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New C_2- and C_1-Symmetric Phosphorus Ligands Based on Carbohydrate Scaffolds and Their Use in the Iridium-Catalysed Hydrogenation of Ketimines

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The C_2-symmetric diphosphinite ligands **10a–d**, which have different electron-donating or electron-withdrawing groups in the aryl group, and C_1-symmetric phosphinite–phosphite ligands **11a**,**b**, were directly prepared from glucosamine. Various procedures for synthesising the phosphinite function were explored in order to improve the yield of the reaction. Results were best when Ph_2PNEt_2 was used in the presence of tetrazol as catalyst. These ligands were added to iridium complexes to give catalyst precursors that are active in the hydrogenation of imines **17** and **19**. Cationic iridium complexes gave rise to catalytic systems that were more active than the neutral iridium complexes. The use of additives was, in general, detrimental to both the conversion and the enantioselectivity. In the hydrogenation of **17**, results were best with ligand **11a** (76% *ee*), but in the hydrogenation of **19** (70% *ee*) they were best with ligand **10b**.

Introduction

In recent decades carbohydrates have been widely used as chiral synthons for the synthesis of enantiomerically pure compounds.[1] A variety of structures can be obtained from carbohydrates, mainly pyranoses and furanoses, through well-established procedures. Ligands with C_1- and C_2-symmetry based on carbohydrates have been synthesised and successfully used in asymmetric catalysis and, because hydroxy groups are present, phosphinite, phosphonite and phosphite functional groups are easily introduced, which means that they can be used as ligands in metal-catalysed reactions in addition to the more commonly used phosphanes. Selke[2] has found that diphosphinite **1** (Figure 1) provides excellent enantioselectivity in the hydrogenation of enamido acids, and RajanBabu has reported successful examples of rhodium-catalysed hydrogenation of enamido acids[3] and nickel-catalysed hydrocyanation of alkenes[4] using this ligand electronically modified by changing the electronic properties of the aryl groups bonded to the phosphorus atoms.[5]

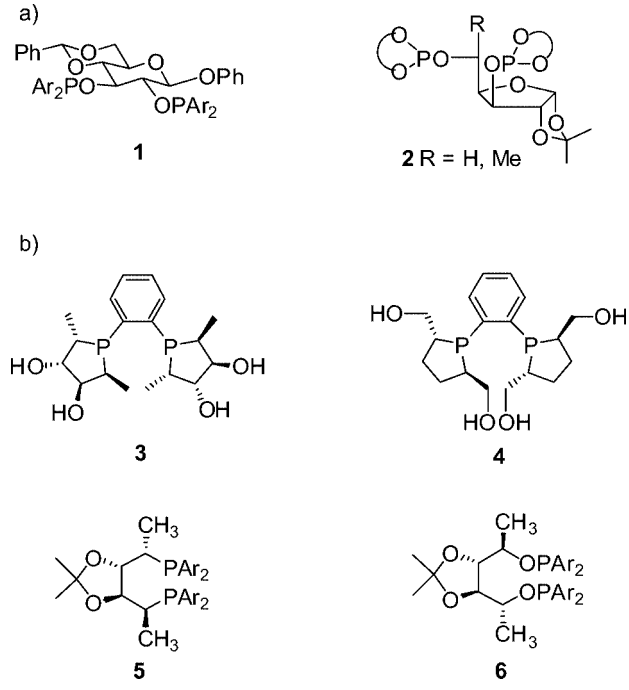

Figure 1. C_1-Symmetric ligands derived from carbohydrates. b) C_2-Symmetric ligands derived from carbohydrates.

Our group has prepared ligands such as **2** and its analogues, which have proved to be efficient in rhodium-catalysed hydrogenation[6,7] and hydroformylation,[8,9] and palladium-catalysed allylic alkylation.[10]

Notable examples of C_2-symmetric carbohydrate ligands are the duphos analogues **3**[11] and **4**,[12] where the phos-

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pholane ring is prepared from D-mannitol. The diop analogue **5**[13] and the related diphosphinite **6**[14] have also been prepared from mannitol and provide excellent enantioselectivity in asymmetric hydrogenation.

Recently, our group[15] has reported two new families of C_2-symmetric diphosphinites (**7** and **8**; Figure 2) based on 2,5-anhydromannitol and 2,5-anhydroiditol backbones, respectively. A comparative study of the asymmetric rhodium-catalysed hydrogenation of enamido esters using ligands **7**–**9** showed that the remote stereocentres (C2 and C5 of the tetrahydrofuran ring) in ligands **7** and **8** have a strong influence on the enantioselectivity. The results were best with ligand **7** (R = TBDPS).

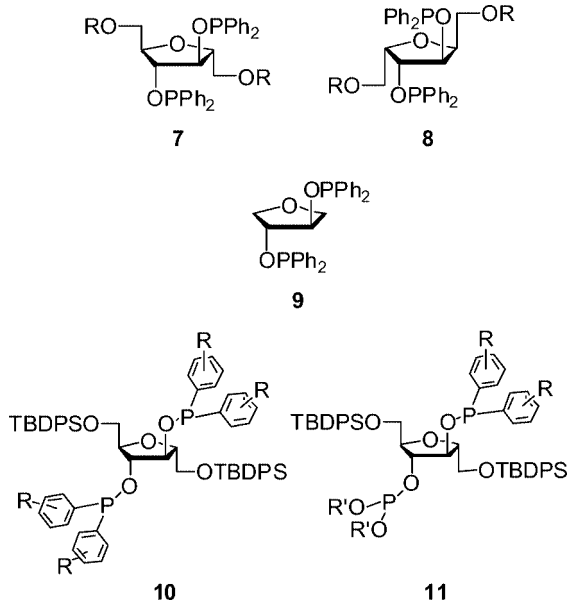


Figure 2. Diphosphinite and phosphinite–phosphite ligands with a tetrahydrofuran backbone obtained from D-glucosamine (**7**, **8**, **10**, and **11**) and from diethyl tartrate (**9**).

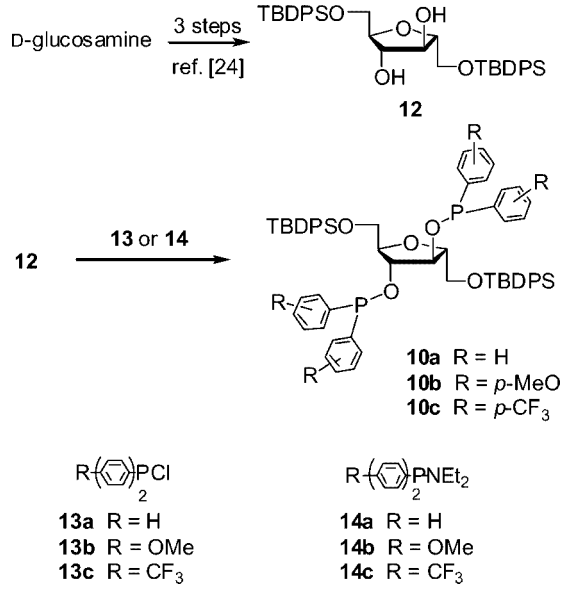
The synthesis of enantiomerically enriched amines from prochiral compounds is of considerable industrial interest, and, consequently, developing efficient catalysts for the enantioselective conversion of prochiral imines into the corresponding chiral amines is a major research target.[16] Although the enantioselective hydrogenation of olefins and ketones has been successfully achieved with several catalytic systems using phosphorus ligands, in the hydrogenation of imines enantioselectivities are only high in a few cases.[17]

The most remarkable achievement in this field is provided by the ferrocenylphosphane ligand Xyliphos,[18] which provides a very active iridium catalyst that can hydrogenate the MEA-imine with a turnover frequency (TOF) greater than 180000 h^{-1} and an *ee* of 79% (precursor of Metolachlor, one of the most important grass herbicides) with high enantioselectivity. The highest enantioselectivity (>99% *ee*) achieved in the asymmetric hydrogenation of imines to date has been obtained with the Ir-ferrocene binaphane complex.[19] Cationic Ir^I complexes with diphenylphosphanyloxazolines as ligands have been used in the reduction of imines, with enantioselectivities up to 89% in acyclic substrates.[20a,20b] Similar Ir/diphenylphosphanylimidazoline catalytic systems provided 51% *ee*.[20c] It has also been shown that the cationic iridium catalyst [Ir(COD)-{(*S*,*S*)-BDPP}]PF_6 adsorbed on montmorillonite[21] can be reused several times with no loss of enantioselectivity. However, there are only a few examples of rhodium and iridium complexes with chiral diphosphinite and diphosphite ligands used in the asymmetric hydrogenation of imines.[22,23]

In this paper, we report the synthesis of a family of C_2 diphosphinite ligands **10a**–**d** related to structure **7** (R = TBDPS) with different electronic properties, and the C_1 phosphinite/phosphite ligands **11a**,**b** as a strategy for controlling the regio- or stereoselectivity in the iridium-catalysed asymmetric reduction of imines.

Results and Discussion

C_2-Diphosphinites **10a**–**c** (Scheme 1, Table 1), and C_1-phosphinite–phosphites **11a**,**b** (Scheme 3) were prepared from the 2,5-anhydro-D-mannitol derivative **12**, which can be easily obtained from D-glucosamine in three steps.[24]



Scheme 1. Synthesis of diphosphinite ligands **10a**–**c** from glucosamine.

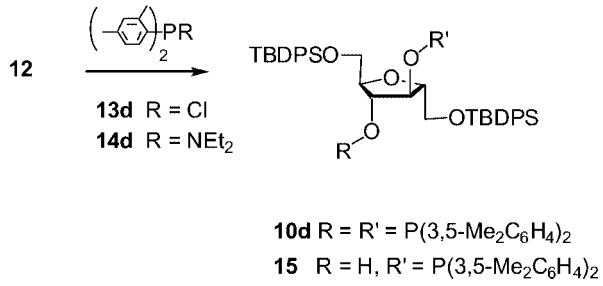
Table 1. Synthesis of ligands **10a**–**d** from **12**.

Entry	Reagents	Solvent	*T* [°C]	Time [h]	Product	Conv. [%]	Yield [%]
1	**13a**	–	–	–	**10a**	–	81[15]
2	**14b**	toluene	110	24	**10b**	100	23
3	**14c**	toluene	110	24	**10c**	100	28
4	**14b**[a]	CH_3CN/CH_2Cl_2	r.t.	0.5	**10b**	100	59
5	**14d**[a]	CH_3CN/CH_2Cl_2	r.t.	3	**10d/15**[b]	100	n.d.
6	**14d**[c]	CH_3CN	r.t.	24	**10d/15**[d]	100	41

[a] 4 Equiv. of **4d** and 5.6 equiv. of tetrazole. [b] Ratio **10d/15** = 1:3. [c] 8 Equiv. of **4d** and 11.2 equiv. of tetrazole. [d] Ratio **10d/15** = 1:1.

Ligand **10a** was prepared by treating **12** with Ph_2PCl (**13a**) in basic medium[15] (Table 1, entry 1). Ligands **10b** and **10c** were prepared in low yield (23% and 28%, respectively) by a non-optimised direct reaction of diol **12** with aminophosphanes **14b** or **14c** in refluxing toluene[25] (Table 1, entries 2 and 3). In an attempt to find milder reaction conditions, aminophosphane **14b** was treated with the weak acid 1*H*-tetrazole before **12** was added.[26] This reaction to form ligand **10b** was more efficient, and the yield increased to 59% (Table 1, entry 4).

The synthesis of diphosphinite **10d** turned out to be more difficult than expected. Initially, we tried the reaction with THF as the solvent and NEt_3 at room temperature, and obtained the monodentate ligand **15** in a 48% yield together with significant amounts of the secondary product $Ph_2P(O)$-PPh_2 (Scheme 2).



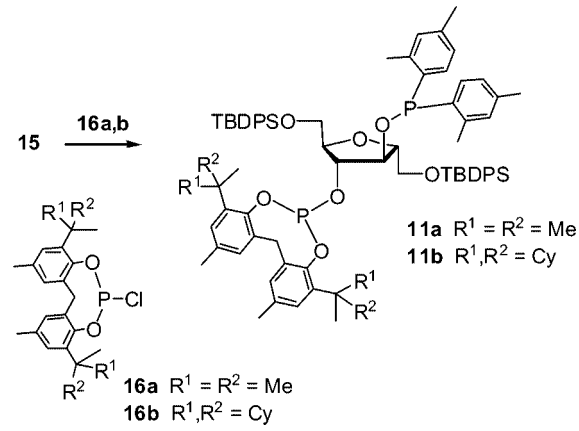
Scheme 2. Synthesis of compounds **10d** and **15** from **12**.

Upon treating diol **12** with the aminophosphane **14d** and 1*H*-tetrazol under standard conditions[26] we managed to obtain a mixture of the di- and monosubstituted ligands **10d** and **15** in a ratio of 1:3 (Table 1, entry 5); no secondary products were obtained. Several attempts were made to force the reaction in order to obtain the disubstituted compound **10d**. When the temperature and reaction time were increased only the starting material was recovered. This seems to indicate that the reaction is reversible under these conditions. A 1:1 ratio of **10d** and **15** was obtained when we used an excess of aminophosphane **14d** and 1*H*-tetrazole (Table 1, entry 6).

The phosphinite–phosphite ligands **11a** and **11b** (Scheme 3) were isolated after purification in 40% and 32% yield, respectively, by treating **15** with the phosphorochloridites **16a** and **16b**, respectively, in a mixture of toluene and pyridine.[27]

The diphosphinites (**10a**–**d**) and phosphinite–phosphites (**11a**,**b**) were used in the iridium-catalysed asymmetric hydrogenation of acyclic and cyclic ketimines to evaluate their potential as ligands in the reduction of C=N. Two acyclic imines were chosen as model substrates to be reduced: *N*-(phenylethylidene)benzylamine (**17**) and *N*-(phenylethylidene)aniline (**19**).

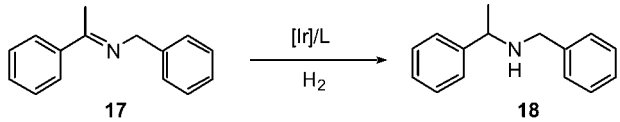
The catalytic systems were generated in situ from both $[Ir(COD)Cl]_2$ and $[Ir(COD)_2]BF_4$ by adding diphosphinites **10a**–**d** or phosphinite–phosphite **11a** (Table 2). These catalysts provided hydrogenation of imine **17** with conversions of between 70 and 100% within 16 hours at 70 bar of H_2



Scheme 3. Synthesis of phosphinite–phosphite ligands **11a**,**b**.

pressure in CH_2Cl_2. However, together with the desired secondary amine **18**, hydrogenolysis products formed by cleavage of the nitrogen–benzyl bond were also detected.[28] In general, the phosphane–phosphite **11** provided better conversions (entries 4 and 8) than the diphosphinites **10**. Ligand **11a** gave full conversion under these conditions with both catalyst precursors (entries 4 and 8). For the catalytic systems with the diphosphinites **10a**–**10c**, the use of the precursor $[Ir(COD)Cl]_2$/**10** (Table 2 entries 1–3) led to activities higher than the cationic $[Ir(COD)_2]$ BF_4/**10** precursors (Table 2, entries 5–7). The systems based on ligand **10a** provided the highest conversion and selectivity. The system based on **10b** (entries 2 and 6), which is a stronger electron donor than **10c**, gave lower conversion than the systems based on ligand **10c**.

Table 2. Hydrogenation of **17** with Ir/L catalytic systems. Effect of the precatalyst.[a]



17 18

Entry	Precatalyst	Conv. [%]	Select. [%]	*ee*[b] [%]
1	$[Ir(COD)Cl]_2$/**10a**	100	95	0
2	$[Ir(COD)Cl]_2$/**10b**	74	85	0
3	$[Ir(COD)Cl]_2$/**10c**	93	92	5 (–)
4	$[Ir(COD)Cl]_2$/**11a**	100	90	0
5	$[Ir(COD)_2]BF_4$/**10a**	82	76	9 (–)
6	$[Ir(COD)_2]BF_4$/**10b**	70	68	0
7	$[Ir(COD)_2]BF_4$/**10c**	85	76	11 (–)
8	$[Ir(COD)_2]BF_4$/**11a**	100	85	73 (–)

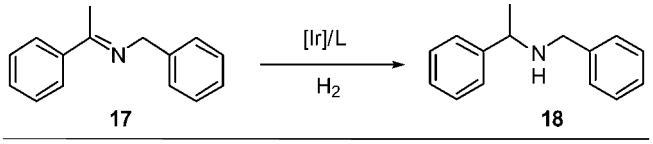
[a] Reaction conditions: 1 mol-% [Ir], 1.25 mol-% ligand, 70 bar H_2, 16 h, 25 °C, CH_2Cl_2. [b] Absolute configuration was not determined.

Catalytic systems involving ligands **10a**–**c** gave very low enantioselectivities in the hydrogenation of **17**. Börner has studied the hydrogenation of **17** using the catalytic system Rh/**1** and Rh/(*R*,*R*)-bdpch [(*R*,*R*)-1,2-cyclohexanolbis(diphenylphosphinite)], obtaining total conversion with enantioselectivities up 72% with the second catalytic system. The use of iridium complexes with the same ligands

provided less active catalytic systems and very low enantioselectivity, in agreement with our observations.

However, the use of the Ir/**11a** catalytic system afforded a remarkable 73% *ee*. It should be pointed out that the different results obtained depend on the catalyst precursor. Thus, while a racemate was obtained with $[Ir(COD)Cl]_2$/**11a**, a 73% *ee* was obtained with $[Ir(COD)_2]BF_4$/**11a** (Table 2, entries 4 and 8). This finding is in agreement with other reports and highlights the influence of the catalytic precursor on the enantioselectivity.[22,29] When shorter reaction times or lower temperatures (0 °C) were used (Table 3, entries 2 and 3), the activity of the catalytic system and the optical yield decreased. After half an hour conversion was only 24%, which gives a TOF of 48 h^{-1} (Table 3, entry 2). The lower enantiomeric excess obtained at shorter times or at low temperatures suggests that the catalytic species responsible for enantiocontrol needs longer reaction times or higher temperatures to be formed.

Table 3. Hydrogenation of **17** with $[Ir(COD)_2]BF_4$/**11a**,**b**. Study of the effect of temperature and additive.[a]



17 18

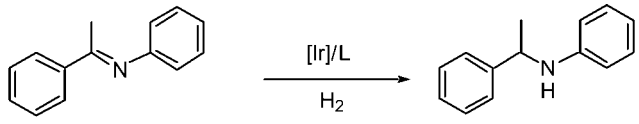
Entry	Ligand	Additive[b]	Temp. [°C]	Time [h]	Conv. [%]	Select. [%]	*ee*[c] [%]
1	**11a**	–	25	16	100	85	73 (–)
2	**11a**	–	25	0.5	24	100	68 (–)
3	**11a**	–	0	2	4.3	100	40 (–)
4	**11a**	Bu_4NI	25	16	9.5	100	16 (–)
5	**11a**	I_2	25	16	100	67	1.4 (–)
6	**11a**	Phthalimide	25	16	100	89	75 (–)
7	**11a**	$BnNH_2$	25	16	97	91	76 (–)
8[d]	**11b**	–	25	2	17	93	52 (–)
9	**11b**	Bu_4NI	25	16	9	100	11 (–)
10	**11b**	I_2	25	16	100	87	0
11	**11b**	Phthalimide	25	16	63	100	54 (–)
12	**11b**	$BnNH_2$	25	16	91	81	58 (–)

[a] Reaction conditions: 1 mol-% catalyst, 1.2 mol-% ligand, 70 bar H_2, 25 °C, 16 h, CH_2Cl_2. [b] 10 mol-% additive. [c] Absolute configuration was not determined. [d] 30 Bar H_2.

The catalytic system $[Ir(COD)_2]BF_4$/**11a**, with *tert*-butyl substituents on the phosphite moiety, gave higher enantioselectivity than $[Ir(COD)_2]BF_4$/**11b**, which contains cyclohexyl substituents (entries 1 and 8).

Several reports have shown that additives may improve catalytic activity and enantioselectivity.[29a,30] Halides and amines are the most widely used additives.[31] The results obtained with both our catalysts depend heavily on the presence of iodide ions. Addition of Bu_4NI deactivates the catalyst and causes a sharp decrease in conversion and enantioselectivity (Table 3, entries 1 and 4, and 8 and 9). Iodine also has a dramatic effect on the selectivity and enantioselectivity of the catalytic system: the selectivity in the desired amine **18** decreased strongly and the hydrogenolysis of imine **17** was favoured (Table 3, entries 5 and 10). Furthermore, the *ee* dropped to almost zero when the experiments were carried out in the presence of 10 mol-% of I_2 at 25 °C (Table 3, entries 5 and 10). The addition of phthalimide and benzylamine did not have a strong influence, at least at 25 °C, and both conversion and enantioselectivity were maintained (Table 4, entries 6, 7, 11 and 12). A similar behaviour has been observed in previous reports with diphosphinite ligands.[22] This indicates that these amines, which are also the reaction products, do not deactivate the catalyst, since conversion of the substrate is almost total.

Table 4. Hydrogenation of imine **19** using the $[Ir(COD)_2]BF_4$/L catalytic system. Effect of the additive.[a]



19 20

Entry	Ligand	Time [h]	Additive[b]	Conv. [%]	Select. [%]	*ee*[c] [%]
1	**10a**	16	–	100	100	65 (+)
2	**10b**	16	–	100	100	70 (+)
3	**10b**	1	–	98	100	70 (+)
4	**10b**	0.25	–	26	100	n.d.[d]
5	**10c**	16	–	100	100	31 (–)
6	**10d**	1	–	6	100	15 (–)
7	**11a**	16	–	99	100	0
8	**10a**	16	Bu_4NI	42	100	19 (–)
9	**10a**	16	I_2	100	100	10 (–)
10	**10a**	16	phthalimide	98	100	66 (+)
11	**10a**	16	$BnNH_2$	52	97	42 (+)
12	**10b**	16	Bu_4NI	71.1	100	19 (+)
13	**10b**	16	I_2	100	100	5 (–)
14	**10b**	16	phthalimide	99.3	100	70 (+)
15	**10b**	16	$BnNH_2$	43.6	94	52 (+)
16	**10c**	16	Bu_4NI	100	100	12 (+)
17	**10c**	16	I_2	100	100	4 (–)
18	**10c**	16	phthalimide	99	100	9 (–)
19	**10c**	16	$BnNH_2$	25	90	10 (–)

[a] Reaction conditions: 1 mol-% $[Ir(COD)_2]BF_4$, 1 mol-% ligand, 70 bar, 25 °C, 16 h, CH_2Cl_2. [b] 4 mol-% additive. [c] Absolute configuration was not determined. [d] Not determined.

A rather broad screening of different ligands and reaction conditions was also carried out with *N*-arylimine **19**. The homogeneous catalysts were based on iridium and modified by adding diphosphinites **10a**–**d** or phosphinite–phosphite **11a**. The effect of the catalyst precursor and additives on the conversion to the amine and the optical yield were also investigated. Both iridium systems $[IrCODCl]_2$/L and $[Ir(COD)_2]BF_4$/L (L = **10a**–**d**, **11a**) behave as catalytic precursors for the hydrogenation of imine **19** to secondary amine **20** at 70 bar of H_2 pressure in CH_2Cl_2. Whereas the catalysts $[IrCODCl]_2$/L provided low enantioselectivities (up to 10%), the $[Ir(COD)_2]BF_4$/L systems proved to be more efficient and gave *ee* values as high as 70%. The results obtained with the systems $[Ir(COD)_2]BF_4$/L are presented in Table 4.

The catalytic system $[Ir(COD)_2]BF_4$/**10a** afforded total conversion in 16 hours with 65% *ee*, while when ligand **10b**

was used the *ee* reached 70% (Table 4, entries 1–3). The substrate was almost completely reduced within one hour (entries 3–4). The catalytic system $[Ir(COD)_2]BF_4$/**10c**, with an electron-poorer ligand, gave low enantioselectivities and promoted the formation of the opposite enantiomer (Table 4, entry 5). When the catalytic system was based on the diphosphinite ligand **10d**, which contains methyl groups on the aromatic rings to increase both the electron density on phosphorus and the steric hindrance, conversion was only 6% with an *ee* of 15% in one hour (Table 4, entry 6). In this case the cationic iridium complex with phosphinite–phosphite **11a** provided the racemic mixture (Table 4, entry 7).

The effect of adding halide ions or amine derivatives to these catalytic systems was also examined. When Bu_4NI or I_2 were added to $[Ir(COD)_2]BF_4$/**10a**–**c** the enantioselectivity dropped sharply (Table 4, entries 8, 9, 12, 13, 16 and 17), favouring the formation of the reduced product with the opposite configuration. This behaviour seems to be general for the hydrogenation of acyclic imines **17** and **19** with these catalytic systems when iodine derivatives are used as additives. In general, when amines were used as additives there was no notable effect on the enantioselectivity (Table 4, entries 10, 11, 14, 15, 18 and 19). Nevertheless, the addition of benzylamine slowed the reaction down considerably and the activity of the catalytic system decreased.

Concerning the effect of electron-withdrawing or -donating groups present in the diphosphinite function, in the case of ligands **10a**–**c** we observed an increase in the enantioselectivity when donating groups were used, which is similar to the tendency observed in the hydrogenation of enamino acids using other metals.[32] A general conclusion about the role of electron-withdrawing or -donating substituents in ligands used in imine hydrogenation cannot be established at the moment and will require additional studies.

On the other hand, diphosphinites **10a**–**c** and phosphinite–phosphites **11a**,**b** show a high substrate selectivity for ketimines **17** and **19**, which should be related to the conformation and steric interaction of the coordinated ligands in the complexes.[15,33]

Conclusions

We have synthesised new tunable diphosphinite (**10a**–**d**) and phosphinite–phosphite (**11a**,**b**) ligands for use in asymmetric catalysis from aminoglucose, and we have optimised the formation of the phosphinite function. These ligands form catalytic systems in the presence of neutral or cationic iridium complexes that are active in imine hydrogenation. Precursors based on cationic $[Ir(COD)_2]BF_4$ provided better yields and enantioselectivities than the neutral ones. The catalytic systems $[Ir(COD)_2]BF_4$/**10a**–**c** did not afford significant enantioselectivities in the hydrogenation of the imine **17**. However, when $[Ir(COD)_2]BF_4$/**11a** was used the *ee* was 76%. Diphosphinite ligands **10**, on the other hand, were more effective in the reduction of imine **19**, and when ligand **10b** was used the *ee* was 70%. In this case, the electronic effect on the enantioselectivity are considerable. Results were best when electron-donating groups are present on the phenyl rings. The use of additives was, in general, detrimental to both conversion and enantioselectivity.

Experimental Section

General Remarks: All reactions were carried out under argon using standard Schlenk techniques. Solvents were distilled and degassed prior to use. ^1H, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$ and $^{19}F\{^1H\}$ NMR spectra were recorded with a Varian Gemini spectrometer at 300 and 400 MHz. Chemical shifts are reported relative to tetramethylsilane for ^1H and $^{13}C\{^1H\}$ as internal reference, 85% H_3PO_4 for $^{31}P\{^1H\}$ and trichlorofluoromethane for $^{19}F\{^1H\}$ as external references. Elemental analyses were carried out with a Carlo–Erba Microanalyser EA 1108. A VG-Autospec apparatus was used for FAB mass spectral analyses with 3-nitrobenzyl alcohol as matrix. EI mass spectra were obtained with an HP 5989 A spectrometer at an ionizing voltage of 70 eV. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter.

Single hydrogenation reactions were carried out in a Berghof or Parr 100-mL, stainless-steel autoclave and multi-screening hydrogenations were performed in a home-made 96-micro-titer plate by Bayer AG (Leverkusen, Germany). The catalytic reactions were monitored by GC on a Hewlett–Packard 5890A. Conversion was measured in an Ultra-2 (5% diphenylsilicone/95% dimethylsilicone) column (25 m × 0.2 mm Ø). The enantiomeric excess was measured directly in the reaction crude by NMR spectroscopy or gas chromatography. *N*-(Phenylethylidene)benzylamine (**17**) was determined by ^1H NMR spectroscopy (with mandelic acid as the resolution agent) or by GC, after derivatisation into the trifluoroacetamide compound, in a β-cyclodextrin phase. The enantiomeric excess of *N*-(phenylethylidene)aniline (**19**) was determined by GC, after derivatisation into the acetamide compound, in an MN Hydrodex-6-TBDM (25 m × 0.25 mm × 0.25 m) column.

3,4-Bis-*O*-[bis(4-methoxyphenylphosphanyl)]-1,6-di-*O*-(*tert*-butyldiphenylsilyl)-2,5-anhydro-D-mannitol (10b). Procedure A: A flask equipped with a reflux condenser was charged with 2,5-anhydro-D-mannitol derivative **12** (100 mg, 0.156 mmol). A solution of (diethylamino)bis(4-methoxyphenyl)phosphane (**14b**; 109 mg, 0.343 mmol) in anhydrous toluene (2.2 mL) was added. The mixture was refluxed overnight and followed by TLC (hexane/ethyl acetate, 5:1; R_f = 0.25). The residue was then purified by column chromatography on silica gel under argon to give 40 mg (22.7% yield) of compound **10b** as a foam.

Procedure B: A solution of (diethylamino)bis(4-methoxyphenyl)-phosphane (**14b**; 569 mg, 1.79 mmol) and tetrazole (5.1 mL, 0.45 M in CH_3CN) was stirred for 10 min at room temperature under argon. A solution of **12** (288 mg, 0.45 mmol) in anhydrous dichloromethane (3 mL) was then added and stirred for 30 min at room temperature. The reaction was followed by TLC (hexane/ethyl acetate, 5:1; R_f = 0.25). The residue was then purified by column chromatography on silica gel under argon to give 301.2 mg (59% yield) of compound **10b** as a foam. $[\alpha]_D^{20}$ = 6.5 (*c* = 0.83, CH_2Cl_2). MS (FAB): *m*/*z* (%) = 1129.31 (2.73) [M^+]. HRMS (L-SIMS): calcd. for $C_{66}H_{75}O_9P_2Si_2$ 1129.4069; found 1129.4130. ^1H NMR (400 MHz, C_6D_6, 25 °C): δ = 7.93 (m, 8 H, arom.), 7.67 (m, 8 H, arom.), 7.26 (m, 12 H, arom.), 6.84 (m, 8 H, arom.), 5.38 (dd, *J* = 7.9, *J* = 4 Hz, 2 H, CH), 4.59 (m, 2 H, CH), 4.09 (dd, *J* = 10.9, *J* = 4.2 Hz, 2 H, CH_2), 3.99 (dd, *J* = 10.9, *J* = 4.2 Hz, 2 H, CH_2),

3.37 (s, 6 H, CH_3O), 3.35 (s, 6 H, CH_3O), 1.32 (s, 9 H, CH_3), 1.27 (s, 9 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.7–113.9 (arom.), 85.0 (m, CH), 84.5 (CH), 64.1 (CH_2), 55.25 (CH_3O), 55.23 (CH_3O), 27.0 [C(CH_3)$_3$], 19.4 [C(CH_3)$_3$] ppm. ^{31}P NMR (161.9 MHz, $CDCl_3$, 25 °C): δ = 115.1 ppm.

3,4-Bis-*O*-[bis(4-trifluoromethylphenylphosphanyl)]-1,6-di-*O*-(*tert*-butyldiphenylsilyl)-2,5-anhydro-D-mannitol (10c): A flask equipped with a reflux condenser was charged with 2,5-anhydro-D-mannitol derivative **12** (213 mg, 0.332 mmol). A solution of (diethylamino)-bis(4-trifluoromethylphenyl) phosphane (**14c**; 352 mg, 0.897 mmol) in anhydrous toluene (2.5 mL) was added. The mixture was refluxed overnight and followed by TLC. The residue was then purified by column chromatography on silica gel under argon to give 40 mg (28% yield) of compound **10c** as a foam. HRMS (L-SIMS): calcd. for $C_{66}H_{63}F_{12}O_5P_2Si_2$ 1281.3498: found 1281.3583. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.65–7.25 (m, 36 H, arom), 5.01 (m, 2 H, CH), 4.18 (m, 2 H, CH), 3.82 (dd, ^2J = 11.2, ^3J = 4 Hz, 2 H, CH_2), 3.62 (dd, ^2J = 11.2, ^3J = 4 Hz, 2 H, CH_2), 1.05 (s, 9 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 134.3–125.3 (arom.), 122.7 (CF_3), 86.2 (m, CH), 83.4 (CH), 63.6 (CH_2), 27.0 [C(CH_3)$_3$], 19.5 [C(CH_3)$_3$] ppm. ^{31}P NMR (161.9 MHz, $CDCl_3$, 25 °C): δ = 110.5 ppm.

3,4-Bis-*O*-[bis(2,4-dimethylphenylphosphanyl)]-1,6-di-*O*-(*tert*-butyldiphenylsilyl)-2,5-anhydro-D-mannitol (10d) and 3-*O*-[Bis(2,4-dimethylphenylphosphanyl)]-1,6-di-*O*-(*tert*-butyldiphenylsilyl)-2,5-anhydro-D-mannitol (15): A solution of (diethylamino)bis(2,4-dimethylphenyl)phosphane (**14d**; 3.4 g, 10.9 mmol) and tetrazole (34 mL, 0.45 M in CH_3CN, 15.3 mmol) was stirred for 10 min at room temperature under argon. Compound **12** (878 mg, 1.37 mmol) was added to this solution and stirred for 2 h at room temperature. The reaction was followed by TLC (hexane/ethyl acetate, 10:1; R_f = 0.47). The residue was then purified by column chromatography on silica gel under argon to give 630 mg (41% yield) of compound **10d** and 446 mg (37% yield) of **15**.

10d: $[\alpha]_D^{20}$ = 8.0 (c = 0.71, CH_2Cl_2). HRMS (L-SIMS): calcd. for $C_{70}H_{83}O_5P_2Si_2$ 1121.5254; found 1121.5290. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.55–6.70 (m, 32 H, arom.), 4.66 (m, 1 H, CH), 4.09 (m, 1 H, CH), 3.65 (m, 2 H, CH), 3.54 (m, 2 H, CH), 2.14 (s, 6 H, CH_3), 2.13 (s, 6 H, CH_3), 2.12 (s, 6 H, CH_3), 2.11 (s, 6 H, CH_3), 0.74 (s, 18 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 141.0–126.7 (arom.), 85.5 (m, CH), 84.5 (CH), 64.2 (CH_2), 27 [C(CH_3)$_3$], 20.7 (d, ^3J = 7.74 Hz, CH_3), 20.5 (d, ^3J = 6.84 Hz, CH_3), 20.5 (br., CH_3), 19.4 [C(CH_3)$_3$] ppm. ^{31}P NMR (161.9 MHz, $CDCl_3$, 25 °C): δ = 102.6 ppm.

15: $[\alpha]_D^{20}$ = 17.8 (c = 0.89, CH_2Cl_2). MS (FAB): m/z (%) = 881.46 (4.39) [M^+]. HRMS (L-SIMS): calcd. for $C_{54}H_{65}O_5PSi_2$ 881.2357; found 881.2385. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.59–6.87 (m, 26 H, arom.), 4.47 (m, 1 H, CH), 4.31 (m, 1 H, CH), 3.99 (m, 2 H, CH), 3.69 (m, 3 H, CH_2), 3.54 (dd, 1 H, CH_2), 2.79 (s, OH), 2.30 (s, 3 H, CH_3), 2.17 (s, 3 H, CH_3), 2.11 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 0.96 (s, 9 H, CH_3), 0.94 (s, 9 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 138.1–127.6 (CH, C, arom.), 86.0 ($^2J_{C,P}$ = 18 Hz, CH), 84.9 (CH), 83.9 ($^3J_{C,P}$ = 6.13 Hz, CH), 78.0 ($^3J_{C,P}$ = 4.5 Hz, CH), 64.7 (CH_2), 64.1 (CH_2), 27.2 [C(CH_3)$_3$], 27.0 [C(CH_3)$_3$], 21.44 [C(CH_3)$_3$],21.45 [C(CH_3)$_3$], 20.5 (d, ^3J = 12.17 Hz, CH_3), 20.3 (d, ^3J = 12.27 Hz, CH_3), 19.6 (s, CH_3), 19.5 (s, CH_3) ppm. ^{31}P NMR (161.9 MHz, $CDCl_3$, 25 °C): δ = 102.7 ppm.

1,6-Di-*O*-(*tert*-butyldiphenylsilyl)-4-*O*-(4,8-di-*tert*-butyl-2,10-dimethyl-12*H*-dibenzo[δ,γ][1,3,2]dioxaphosphocine)-3-*O*-(2,4-dimethylphenylphosphanyl)-2,5-anhydro-D-mannitol (11a): Monophosphinite **15** (178 mg, 0.202 mmol) was dissolved in anhydrous toluene (1 mL) and anhydrous pyridine (100 μL), cooled to 0 °C and a solution of 4,8-di-*tert*-butyl-6-chloro-2,10-dimethyl-12*H*-dibenzo[δ,γ][1,3,2]dioxaphosphocine (**18a**; 100 mg, 0.252 mmol) in anhydrous toluene (1 mL) and anhydrous pyridine (100 μL) was added dropwise. The reaction mixture was then warmed to room temperature and stirred, following the reaction by TLC (hexane/ethyl acetate, 10:1; R_f = 0.55). Purification by column chromatography on silica gel gave 100 mg (39.6% yield) of compound **11a** as a foam. $[\alpha]_D^{20}$ = 17.4 (c = 0.42, CH_2Cl_2). MS (FAB): m/z (%) = 1249.12 (3.91) [M^+]. HRMS (L-SIMS): calcd. for $C_{77}H_{95}O_7P_2Si_2$ 1249.6092; found 1249.6030. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.69–6.73 (m, 30 H, arom.), 5.79 (m, 1 H, CH), 4.92 (m, 1 H, CH), 4.67 (m, 1 H, CH), 4.30 (m, 1 H, CH_2), 4.13 (d, ^2J = 12.4 Hz, CH_2), 3.98–3.72 (m, 4 H, CH_2), 3.15 (d, ^2J = 12.4 Hz,1 H, CH_2), 2.31 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 2.26 (s, 9 H, CH_3), 2.19 (s, 3 H, CH_3), 1.29 (s, 9 H, CH_3), 1.22 (s, 9 H, CH_3), 1.04 (s, 9 H, CH_3), 0.98 (s, 9 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 145.6–126.8 (CH, C, arom.), 85.9 (m, CH), 85.4 (CH), 85.2 (CH), 80.3 (m, CH), 64.3 (CH_2), 63.9 (CH_2), 34.8 (CH_2), 31.2 [C(CH_3)$_3$], 31.1 [C(CH_3)$_3$], 27.0 [C(CH_3)$_3$], 26.9 [C(CH_3)$_3$], 21.5 (CH_3), 21.4 (CH_3), 21.3 (CH_3), 20.8 (d, ^3J = 13.7 Hz, CH_3), 20.6 (d, ^3J = 13.7 Hz, CH_3), 19.5 [C(CH_3)$_3$], 19.4 [C(CH_3)$_3$] ppm. ^{31}P NMR (161.9 MHz, $CDCl_3$, 25 °C): δ = 127.9, 102.8 ppm.

1,6-Di-*O*-(*tert*-butyldiphenylsilyl)-4-*O*-{2,10-dimethyl-4,8-bis(1-methylcyclohexyl)-12*H*-dibenzo[δ,γ][1,3,2]dioxaphosphocine}-3-*O*-(2,4-dimethylphenylphosphanyl)-2,5-anhydro-D-mannitol (11b): Diphosphinite **15** (145 mg, 0.164 mmol) was dissolved in anhydrous toluene (0.5 mL) and anhydrous pyridine (100 μL) and cooled to 0 °C. A solution of 6-chloro-2,10-dimethyl-4,8-bis(1-methylcyclohexyl)-12*H*-dibenzo[δ,γ][1,3,2]dioxaphosphocine (**18b**; 100 mg, 0.252 mmol) in anhydrous toluene (1 mL) and anhydrous pyridine (100 μL) was added dropwise. The reaction mixture was then warmed to room temperature and stirred. Dry hexane was then added to the mixture and the solution was filtered under argon. Purification by column chromatography on silica gel under argon gave 71 mg (32.4% yield) of compound **11b** as a foam. $[\alpha]_D^{20}$ = 22.6 (c = 0.50, CH_2Cl_2). MS (FAB): m/z (%) = 1328.16 (1.45) [M^+]. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.71–6.74 (m, 30 H, arom.), 5.67 (m, 1 H, CH), 4.85 (m, 1 H, CH), 4.62 (m, 1 H, CH), 4.30 (m, 1 H, CH), 4.12 (d, ^2J = 12.8 Hz, 1 H, CH_2), 4.01–3.74 (m, 4 H, CH_2), 3.15 (d, ^2J = 12.8 Hz, 1 H, CH_2), 2.36 (s, 3 H, CH_3), 2.29 (s, 2 H, CH_3), 2.28 (s, 3 H, CH_3), 2.27 (br., 6 H, CH_3), 2.24 (s, 3 H, CH_3), 1.54–1.12 (m, CH_2), 1.16 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.05 (s, 9 H, CH_3), 0.97 (s, 9 H, CH_3) ppm. ^{31}P NMR (161.9 MHz, $CDCl_3$, 25 °C): δ = 127.8, 103.2 ppm.

General Procedure for the Ir-Catalysed Hydrogenation of Imines: The initial screening of ligands used a homemade micro-titer plate, and the best results were then tested in a single reactor using the following procedure. $[Ir(COD)Cl]_2$ (0.022 mmol) or $[Ir(COD)_2]BF_4$ (0.045 mmol) was dissolved in 10 mL of dry, degassed CH_2Cl_2 in a Schlenk tube. The corresponding ligand (0.055 mmol) was then added, followed by the corresponding imine (4.4 mmol for a 100:1 imine/Ir ratio). The solution was transferred under argon into the autoclave with a syringe. The reaction mixture was stirred overnight at room temperature under 70 bar of H_2 pressure.

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[1] R. I. Hollinsworth, G. Wang, *Chem. Rev.* **2000**, *100*, 4267–4282.

[2] a) R. Selke, H. Pracejus, *J. Mol. Catal.* **1986**, *37*, 213–225; b) R. Selke, M. Schwarze, H. Baudisc, I. Grassert, M. Michalik, G. Oehme, N. Stoll, B. Costisella, *J. Mol. Catal.* **1993**, *84*, 223–237.
[3] T. V. RajanBabu, T. A. Ayers, A. L. Casalnuovo, *J. Am. Chem. Soc.* **1994**, *116*, 4101–4102.
[4] T. V. RajanBabu, A. L. Casalnuovo, *J. Am. Chem. Soc.* **1992**, *114*, 6265–6266.
[5] A. L. Casalnuovo, T. V. RajanBabu, T. A. Ayers, T. H. Warren, *J. Am. Chem. Soc.* **1994**, *116*, 9869–9882.
[6] a) O. Pàmies, M. Diéguez, G. Net, A. Ruiz, C. Claver, *Chem. Commun.* **2000**, *12*, 2383–2384; b) O. Pàmies, M. Diéguez, G. Net, A. Ruiz, C. Claver, *J. Org. Chem.* **2001**, *66*, 8364–8369.
[7] M. Diéguez, A. Ruiz, C. Claver, *J. Org. Chem.* **2002**, *67*, 3796–3801.
[8] a) M. Diéguez, O. Pàmies, A. Ruiz, S. Castillón, C. Claver, *Chem. Eur. J.* **2001**, *7*, 3086–3094; b) M. Diéguez, O. Pàmies, A. Ruiz, S. Castillón, C. Claver, *Chem. Commun.* **2000**, 1607–1608.
[9] M. Diéguez, O. Pàmies, A. Ruiz, C. Claver, *New J. Chem.* **2002**, *26*, 826–833.
[10] M. Diéguez, S. Jansat, M. Gómez, A. Ruiz, G. Muller, C. Claver, *Chem. Commun.* **2001**, 1132–1133.
[11] a) A. Bayer, P. Mursat, U. Tewalt, B. Rieger, *Eur. J. Inorg. Chem.* **2002**, 2614–2624; b) T. V. RajanBabu, Y.-Y. Yan, S. Sin, *J. Am. Chem. Soc.* **2001**, *123*, 10207–10213; c) W. Li, Z. Zhang, D. Xiao, X. Zhang, *J. Org. Chem.* **2000**, *65*, 3489–3496; d) W. Li, Z. Zhang, D. Xiao, X. Zhang, *Tetrahedron Lett.* **1999**, *40*, 6701–6704.
[12] J. Holz, R. Stürmer, U. Schmidt, H.-J. Drexler, D. Heller, H.-P. Krimmer, A. Börner, *Eur. J. Org. Chem.* **2001**, *63*, 4621–4624.
[13] Y. Y. Yan, T. V. RajanBabu, *Org. Lett.* **2000**, *2*, 4137–4140.
[14] Y. Y. Yan, T. V. RajanBabu, *J. Org. Chem.* **2000**, *65*, 900–906.
[15] M. Aghmiz, A. Aghmiz, Y. Díaz, A. Masdeu-Bultó, C. Claver, S. Castillón, *J. Org. Chem.* **2004**, *69*, 7502–7510.
[16] a) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), J. Wiley & Sons, New York, **1993**; b) *Comprehensive Asymmetric Catalysis*, Vol 1 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.
[17] a) F. Spindler, H.-U. Blaser, "Enantioselective Reduction of C=N Bonds and Enamines with Hydrogen", in *Transition Metals for Organic Synthesis*, vol. 2 (Eds.: M. Beller, C. Bolm), J. Wiley & Sons, Weinheim, **1998**, p. 69. Reviews of asymmetric hydrogenation of C=C and C=N: b) M. J. Palmer, M. Wills, *Tetrahedron: Asymmetry* **1999**, *10*, 2045–2061; c) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069; d) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, S. Heinz, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103–151.
[18] a) A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062–4066; b) H.-U. Blaser, W. Brieden, B. Pugin, F. Spindler, M. Studer, A. Togni, *Isotopics* **2002**, *19*, 3–16.
[19] D. Xiao, X. Zhang, *Angew. Chem. Int. Ed.* **2001**, *40*, 3425–3428.
[20] a) P. von Matt, A. Pfaltz, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566; b) A. Pfaltz, *Chimia* **2001**, *55*, 708–714; c) E. Guiu, C. Claver, J. Benet-Buchhold, S. Castillón, *Tetrahedron: Asymmetry* **2004**, *15*, 3365–3373.
[21] R. Margalef-Catala, C. Claver, F. Medina, P. Salagre, E. Fernandez, *Tetrahedron: Asymmetry* **2000**, *11*, 1469–1476.
[22] E. Guiu, B. Muñoz, C. Claver, S. Castillón, *Adv. Synth. Catal.* **2003**, *345*, 169–171.
[23] a) V. I. Tararov, R. Kadyrov, T. H. Riermeier, J. Holz, A. Börner, *Tetrahedron: Asymmetry* **1999**, *10*, 4009–4015; b) S. Vargas, M. Rubio, A. Suárez, A. Pizzano, *Tetrahedron Lett.* **2005**, *46*, 2049–2052.
[24] a) D. Horton, K. D. Philips, *Carbohydr. Res.* **1973**, *30*, 367–374; b) D. A. Otero, R. Simpson, *Carbohydr. Res.* **1984**, *128*, 79–86.
[25] M. Reetz, A. Gosberg, *Tetrahedron: Asymmetry* **1999**, *10*, 2129–2137.
[26] a) N. C. R. van Straten, G. A. van der Marel, J. H. van Boom, *Tetrahedron* **1997**, *53*, 6523–6538; b) N. C. R. van Straten, N. M. A. J. Kriek, Z. A. C. Cziria, G. A. van der Marel, J. H. van Boom, *Tetrahedron* **1997**, *53*, 6539–6554; c) S. Hamamoto, H. Takaku, *Chem. Lett.* **1986**, 1401–1404; d) T. Tanaka, S. Tamatsukuri, M. Ikehara, *Tetrahedron Lett.* **1986**, *27*, 199–202.
[27] G. J. H. Buisman, M. E. Martin, E. J. Vos, A. Klootwijk, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Tetrahedron: Asymmetry* **1995**, *6*, 719–738.
[28] a) C. Bianchini, A. Meli, F. Vizza, *Eur. J. Inorg. Chem.* **2001**, 43–68; b) P. Barbaro, C. Bianchini, A. Meli, M. Moreno, F. Vizza, *Organometallics* **2002**, *21*, 1430–1437.
[29] a) T. Morimoto, K. Achiwa, *Tetrahedron: Asymmetry* **1995**, *6*, 2661–2664; b) T. Morimoto, N. Nakajima, K. Achiwa, *Synlett* **1995**, 748–750; c) R. Sablong, J. A. Osborn, *Tetrahedron Lett.* **1996**, *37*, 4937–4940.
[30] G. Zhu, X. Zhang, *Tetrahedron: Asymmetry* **1998**, *9*, 2415–2418.
[31] a) F. Spindler, B. Pugin, H.-U. Blaser, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 558–559; b) K. Tani, J. Onouchi, T. Yamagata, Y. Kataoka, *Chem. Lett.* **1995**, 955–956.
[32] T. V. Rajanbabu, T. A. Ayers, G. Halliday, K. K. You, J. Calabrese, *J. Org. Chem.* **1997**, *62*, 6012–6028.
[33] W. Li, J. P. Waldkirch, X. Zhang, *J. Org. Chem.* **2002**, *67*, 7618–7623.

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