Asymmetric Hydrogenation Catalysts

DOI: 10.1002/anie.200601529

Iridium Catalysts with Bicyclic Pyridine–Phosphinite Ligands: Asymmetric Hydrogenation of Olefins and Furan Derivatives**

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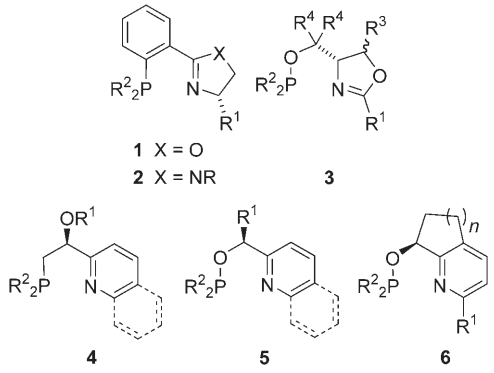
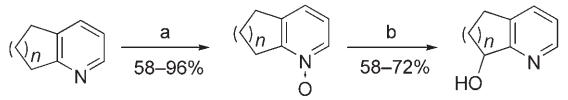
Iridium complexes with chiral N,P ligands have established themselves as efficient catalysts for the asymmetric hydrogenation of olefins, with largely complementary scope to Rh and Ru diphosphane complexes.[1] In contrast to Rh and Ru catalysts, they do not require a coordinating polar group next to the C=C bond. Initial experiments with cationic phosphanyloxazoline (phox)[2] complexes ($[Ir(\mathbf{1})(cod)]^+X^-$) (cod = cyclooctadiene) showed that these catalysts are highly active in the hydrogenation of unfunctionalized tri- and even tetrasubstituted olefins.[3] In this respect, they resemble Crabtree's catalyst, $[(Cy_3P)(pyridine)Ir(cod)]PF_6$ (Cy = cyclohexyl),[4] which provided the stimulus for the development of these catalysts. In these studies, we also found that the choice of solvent and anion is crucial as only in weakly coordinating solvents like dichloromethane or toluene with a virtually non-coordinating anion such as BAr_F (tetrakis[bis-3,5-(trifluoromethyl)phenyl]borate) could high turnover numbers (> 5000) be obtained.[1a,5] Although high enantioselectivities were obtained in the hydrogenation of certain trisubstituted aryl alkenes such as (*E*)-methylstilbene, the application range of Ir-phox catalysts proved to be limited. However, subsequent work has led to new classes of N,P ligands, which have broadened the scope of Ir-catalyzed hydrogenation considerably.[1,6,7]



Among the many structures we investigated, oxazoline-phosphinites such as **3**[1,6a,b] and certain imidazoline analogues[6c] proved to be particularly efficient, giving high enantiomeric excesses with a wide range of unfunctionalized as well as certain functionalized olefins. With the intention of mimicking the coordination sphere of the Crabtree catalysts more closely, we also examined a series of pyridine- and quinoline-derived ligands **4** and **5**.[8] As the results were quite encouraging, we decided to extend our studies to bicyclic analogues of type **6** because we thought that the more rigid conformation imposed by the additional ring could result in even higher enantioselectivities. Here we report the syntheses of a series of pyridyl–phosphinites **6** and their evaluation as ligands for Ir-catalyzed asymmetric hydrogenation.

As shown in the schemes below, ligands of this type are readily accessible from simple, commercially available starting materials via the corresponding pyridyl alcohols. By changing the substituents at the pyridine ring and the P atom, or altering the size of the carbocyclic ring, the steric and electronic properties of these ligands and the coordination geometry can be optimized for a specific substrate.

Ligands with unsubstituted backbones (**6**, $R^1 = H$) were synthesized from commercially available precursors **12–14** via pyridyl alcohols **7–9** (Scheme 1). Oxidation to the corresponding N-oxides **15–17** with aqueous hydrogen peroxide and catalytic amounts of methyltrioxorhenium (MTO),[9] subsequent Boekelheide rearrangement induced by trifluoroacetic anhydride (TFAA), and hydrolysis with aqueous LiOH led to pyridyl alcohols **7–9** in overall yields of 40, 69, and 54%, respectively.[10] Alternatively, **8** could be prepared from 8-hydroxyquinoline by hydrogenation with PtO_2 in CF_3CO_2H. However, the yield of this reaction was only 27%.



Scheme 1. Synthesis of pyridyl alcohols **7–9**: a) 0.5–5 mol% MTO (methyltrioxorhenium), 30% aq. H_2O_2 (2 equiv), CH_2Cl_2, RT; b) TFAA (trifluoroacetic anhydride) (2.5 equiv), CH_2Cl_2, 0°C to RT, 4 h; 2 M LiOH, CH_2Cl_2, RT, 3 h.

The analogous substituted pyridyl alcohols **10** and **11** were synthesized from acetophenone by the five-step sequence

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[**] Financial support from the Swiss National Science Foundation and the Federal Commission for Technology and Innovation (KTI) is gratefully acknowledged.

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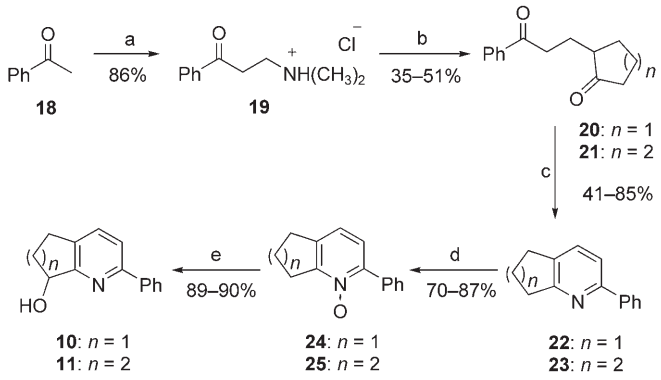
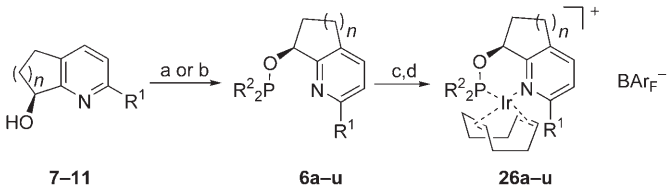
shown in Scheme 2 in overall yields of 30 and 10%, respectively.[11] In this case, 3-chloroperbenzoic acid gave better yields of pyridine N-oxides than MTO/H_2O_2.



Scheme 2. Synthesis of pyridyl alcohols **10** and **11**: a) $[H_2C{=}N(CH_3)_2]Cl$ (1 equiv), acetonitrile, reflux, 1 h; b) cyclopentanone morpholine enamine or cyclohexanone pyrrolidine enamine, dioxane, reflux, 16 h; c) HO-NH_3Cl (1 equiv), ethanol, reflux, 3 h; d) *m*-CPBA (1.2 equiv), CH_2Cl_2, 0°C to RT, overnight; e) TFAA (2.5 equiv), CH_2Cl_2, 0°C to RT, 4 h; 2 M LiOH, CH_2Cl_2, RT, 3 h.

The racemic pyridyl alcohols **7**–**11** were resolved by preparative HPLC on a chiral column.[12] This method proved to convenient for preparing ligands on a 0.5 to 5.0-g scale. However, enantioselective routes based on kinetic resolution or asymmetric reduction of the corresponding ketones are available.[13,14] The enantiopure alcohols **7**–**11** were converted into the corresponding phosphinites **6** either by treatment with diaryl (*N*,*N*-diethylamino)phosphane/4,5-dichloroimidazole/NEt_3 in CH_2Cl_2 or by deprotonation with NaH in THF/DMF (9:1) and subsequent treatment with dialkyl chlorophosphane (Scheme 3). The corresponding Ir(cod) complexes

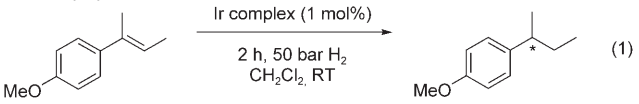


Scheme 3. Synthesis of phosphinite complexes **26a**–**u**: a) Ar_2PNEt_2/4,5-dichloroimidazole/triethylamine (1:1:1, 2 equiv), CH_2Cl_2, 0°C to RT, 1 to 9 d; b) Alk_2PCl (1 equiv), NaH (1.3 equiv), THF/DMF (9:1), 0°C to RT, 1 to 4 d; c) $[Ir(cod)Cl]_2$ (0.5 equiv), CH_2Cl_2, 50°C, 2 h; $NaBAr_F$ (1.3 equiv), RT, 2 min; H_2O, RT, 15 min.

26 were obtained following the standard protocol[3] as orange to red crystalline solids. The absolute configuration of complexes **26c**, **26f**, **26k**, **26o**, **26t**, and **26u** was assigned by X-ray analysis.[13] The absolute configuration of the corresponding phosphinites and pyridyl alcohols was deduced based on these structures.

Complexes **26a**–**u** were evaluated as catalysts in the hydrogenation of a series of alkenes that have previously been used as test substrates.[1] Table 1, which lists a comprehensive data set for alkene **27**, reveals several important trends in the

Table 1: Iridium-catalyzed hydrogenation of (*E*)-2-(4-methoxyphenyl)-2-butene (**27**).[a,b]

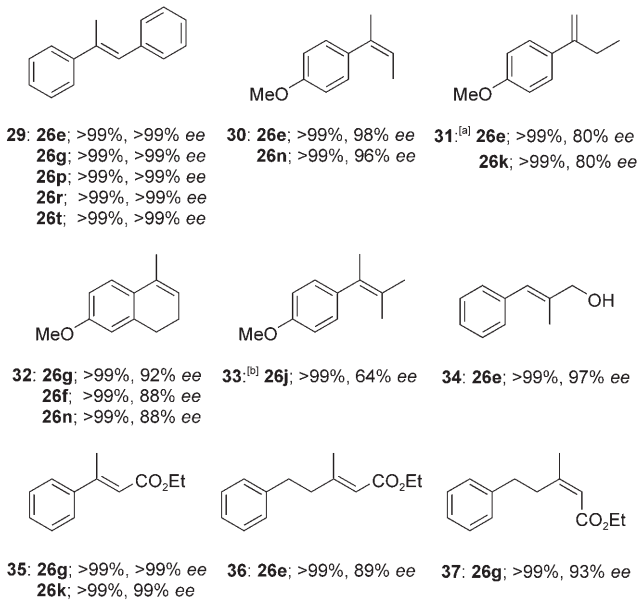


Catalyst	*n*	R^1	R^2	*ee* [%][c]
26a (*R*)	1	H	Ph	78 (*R*)
26b (*R*)	1	H	*o*Tol	74 (*R*)
26c (*R*)	1	H	Cy	68 (*R*)
26d (*R*)	1	H	*t*Bu	72 (*R*)
26e[d] (*R*)	1	Ph	*o*Tol	>99 (*R*)
26f (*R*)	1	Ph	Cy	97 (*R*)
26g (*S*)	1	Ph	*t*Bu	>99 (*S*)
26h (*R*)	2	H	Ph	82 (*R*)
26i (*S*)	2	H	*o*Tol	83 (*S*)
26j (*R*)	2	H	Cy	70 (*R*)
26k (*S*)	2	H	*t*Bu	75 (*S*)
26l (*S*)	2	H	furyl	71 (*S*)
26m[18] (*R*)	2	Me	Ph	86 (*R*)
26n[18] (*R*)	2	Me	*o*Tol	97 (*R*)
26o[18] (*S*)	2	Me	Cy	95 (*S*)
26p[18] (*S*)	2	Me	*t*Bu	97 (*S*)
26q (*S*)	2	Ph	Ph	96 (*S*)
26r (*S*)	2	Ph	*o*Tol	>99 (*S*)
26s (*R*)	2	Ph	Cy	89 (*R*)
26t (*S*)	2	Ph	*t*Bu	96 (*S*)
26u (*S*)	3	H	Ph	82 (*S*)

[a] See Equation (1) for conditions and Refs. [1a, 3] for experimental procedures. [b] Conversion was determined by GC.[3] [c] Determined by chiral HPLC.[3] [d] The diphenylphosphinite analogue formed only catalytically inactive $[IrL_2][BAr_F]$.

observed enantioselectivities. Introduction of a substituent next to the pyridine N atom strongly increases the *ee* obtained (cf. **26b** vs. **26e** and **26i** vs. **26n** and **26r**). For catalysts **26m** and **26q**, which contain a substituted pyridine ring, the enantioselectivities rise substantially when the P-phenyl groups are replaced by *ortho*-tolyl groups, an effect that has also been observed for phox ligands.[3] Di-*tert*-butyl phosphinites (in particular **26g** and **26t**) give better results than the analogous cyclohexyl phosphinites (**26f** and **26s**). For unsubstituted pyridine derivatives **26a**, **26h**, and **26u** the size of the carbocyclic ring seems to have little influence. However, for substituted analogues ($R^1 = Ph$) larger differences are observed between the five- and six-membered ring derivatives (cf. **26g** vs. **26t** and **26f** vs. **26s**). In general, the five-membered ring derivatives induce higher enantioselectivities, although exceptions have been found for other substrates.[15] Three catalysts (**26e**, **26g**, and **26r**) react with essentially 100% enantioselectivity.

Selected results for differently substituted unfunctionalized alkenes **29**–**33**, allylic alcohol **34**, and α,β-unsaturated esters **35**–**37** are listed in Figure 1. A comparison with the results obtained with pyridine- and quinoline-derived ligands **4** and **5** clearly demonstrates that the additional carbocyclic ring improves the enantioselectivity. With the exception of the terminal olefin **31** and the problematic tetrasubstituted alkene **33**, for which no highly selective Ir catalyst has yet been reported,[16] the enantiomeric excesses match or, as in



29: **26e**; >99%, >99% *ee*
26g; >99%, >99% *ee*
26p; >99%, >99% *ee*
26r; >99%, >99% *ee*
26t; >99%, >99% *ee*

30: **26e**; >99%, 98% *ee*
26n; >99%, 96% *ee*

31:[a] **26e**; >99%, 80% *ee*
26k; >99%, 80% *ee*

32: **26g**; >99%, 92% *ee*
26f; >99%, 88% *ee*
26n; >99%, 88% *ee*

33:[b] **26j**; >99%, 64% *ee*

34: **26e**; >99%, 97% *ee*

35: **26g**; >99%, >99% *ee*
26k; >99%, 99% *ee*

36: **26e**; >99%, 89% *ee*

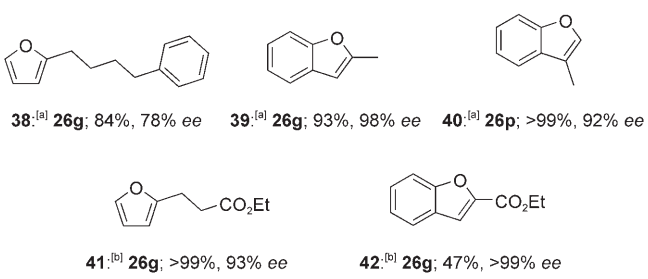
37: **26g**; >99%, 93% *ee*

Figure 1. Selected hydrogenation results; see Table 1 for reaction conditions. [a] 30 min, 1 bar H_2; [b] 2 mol% catalyst.

the case of substrate **30**, surpass the best values reported to date.[1]

Subsequent screening of other potential substrates showed that these catalysts also allow the asymmetric reduction of furan derivatives, a class of substrate for which no efficient enantioselective catalysts were known. In previous studies of furyl-substituted alkenes, we had found that with certain Ir complexes derived from oxazoline–dialkylphosphinite ligands **3**, both the olefinic C=C bond and the furan π system were reduced.[17] The stereoselectivities were, however, moderate. Catalysts **26g** and **26p** proved to be more efficient and induced good to excellent enantioselectivities in the hydrogenation of a series of substituted furans and benzofurans (Figure 2). As expected, the benzene ring of substrates **40** and **42** was not reduced. Ligands with bulky electron-rich $(t\mathrm{Bu})_2$P groups were found to be best suited for this class of substrate. Ligands with cyclohexyl substituents at the P atom gave lower conversion and *ee*, whereas catalysts with analogous diphenylphosphinite ligands showed essentially no activity. Because of the low reactivity of the furan and benzofuran π systems, elevated temperatures and relatively long reaction times were necessary. The benzofuran carboxylate ester **42**, in particular, reacted only sluggishly, albeit with virtually perfect enantioselectivity. Overall, catalysts like **26g** and **26p** open up an attractive enantioselective route to tetrahydrofuran and benzodihydrofuran systems, which are structural motifs found in many natural products and biologically active compounds.

In summary, the results obtained so far indicate a remarkably broad scope for Ir catalysts derived from pyridine–phosphinite ligands **6**. Moreover, we have recently found that complexes **26e**, **26g**, and **26r** are also highly efficient catalysts for the asymmetric hydrogenation of purely alkyl-substituted olefins.[15] Thus, we are confident that these catalysts will find many further applications in asymmetric hydrogenation.



38:[a] **26g**; 84%, 78% *ee*

39:[a] **26g**; 93%, 98% *ee*

40:[a] **26p**; >99%, 92% *ee*

41:[b] **26g**; >99%, 93% *ee*

42:[b] **26g**; 47%, >99% *ee*

Figure 2. Representative hydrogenation results for furan and benzofuran derivatives. [a] 1 mol% catalyst, 50 bar H_2, 24 h, 40°C; [b] 2 mol% catalyst, 100 bar H_2, 24 h, 40°C.

Received: April 18, 2006
Published online: July 5, 2006

Keywords: asymmetric catalysis · hydrogenation · iridium · ligand design · N,P ligands

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[18] For preparation of complexes **26m–p** see the Supporting Information.

