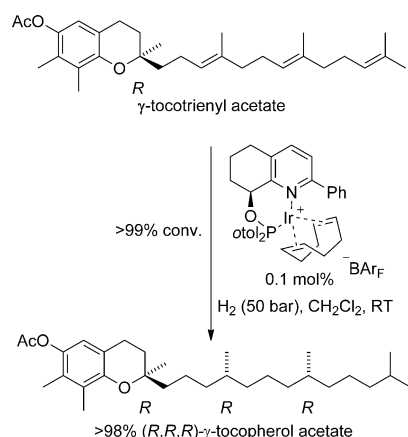


Chiral N-Heterocyclic Carbene/Pyridine Ligands for the Iridium-Catalyzed Asymmetric Hydrogenation of Olefins**

Andreas Schumacher, Maurizio Bernasconi, and Andreas Pfaltz*

The development of chiral iridium catalysts, which were inspired by the Crabtree catalyst,^[1] has considerably enhanced the application range of the asymmetric hydrogenation of olefins.^[2] In contrast to rhodium and ruthenium diphosphine complexes, the iridium-based catalysts do not require a coordinating group near the C=C bond and, therefore, enable the hydrogenation of a much wider range of alkenes.

Most iridium catalysts developed so far are cationic iridium(I) complexes derived from chiral bidentate N,P ligands containing an oxazoline or another N heterocycle as a coordinating unit.^[2,3] Typical examples are pyridine phosphinite complexes such as the catalyst shown in Scheme 1,



Scheme 1. Diastereoselective synthesis of (*R,R,R*)- γ -tocopherol acetate.^[4]

which for the first time have allowed the hydrogenation of purely alkyl-substituted C=C bonds with high efficiency and enantioselectivity.^[4] The potential of these catalysts is illustrated by the highly stereoselective, catalyst-controlled hydrogenation of γ -tocotrienyl acetate, thus introducing two stereogenic centers in the desired *R,R* configuration in one

step.^[4a,d] In addition to alkenes bearing only alkyl or aryl substituents in the vicinity of the C=C bond, a wide variety of functionalized olefins with coordinating or noncoordinating groups, as well as furans and indoles have been successfully hydrogenated with high enantioselectivity using chiral iridium N,P-complexes.^[2,5]

Burgess and co-workers have introduced a new type of oxazoline-based C,N ligand containing an N-heterocyclic carbene (NHC) instead of a phosphine unit.^[6] The iridium C,N-complex **1** (Figure 1) with a 2-adamantylloxazoline moiety and an *N*-(2,5-diisopropylphenyl) NHC unit proved to be an efficient and highly enantioselective hydrogenation catalyst. Other derivatives with different substituents at the oxazoline or NHC ring, as well as NHC-based ligands with other carbon scaffolds,^[7] gave only low to moderate enantioselectivities. The complex **1** possesses distinct features which distinguish this catalyst from iridium N,P-ligand complexes. As shown by Burgess and co-workers, iridium hydride complexes which are formed from **1** during hydrogenation are much less acidic than analogous iridium hydrides derived from N,P-ligand complexes.^[8]

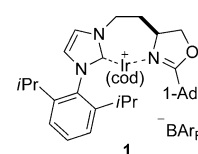


Figure 1. The iridium C,N-complex **1** from Burgess and co-workers.^[6] cod = cyclo-1,5-octadiene.

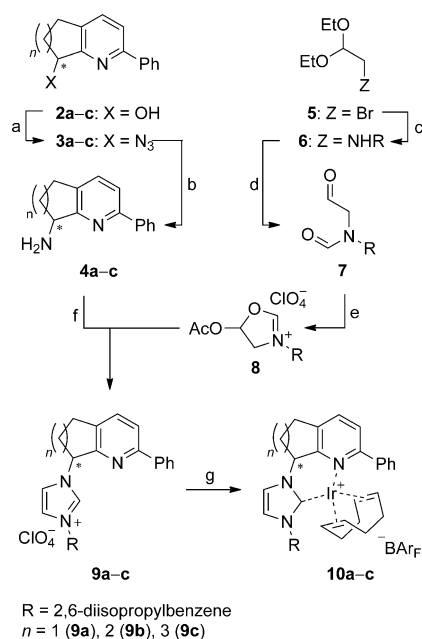
This difference in acidity, which can be explained by the different electronic features of NHC and phosphine ligands, has important consequences in the hydrogenation of acid-sensitive substrates. Burgess et al. have compared the performance of iridium N,P-ligand complexes and their catalyst **1** in the hydrogenation of enol ethers. While the N,P complexes produced substantial amounts of acid-induced side products, the NHC-based catalyst gave only the desired hydrogenation product.^[8] We too encountered problems related to acid-induced side reactions such as water elimination in the hydrogenation of certain acid-sensitive allylic alcohols^[9] or desilylation of silyl-protected alcohols in hydrogenations with N,P-ligand complexes.

As **1** is the only efficient catalyst of this type available today, it seemed desirable to explore other NHC-based C,N-ligand systems which could serve as an alternative in reactions that do not proceed well with catalyst **1**. In view of the many successful applications of pyridine phosphinite ligands (Scheme 1), we decided to prepare a series of NHC pyridine analogues (Scheme 2). The bicyclic pyridyl alcohols **2a–c** having a five-, six-, or seven-membered carbocyclic ring, which were chosen as starting materials, were readily prepared following published procedures^[4b] and conveniently obtained as enantiomerically pure *R* or *S* alcohols through

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Scheme 2. Synthesis of the iridium NHC pyridine complexes **10a–c**: a) MsCl, Et₃N, DMAP (cat.), NaN₃, THF, 0°C, 20 min, then DMSO, RT, 2.5 h (quant.). b) Pd/C, H₂, RT, 4 h, EtOH (quant.). c) *n*BuLi, RNH₂, THF (95%). d) HCO₂H, Ac₂O, THF (87%). e) Ac₂O, HClO₄ (aq.) (75–80%). f) Toluene; Et₂O, HClO₄ (aq.) (41–65%). g) LiOtBu, THF, [(Ir(cod)Cl)₂], RT, 2 h, then NaBAR_F, CH₂Cl₂, 30 min (44–72%). DMAP = 4-(*N,N*-dimethylamino)pyridine, DMSO = dimethylsulfoxide, Ms = methanesulfonyl, THF = tetrahydrofuran.

enzymatic kinetic resolution.^[10] Initially, we planned to introduce the NHC unit by converting the hydroxy group of the pyridyl alcohol into a leaving group such as tosylate or iodide with subsequent N alkylation of the corresponding imidazole. However, this approach proved to be unsuitable because of concomitant racemization. Nevertheless, the racemic iridium complex **10b** prepared in this way could be crystallized and subjected to X-ray analysis.

Comparison of the X-ray structures of the iridium complex **10b** and its dicyclohexyl phosphinite analogue show a very similar orientation of the 2-phenyl-tetrahydroquinoline component and a boat conformation of the chelate ring in both cases (Figure 2).^[11,12] The distance between the pyridine nitrogen atom and the iridium center is 2.14 Å in both complexes, whereas the P–Ir bond (2.29 Å) is signifi-

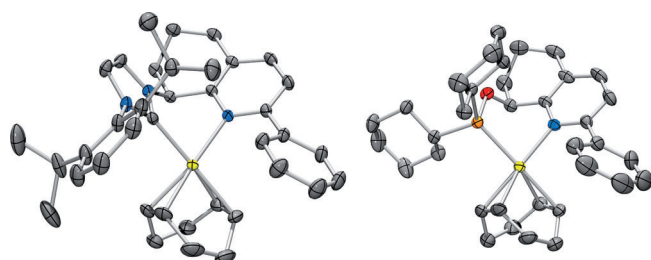


Figure 2. Comparison of the X-ray structures of the iridium complex **10b** and its dicyclohexyl phosphinite analogue. Hydrogen atoms and BARF[−] ions in both structures have been omitted for clarity.^[11]

cantly longer than the Ir–C bond to the NHC unit (2.05 Å). Space-filling models show that the NHC and the phosphinite moieties occupy similar regions in space. In particular, the chiral arrangement of the pyridine-bound phenyl group, which plays a crucial role in the enantioselection process,^[2] is virtually identical in the two complexes. Therefore, similar enantioselectivities were expected for NHC- and phosphinite-based catalysts such as **10a** and **11**, or **10b** and **12**, respectively.

For the synthesis of the enantiomerically pure ligands **9a–c** the strategy of Fürstner et al.^[13] was chosen, and involved imidazolium ring formation by condensation of the dihydrooxazolium salt **8** with a primary amine. The required enantiomerically pure amines **4a** and **4b** were prepared in essentially quantitative yields from the corresponding alcohols by mesylation and subsequent reaction with sodium azide followed by reduction with Pd/C.^[14] The seven-membered ring derivative **4c**, however, did not form the azide and racemic mesylate was isolated instead. MM2 calculations suggest that the lack of reactivity of the mesylate is due to the unfavorable conformation of the seven-membered ring, which sterically impedes an S_N2 reaction with azide. Thus, the corresponding amine **4c** was prepared by an oxidation/oxime formation/reduction sequence (see the Supporting Information).

The dihydrooxazolium salt **8** was prepared in 75–80% overall yield from bromoacetaldehyde diethylacetal according to the procedures of Fürstner et al.^[13] Condensation with the amines **4a–c** led to the corresponding imidazolium salts **9a–c** in yields of 41–65%. When the imidazolium salts were treated with lithium *tert*-butoxide in THF in the presence of [(Ir(cod)Cl)₂] the desired Ir/NHC complexes were formed, and after anion exchange were isolated as the BAR_F salts **10a–c** in 44–72% yield (Figure 3).

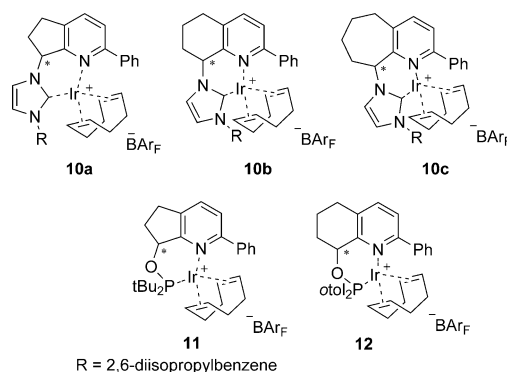
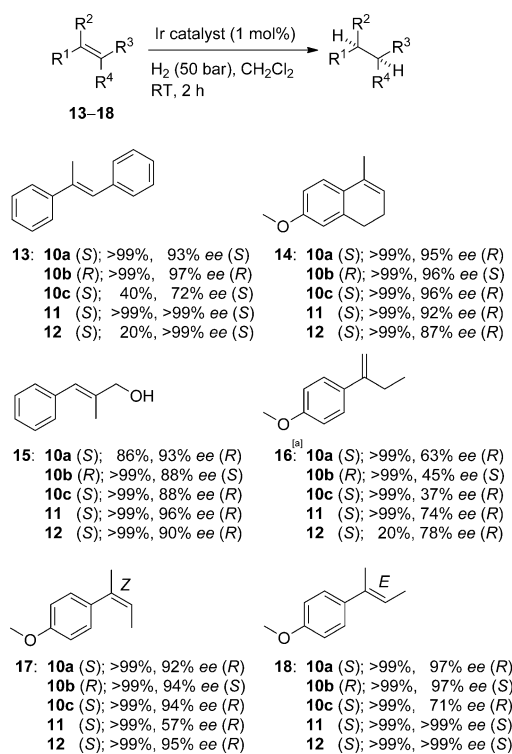


Figure 3. The iridium NHC pyridine catalysts and their phosphinite analogues.

The new NHC-based iridium catalysts **10a–c** were evaluated in the asymmetric hydrogenation of six typical test substrates and compared with the analogous pyridine phosphinite catalysts **11** and **12** (Scheme 3). All three complexes showed high catalytic activity and, with two exceptions (**10c** with substrate **13**; **10a** with **15**), led to full conversion within 2 hours under standard conditions at a 1 mol% catalyst loading.^[15] With the exception of the terminal alkene **16** all

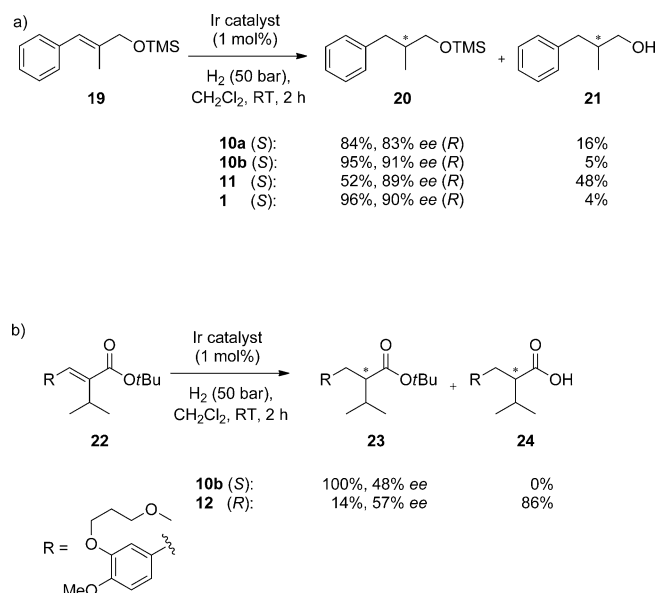


Scheme 3. Asymmetric hydrogenation of the substrates **13–18** with the iridium NHC-based catalysts **10a–c** and the analogous pyridine phosphinite complexes **11** and **12**. [a] 1.0 bar H₂.

other substrates gave excellent enantioselectivities, comparable to those obtained with analogous pyridine phosphinite complexes **11** or **12**. Overall, the complexes **10a** and **10b** outperformed **10c**, which gave inferior results in the hydrogenation of **13**, **16**, and **18**. In addition to catalyst **10b** an analogous complex bearing an N-mesityl substituent at the NHC ring was prepared and tested. Overall, this catalyst proved to be less active, thus giving lower conversion and in most cases lower *ee* values.

The enantioselectivities of the catalysts **10a** and **10b** in the hydrogenation of alkenes **13**, **15**, and **18** were similar to those reported for the Burgess catalyst **1**.^[6] For substrates **16** and **17** the enantioselectivities of the pyridine- and oxazoline-based catalysts were distinctly different, and is not surprising considering the differences in geometry and steric demand between these ligand systems. For the terminal alkene **16** the Burgess catalyst **1** was superior (89% *ee* versus 63% *ee* with **10a**), whereas the *Z*-alkene **17** gave better results with catalysts **10a–c** (92–94% *ee* versus 80% *ee* with **1**). These results indicate that the pyridine-derived ligands are a useful addition to the oxazoline-derived catalyst **1**, and enhance the application range of NHC-based iridium catalysts.

To test the compatibility of the new NHC-based catalysts with acid-sensitive substrates, we studied the hydrogenation of the silyl-protected allylic alcohol **19** (Scheme 4a). For comparison the reaction was also carried out with the Burgess catalyst **1** and the pyridine phosphinite complex **11**. All catalysts gave full conversion within 2 hours at 50 bar hydrogen pressure at room temperature and a catalyst loading of 1 mol%. As expected, hydrogenation with the pyridine



Scheme 4. Hydrogenation of acid-sensitive substrates. TMS = trimethylsilyl.

phosphinite complex **11** led to substantial amounts of the deprotected saturated alcohol **21**, while for the NHC-based catalysts **10a** and **10b** silylether cleavage occurred to a much lesser extent. The catalyst **10b** afforded the saturated silylether **20** in 95% yield and 91% *ee* with only 5% cleavage product, which is almost identical to the results obtained with the Burgess catalyst **1**.

The acid-sensitive Boc-protected analogue of **19** also underwent clean hydrogenation with the catalyst **10b** to give the Boc-protected saturated alcohol with 69% *ee* in essentially quantitative yield, whereas the corresponding N,P ligand complex **12** gave a complex mixture of products, which contained only 34% of the desired hydrogenation product (see the Supporting Information). The catalyst **10b** also allowed hydrogenation of the substrate **22**^[5a] in quantitative yield without notable cleavage of the *tert*-butylester group (Scheme 4b). In contrast, hydrogenation with the analogous pyridine phosphinite complex **12** afforded the acid **24** as the main product.

In summary, we have shown that replacement of the phosphinite group, in pyridine-based iridium complexes such as **11** or **12**, by a NHC unit leads to efficient and highly enantioselective hydrogenation catalysts. In the hydrogenation of various olefins the phosphinite- and NHC-based catalysts showed very similar enantioselectivities. However, as a result of the lower acidity of iridium hydride intermediates produced from NHC-based complexes, these catalysts are much better suited for the hydrogenation of acid-sensitive substrates. In addition, the new NHC-pyridine ligands may also prove useful for other applications in asymmetric catalysis.

Experimental Section

Representative procedures for the synthesis of imidazolium salts **9** and the corresponding Ir-NHC complexes **10**.

(*S*)-3-(2,6-Diisopropylphenyl)-1-(2-phenyl-5,6,7,8-tetrahydroquinolin-8-yl)-1*H*-imidazol-3-ium perchlorate ((*S*)-**9b**): The amine (*S*)-**4b** (700 mg, 3.12 mmol, 1.00 equiv) was added to a suspension of **8** (1.22 g, 3.12 mmol, 1.00 equiv) in toluene (40 mL) and the reaction mixture was stirred at room temperature for 6 h. During the reaction separation of a second phase was observed. Stirring was discontinued, the toluene phase was removed with a pipette, and the residue was triturated with Et₂O (3 × 10 mL). Toluene (25 mL) was added to the remainder and followed by 70 % aq. HClO₄ (0.27 mL, 1.00 equiv). The mixture was stirred at 80 °C overnight, then the solvent was evaporated and the residue taken up in CH₂Cl₂ (40 mL; if a precipitate appeared at this point, it was filtered off prior to further processing). NH₃ (1.10 mL, 7 M in MeOH, 2.50 equiv) was then added to the clear solution and the precipitate of NH₄ClO₄ was filtered off through a small plug of celite. Evaporation of the solvent and crystallization of the final product with CH₂Cl₂/Et₂O (1:5) provided the corresponding imidazolium salt (*S*)-**9b** as an analytically pure, white powder (1.08 g, 2.02 mmol, 65 %).

(η⁴-1,5-Cyclooctadiene)-{(*S*)-8-(3-(2,6-diisopropylphenyl)-2,3-dihydro-carbene-1-yl)-2-phenyl-5,6,7,8-tetrahydroquinoline]-iridium(I) tetrakis(3,5-bis(trifluoromethyl) phenyl)borate ((*S*)-**10b**): LiOrBu (0.48 mL, 1 M in hexane, 1.50 equiv) was added to a suspension of (*S*)-**9b** (170 mg, 0.32 mmol, 1.00 equiv) and [Ir(cod)Cl]₂ (107 mg, 0.16 mmol, 0.50 equiv) in THF (10 mL) at room temperature. The orange suspension turned dark brown and was stirred for 20 h at 70 °C under argon. After cooling to room temperature the volatiles were removed in vacuo. NaBAR₄ (365 mg, 0.41 mmol, 1.30 equiv) dissolved in CH₂Cl₂ (5 mL) was added and the reaction was stirred for 30 min at room temperature. Then the solvent was evaporated and the residue was purified by column chromatography (SiO₂, 2.5 × 15 cm, MTBE, then CH₂Cl₂) to give complex (*S*)-**10b** as an orange solid (364 mg, 0.23 mmol, 72 %).

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- [1] R. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331–337.
- [2] a) X. Cui, K. Burgess, *Chem. Rev.* **2005**, *105*, 3272–3296; b) K. Källström, I. Munslow, P. G. Andersson, *Chem. Eur. J.* **2006**, *12*, 3194–3200; c) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402–1411; d) T. L. Church, P. G. Andersson, *Coord. Chem. Rev.* **2008**, *252*, 513–531; e) D. H. Woodmansee, A. Pfaltz, *Top. Organomet. Chem.* **2011**, *34*, 31–76; f) D. H. Woodmansee, A. Pfaltz, *Chem. Commun.* **2011**, *47*, 7912–7916; g) A. Cadu, P. G. Andersson, *J. Organomet. Chem.* **2012**, *714*, 3–11.
- [3] For iridium catalysts based on chiral P,O ligands, see: D. Rageot, D. H. Woodmansee, B. Pugin, A. Pfaltz, *Angew. Chem.* **2011**, *123*, 9772–9775; *Angew. Chem. Int. Ed.* **2011**, *50*, 9598–9601.
- [4] a) S. Bell, B. Wüstenberg, S. Kaiser, F. Menges, T. Netscher, A. Pfaltz, *Science* **2006**, *311*, 642–644; b) S. Kaiser, S. P. Smidt, A. Pfaltz, *Angew. Chem.* **2006**, *118*, 5318–5321; *Angew. Chem. Int. Ed.* **2006**, *45*, 5194–5197; c) A. Wang, B. Wüstenberg, A. Pfaltz, *Angew. Chem.* **2008**, *120*, 2330–2332; *Angew. Chem. Int. Ed.* **2008**, *47*, 2298–2300; d) A. Wang, R. P. Fraga, E. Hörmann, A. Pfaltz, *Chem. Asian J.* **2011**, *6*, 599–606; e) Pyridine phosphinite ligands of this type have been independently developed: Q. B. Liu, C. B. Yu, Y. G. Zhou, *Tetrahedron Lett.* **2006**, *47*, 4733–4736.
- [5] a) D. H. Woodmansee, M.-A. Müller, L. Tröndlin, E. Hörmann, A. Pfaltz, *Chem. Eur. J.* **2012**, *18*, 13780–13786; b) A. Ganic, A. Pfaltz, *Chem. Eur. J.* **2012**, *18*, 6724–6728; c) A. Baeza, A. Pfaltz, *Chem. Eur. J.* **2010**, *16*, 2036–2039; d) C. Valla, A. Baeza, F. Menges, A. Pfaltz, *Synlett* **2008**, 3167–3171; e) Y. Zhu, K. Burgess, *Adv. Synth. Catal.* **2008**, *350*, 979–983; f) I. Gazić Smilović, E. Casas-Arcé, S. J. Roseblade, U. Nettekoven, A. Zanotti-Gerosa, M. Kovačević, Z. Časar, *Angew. Chem.* **2012**, *124*, 1038–1042; *Angew. Chem. Int. Ed.* **2012**, *51*, 1014–1018; g) J. Mazuela, P.-O. Norrby, P. G. Andersson, O. Pàmies, M. Diéguez, *J. Am. Chem. Soc.* **2011**, *133*, 13634–13645; h) P. Cheruku, J. Diesen, P. G. Andersson, *J. Am. Chem. Soc.* **2008**, *130*, 5595–5599; i) S. Li, S.-F. Zhu, C.-M. Zhang, S. Song, Q.-L. Zhou, *J. Am. Chem. Soc.* **2008**, *130*, 8584–8585.
- [6] a) M. T. Powell, D. R. Hou, M. C. Perry, X. Cui, K. Burgess, *J. Am. Chem. Soc.* **2001**, *123*, 8878–8879; b) M. C. Perry, X. Cui, M. T. Powell, D. R. Hou, J. H. Reibenspiess, K. Burgess, *J. Am. Chem. Soc.* **2003**, *125*, 113–123; c) M. C. Perry, K. Burgess, *Tetrahedron: Asymmetry* **2003**, *14*, 951–961.
- [7] a) S. Nanchen, A. Pfaltz, *Chem. Eur. J.* **2006**, *12*, 4550–4558; b) S. Nanchen, A. Pfaltz, *Helv. Chim. Acta* **2006**, *89*, 1559–1573; c) C. Bolm, T. Focken, G. Raabe, *Tetrahedron: Asymmetry* **2003**, *14*, 1733–1746.
- [8] Y. Zhu, Y. Fan, K. Burgess, *J. Am. Chem. Soc.* **2010**, *132*, 6249–6253.
- [9] A. Schumacher, M. G. Schrems, A. Pfaltz, *Chem. Eur. J.* **2011**, *17*, 13502–13509.
- [10] M. Maywald, A. Pfaltz, *Synthesis* **2009**, 3654–3660.
- [11] a) CCDC 923981 (*rac*-**10b**), and 923982 (dicyclohexyl phosphinite analogue), contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif; b) The data for dicyclohexyl-phosphinite analog was acquired by S. Kaiser, Dissertation, University of Basel, **2005**. (<http://edoc.unibas.ch/288/>).
- [12] One of the reviewers pointed out that because of the NHC unit bearing two different N substituents, the complex **10b** contains a chirality axis formed by the Ir–C bond as an additional chirality element (see, e.g.: D. Enders, H. Gielen, J. Runsink, K. Breuer, S. Brode, K. Boehn, *Eur. J. Inorg. Chem.* **1998**, 913–919; A. Ros, M. Alcarazo, J. Iglesias-Siguenza, E. Diez, E. Alvarez, R. Fernandez, J. M. Lassaletta, *Organometallics* **2008**, *27*, 4555–4564). However, no experimental evidence for the formation of diastereomeric complexes was found. The conformation around the Ir–C bond is likely dictated by the geometric constraints of the chelate ring, which favor the geometry found in the crystal structure and destabilize other conformers.
- [13] A. Fürstner, M. Alcarazo, V. César, C. W. Lehmann, *Chem. Commun.* **2006**, 2176–2178.
- [14] J. Uenishi, M. Hamada, *Synthesis* **2002**, 625–630.
- [15] Reduction of the catalyst loading to 0.25 mol % in the hydrogenation of the substrate **13** with complex **10a** did not affect the enantioselectivity. However, conversion dropped from > 99 % to 28 % when the catalyst loading was decreased from 0.5 to 0.25 mol %.