiomeric excess increased from 86% at 50 bar to 93% at 10 bar. At 5 bar the *ee* value reached 94% with full conversion after a reaction time of 8 h. Buchwald and co-workers, on the other hand, observed the opposite trend for their zirconocene catalyst, which performed best at high pressures of up to 138 bar.[4]

Only moderate enantioselectivities could be achieved in the hydrogenation of dihydronaphthalene **15** (65% *ee* at 50 bar, 73% *ee* at 5 bar with catalyst Ir-**4k**), whereas the phenyl-substituted analogue **16** gave up to 91% *ee*, albeit with low conversion.[15] Surprisingly, in the hydrogenation of olefins **12–15**, the sense of asymmetric induction depended on the structure of the R^2 substituent at the stereogenic center of the ligand. For example, dihydronaphthalene **15** was converted to the (−)-product in 65% *ee* by (*S*)-Ir-**4k** (R^2 = *i*Pr), while (*S*)-Ir-**4m** ($R^2 = CH_2$*t*Bu) gave the (+)-product in 39% *ee* under the same conditions. Apparently, the coordination mode of the olefin depends crucially on the oxazoline substituent.



7: **4d**; 99%, 79% *ee*
4e; 99%, 75% *ee*
4e; 99%, 89% *ee*[a]

8: **4k**; >99%, 86% *ee*
4k; >99%, 94% *ee*[a]
3a; >99%, 95% *ee*

9: **4k**; >99%, 84% *ee*
4k; >99%, 93% *ee*[a]
3b; 98%, 94% *ee*

10: **4k**; >99%, 90% *ee*
4k; >99%, 94% *ee*[a]
3b; 97%, 95% *ee*

11: **4k**; 99%, 95% *ee*
4k; 78%, 96% *ee* [a]

12: **4k**; 20%, 88% *ee*

13: **4k**; 23%, 93% *ee*

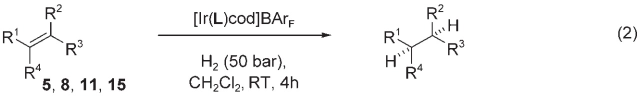
14: **4k**; 14%, 90% *ee*
4p; 21%, 81% *ee*

15: **4k**; >99%, 65% *ee*[b]
4k; >99%, 73% *ee*[a,c]
2a; 46%, 77% *ee*[d]

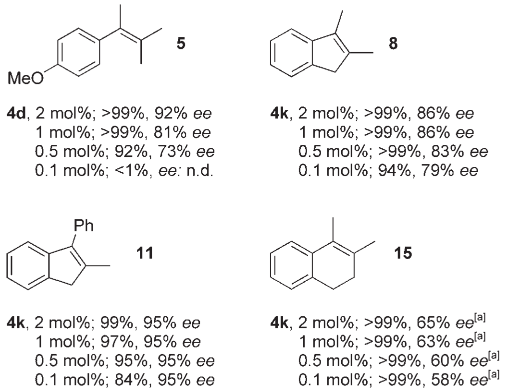
16: **4c**; 32%, 91% *ee*[e]

Scheme 1. Selected hydrogenation results; for reaction conditions, see Equation (1) and the Supporting Information. [a] 5.0 bar H_2, 8 h. [b] Over 99.8% *cis*, conversion includes 3% 1,2-dimethylnaphthalene. [c] Over 99.8% *cis*, conversion includes 11% 1,2-dimethylnaphthalene. [d] 99% *cis*, conversion includes 4% 1,2-dimethylnaphthalene. [e] Only *cis*, conversion includes traces of 2-methyl-1-phenylnaphthalene (less than 1%).

We found that in many cases high enantioselectivities and conversions could be obtained at catalyst loadings of 0.1–0.5 mol% [Eq. (2), Scheme 2]. In the hydrogenation of olefin **11**, for example, the *ee* value did not change when the amount of catalyst was reduced from 2.0 to 0.1 mol%, while conversion after the standard reaction time of 4 h decreased to 84%. Dihydronaphthalene **15**, on the other hand, still gave full conversion with 0.1 mol% of catalyst, but the enantiomeric excess decreased from 65% with 2 mol% of catalyst to 58%. Olefin **5** gave poor results at catalyst loadings below 2 mol%, possibly because of deactivating impurities.



(2)

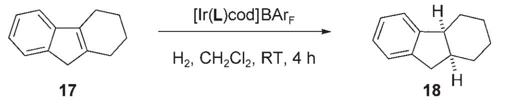


Scheme 2. Catalyst loading for selected substrates using [Ir(L)cod]-BAr_F; see Equation (2) and the Supporting Information for reaction conditions. [a] Over 99.8% *cis*, conversion includes 3% 1,2-dimethylnaphthalene.

The tricyclic ring system of **18** is found in a variety of natural products. The utility of compounds of this type as synthetic building blocks was recently demonstrated by Banwell et al., who synthesized the tetracyclic carbon framework of gibberellins from a racemic methoxy-substituted derivative of **18**.[12] We envisaged that asymmetric hydrogenation of tricycle **17**, which is easily prepared from cyclohexanone and benzaldehyde in three steps,[13] would provide an efficient enantio- and diastereoselective route to structure **18**.

Indeed, substrate **17** reacted smoothly with Ir catalysts based on ligands **4k** or **4p** to afford the desired product with high enantioselectivity and full conversion under standard screening conditions (Table 2). Surprisingly, the Ir complex with the simple, commercially available phox ligand **1a** was an even more effective catalyst and allowed the reaction to be carried out at low catalyst loadings of 0.1 mol% with excellent results. At 5 bar hydrogen pressure ligand **4p** performed best, giving 96% *ee*.

Table 2: Ir-catalyzed hydrogenation of **18**.[a]



L	Catalyst loading [mol%]	*p* [bar]	Conversion [%][b]	*ee* [%][d]
1a	2.0	50	>99	94 (+)
	1.0	50	>99	93 (+)
	0.5	50	>99	93 (+)
	0.1	50	>99	90 (+)
	2.0	5	>99[c]	94 (+)
4k	2.0	50	>99	90 (+)
4p	2.0	50	>99	93 (+)
	2.0	5	>99[c]	96 (+)

[a] For reaction conditions, see the above equation and the Supporting Information. [b] Conversion was determined by GC. [c] *t* = 8 h. [d] Determined by GC on a chiral column.

In conclusion, we have found a set of efficient, readily accessible catalysts for the asymmetric hydrogenation of tetrasubstituted unfunctionalized olefins. The remarkably high catalytic activity towards this notoriously unreactive substrate class and the option to introduce two adjacent stereogenic centers in a single step open up new possibilities in asymmetric hydrogenation.

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Keywords: asymmetric catalysis · hydrogenation · iridium · N,P ligands · tetrasubstituted olefins

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[14] In the hydrogenation of **15**, *trans* product was detected in some cases (Ir-**3b**: 13%); see the Supporting Information.
[15] In the hydrogenation of dihydronaphthalenes **15** and **16**, small amounts of aromatization product were detected; see the Supporting Information.