INDOLPhos: novel hybrid phosphine-phosphoramidite ligands for asymmetric hydrogenation and hydroformylation†

Jeroen Wassenaar and Joost N. H. Reek*

Received 2nd July 2007, Accepted 13th July 2007
First published as an Advance Article on the web 27th July 2007
DOI: 10.1039/b709956h

Hybrid bidentate phosphine-phosphoramidite ligands are prepared in a modular 2-step sequence and their rhodium complexes display high selectivity in rhodium catalysed hydrogenation and hydroformylation reactions.

Enantioselective transition metal catalysis has emerged as a unique tool for the introduction of chirality in pharmaceuticals and fine chemical intermediates. Asymmetric catalytic hydrogenation has become particular important as many different building blocks with a variety of functional groups becomes accessible.[1] Traditionally, chiral bidentate phosphine ligands[2] have dominated this field until more recently Feringa and De Vries,[3] Reetz[4] and Pringle[5] introduced the use of monodentate phosphites and phosphoramidites. Due to their more simple structure, their synthesis is generally much less elaborate enabling the preparation of large ligand libraries, which are required to rapidly find new catalysts that enable asymmetric conversion of new substrates. Although these monodentate based catalyst have been successful for many reactions, bidentate ligands, and heterobidentates in particular, will always be required to achieve high activity, selectivity and stability for a number of transformations. Therefore there is a need to develop novel bidentate ligands, preferentially with straightforward synthetic procedures. A recent advancement in this area is the use of supramolecular bidentate ligands[6,7] which form by assembly of functionalised simple monodentate building blocks. Alternatively, one could devise simple modular synthetic strategies that should lead to easy access to bidentate ligands. Here we present a series of hybrid bidentate phosphine-phosphoramidite ligands **2a–d** that are accessible by a two-step synthetic sequence from cheap commercially available building blocks.[8]‡ The new ligands display unusual coordination properties and are highly active and selective in the rhodium catalysed hydrogenation and hydroformylation.

Browning and co-workers have introduced indolylphosphines **1**, which are appealing to us as they are easily prepared in one step from cheap starting materials and offer further phosphorus functionalisation through the indolyl nitrogen.[10] The novel bidentate phosphine-phosphoramidite ligand (INDOLPhos) contains a two-atom bridge leading to the formation of five-membered coordination cycles as opposed to the frequently reported six-membered cycles.[9] In addition, molecular modelling indicates that the backbone is completely sp^2 hybridised thereby enforcing a high degree of rigidity (Fig. 1). The ridigity is expressed by large phosphine-phosphoramidite couplings in the ^{31}P NMR spectra of ligands **2a–d** (up to 250 Hz, see ESI†), which is also observed for other rigid small bite angle ligands.[8c,15] Therefore, INDOLPhos can be considered as a hybrid analogue of the successful DuPHOS in terms of bite-angle and rigidity, but variation of substituents is far more facile in the current ligand facilitating the synthesis of large and diverse ligand libraries.

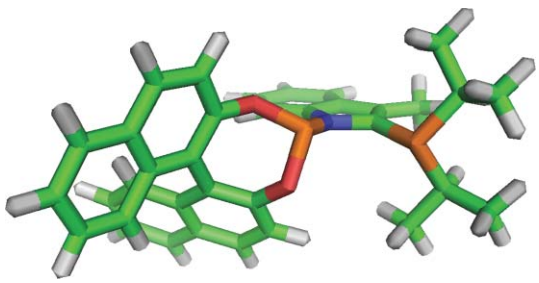


Fig. 1 Calculated (DFT, B3LYP, 6–31G*) structure of INDOLPhos **2b** (green = C, white = H, blue = N, red = O, yellow = P).

We have optimised the synthesis of indolylphosphines by using CO_2 as a protecting and directing group resulting in a one-pot protocol.[11] Deprotonation of the indolyl NH by *n*-BuLi is followed by carboxylation to yield the protected 1-carboxyl-3-methylindole *in situ.* Addition of *t*-BuLi results in selective deprotonation at the *ortho*-position of the carboxyl group to yield the 2-lithiated intermediate, which is reacted with the corresponding chlorophosphine. The carboxyl protecting group is removed by mild acidic work-up to give indolylphosphines **1** in good yield. Initial condensation attempts of **1** with bisnaphthol phosphorchloridites in the presence of weak bases such as triethylamine failed, probably due to the low nucleophilicity of the indolyl NH. Deprotonation using a strong base such as *n*-BuLi proved to be effective and INDOLPhos ligands **2a–d** are obtained in high yield (Scheme 1).

The coordination properties of ligands **2a–d** to cationic rhodium were investigated by ^1H and ^{31}P NMR spectroscopy. Mixing ligand **2a** with one equivalent of $[Rh(nbd)_2]BF_4$ in $CDCl_3$ led to the formation of a 1 : 4 mixture of the expected $[Rh(\mathbf{2a})(nbd)]BF_4$ and a second species exhibiting a complicated AA′XX′ multiplet in the ^{31}P NMR spectrum (Fig. 2). The second species could be identified as $[Rh(\mathbf{2a})_2]BF_4$ where phosphines and phosphoramidites of the two ligands are in mutual *cis* position as indicated by the large $J_{PN,PC}$ of 389 Hz (Fig. 3). To our knowledge this is the second report of such a bis-ligated species for hybrid bidentate phosphorus ligands.[12] Importantly, when changing the steric properties of the ligand to more bulky substituents on either the phosphine (**2b**) or bisnaphthol (**2c**), only mono-ligated species $[Rh(\mathbf{2b})(nbd)]BF_4$

Van't Hoff Institute for Molecular Sciences, University of Amsterdam, Nieuwe Achtergracht 166, 1018 WV Amsterdam, The Netherlands.E-mail: reek@science.uva.nl; Fax: +31 20 5256422; Tel: +31 20 5256437

† Electronic supplementary information (ESI) available: Ligand synthesis, experimental details and additional NMR spectra. See DOI: 10.1039/b709956h

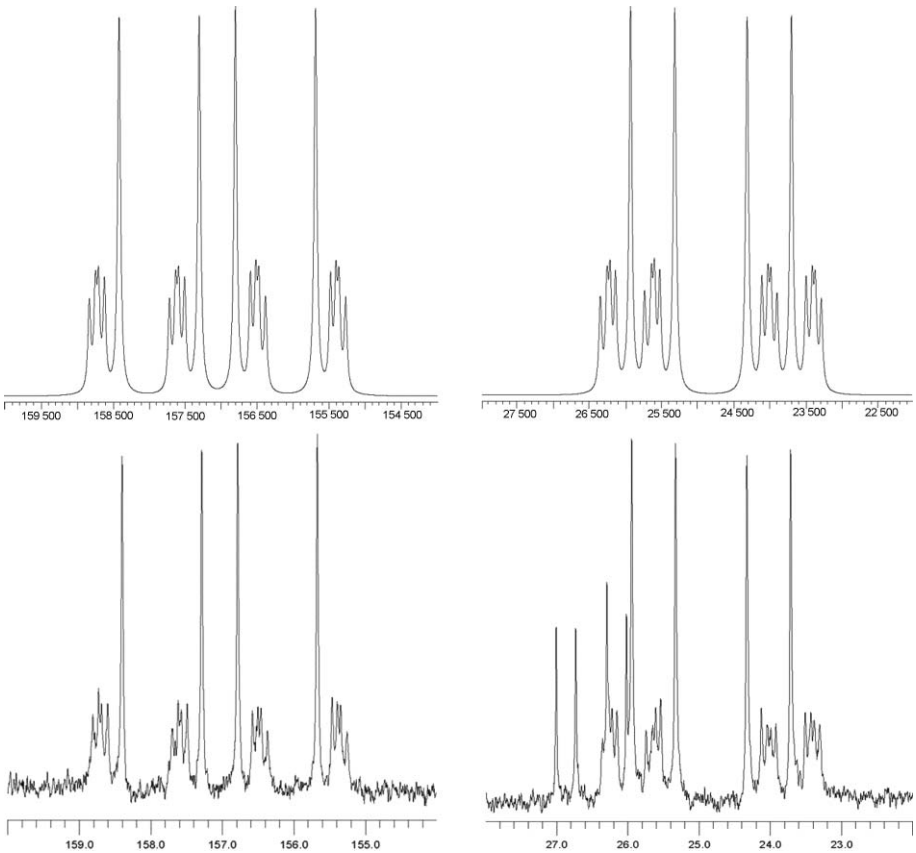
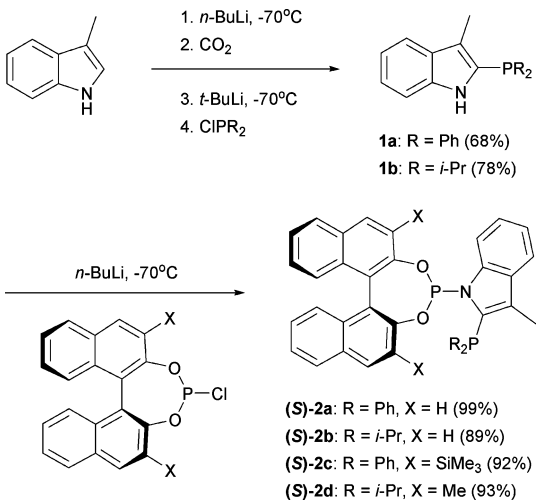


Fig. 2 Calculated (top) and measured (bottom) $^{31}P\{^{1}H\}$ NMR spectra for [Rh(**2a**)$_2$]BF_4. Coupling constants used for the simulated spectrum: $J_{PN,Rh}$ = 225 Hz, $J_{PC,Rh}$ = 124 Hz, $J_{PN,PN}$ = 26 Hz, $J_{PC,PC}$ = 17 Hz, $J_{PN,PC(cis)}$ = −62 Hz, $J_{PN,PC(trans)}$ = 389 Hz. The additional double doublet in the measured spectrum stems from [Rh(**2a**)(nbd)]BF_4.



Scheme 1 Synthesis of INDOLPhos ligands.

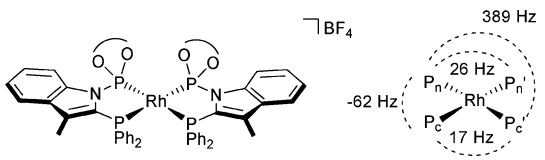
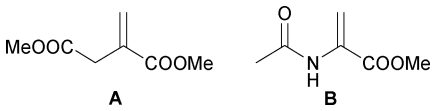


Fig. 3 Structure of [Rh(**2a**)$_2$]BF_4 (left) and assignment of ^{31}P NMR coupling constants (right).

and [Rh(**2c**)(nbd)]BF_4 were formed (Fig. S2–S4 ESI†). Additional factors disfavouring bis-ligated species in the case of **2b** and **2d** are the lack of π-stacking interactions and the stronger *trans*-effect of alkyl phosphines.

The special coordination properties of ligands **2a–d** prompted us to investigate their influence on the catalytic performance in the Rh-catalysed hydrogenation and hydroformylation. The hydrogenation of benchmark substrates dimethyl itaconate (**A**) and methyl 2-acetamidoacrylate (**B**) using ligands **2a–d** was studied (Table 1). To our surprise it was observed that ligand **2a**, although it forms unreactive bis-ligated species, was able to hydrogenate **A** and **B** to full conversion, inducing a considerable amount of ee (entries 1 and 5). It is proposed that the minor mono-ligated species performs most of the catalysis along with the achiral Rh-precursor which lowers the ee. Control experiments showed that ligand free [Rh(nbd)$_2$]BF_4 was able to fully convert **A** and **B** within 12 h. The more bulky ligand **2c** bearing trimethylsilyl groups in *ortho*-position on the bisnaphthol preventing bis-ligated species results in similar activities compared to ligand **2a** as full conversion is obtained. However, the selectivity obtained with the catalyst based on **2c** was rather low (36% and lower entries 3 and 7). Interestingly, full conversion and high selectivities were obtained when the steric bulk was introduced on the phosphine moiety (**2b**, up to 98% entries 2 and 6). For MAA (**B**), the enantioselectivity could be further enhanced by introducing methyl substituents in

Table 1 Rhodium catalysed asymmetric hydrogenation of dimethyl itaconate and methyl 2-acetamidoacrylate[a]



Entry	Ligand	Substrate	% conv.	% ee (config)
1	**2a**	**A**	100	73 (*S*)
2	**2b**	**A**	100	98 (*S*)
3	**2c**[b]	**A**	100	12 (*S*)
4	**2d**	**A**	100	92 (*S*)
5	**2a**	**B**	100	13 (*S*)
6	**2b**	**B**	100	86 (*R*)
7	**2c**[b]	**B**	100	36 (*R*)
8	**2d**	**B**	100	97 (*R*)

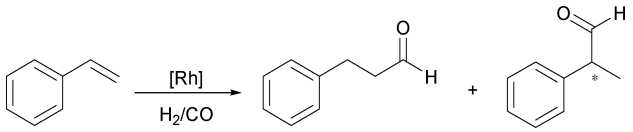
[a] Reactions were performed in CH_2Cl_2, Rh/L = 1 : 1.1, Rh/substrate = 1 : 100, 10 bar of H_2, at 25 °C for 16 h using $[Rh(nbd)_2]BF_4$ as metal precursor. [b] $[Rh(\mathbf{2c})(cod)]BF_4$ was used instead of the *in situ* generated catalyst.

ortho-position of the bisnaphthol moiety (**2d**, up to 97% entries 4 and 8).

In all ligands the absolute configuration of the bisnaphthol, the only source of chirality in the molecule, was identical. It is therefore surprising that **2a** gives the opposite enantiomer of the product compared to **2b–d** in the hydrogenation of **B** (entries 5–8). This result suggests that a different mechanism is operating in the case of **2a**.[13] Jugé *et al.* have described a similar effect when changing substituents on their hybrid aminophosphine–phosphinite system.[14] They observed a reversal of enantioselectivity when aryl substituents were replaced by alkyl, which is explained by steric effects in the intermediate olefin complexes forcing the substrate to coordinate with the other prochiral face. A similar explanation is likely for the origin of the effects we observe as the change in substituents is comparable.

After the promising results obtained in the hydrogenation we investigated the catalytic properties of ligands **2a–d** in the more challenging hydroformylation of styrene (Table 2). We were encouraged by the results of Zhang and co-workers who obtained complete enantioselection in the hydroformylation of styrene using a hybrid phosphine-phosphoramidite ligand derived from NOBIN.[8f] Initial results were disappointing as the application of parent ligand **2a** gave rise to low conversion (entry 1). Since the hydroformylation reaction is carried out in the presence of excess ligand with respect to rhodium, this low activity can be explained by the formation of inactive complexes with two ligands **2a** coordinated to rhodium, as was also observed in the NMR experiments (*vide supra*). Indeed, introduction of sterically more demanding groups suppresses the formation of such species. Instead active catalysts are formed that provide the product with moderate to good ee's with a maximum of 72% ee (ligand **2d** entry 5). A very high selectivity for the branched product with an *b*/*l* ratio of 17 was obtained using ligand **2b** (entry 2). We expect that further optimization of this ligand will lead to a catalyst that will give both high regio- and enantio-selectivity.

Table 2 Rhodium catalysed asymmetric hydroformylation of styrene[a]



Entry	*T*/°C	Ligand	% conv.[b]	*b*/*l*[c]	% ee[d]
1[e]	60	**2a**	3	2	0
2[f]	40	**2b**	84	17	50
3	60	**2b**	55	6	51
4	60	**2c**	99	12	9
5	40	**2d**	96	10	72
6	60	**2d**	97	7	61

[a] $[Rh(acac)(CO)_2]$ = 1.0 mmol l^{-1} in toluene, [ligand] = 4.0 mmol l^{-1}, styrene/rhodium = 1000, pressure = 10 bar (CO/H_2 = 1/1). [b] Percentage conversion; the reaction was stopped after 19 h. [c] Ratio of branched to linear product. [d] In all cases the *R* enantiomer of the product was formed. [e] 48 h. [f] 65 h.

In summary, we have developed a new set of hybrid bidentate phosphine-phosphoramidite ligands based on the indole backbone. Their coordination mode to Rh is controlled by the steric properties of the ligand which has been shown to play a major role in the asymmetric hydrogenation and hydroformylation. High enantioselectivities (up to 98% ee) are obtained with ligands **2b** and **2d** in the hydrogenation. A high selectivity for the branched aldehyde along with good ee (up to 72%) is reached in the hydroformylation of styrene. The modular synthetic sequence allows for easy derivatization of the ligand enabling high-throughput screening of a INDOLPhos library to convert more challenging substrates. We are currently exploring this strategy along with elucidating the true origin of the ligand-size dependent enantioselection in the hydrogenation of **B**.

Acknowledgements

We gratefully acknowledge NRSCC for financial support.

Notes and references

‡ Prices for starting materials according to the 2007–2008 Aldrich catalogue: 3-methylindole, 2.16 € g^{-1}; chlorodiphenylphosphine, 0.69 € g^{-1}; (*S*)-BINOL, 3.14 € g^{-1}; phosphorus trichloride, < 0.02 € g^{-1}.

1 For an exhaustive review on homogeneous hydrogenation see: *The Handbook of Homogeneous Hydrogenation*, ed. J. G. de Vries, C. J. Elsevier, Wiley-VCH, Weinheim, 2007.
2 For a recent review see: W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029 and references cited therein.
3 M. van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries and B. L. Feringa, *J. Am. Chem. Soc.*, 2000, **122**, 11539.
4 M. T. Reetz and G. Mehler, *Angew. Chem., Int. Ed.*, 2000, **39**, 3889.
5 C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen and P. G. Pringle, *Chem. Commun.*, 2000, 961.
6 (*a*) V. F. Slagt, P. W. N. M. van Leeuwen and J. N. H. Reek, *Chem. Commun.*, 2003, 2474; (*b*) V. F. Slagt, P. W. N. M. van Leeuwen and J. N. H. Reek, *Angew. Chem., Int. Ed.*, 2003, **42**, 5619; (*c*) V. F. Slagt, M. Röder, P. C. J. Kamer, P. W. N. M. van Leeuwen and J. N. H. Reek, *J. Am. Chem. Soc.*, 2004, **126**, 4056; (*d*) J. N. H. Reek, M. Röder, P. E. Goudriaan, P. C. J. Kamer, P. W. N. M. van Leeuwen and V. F. Slagt, *J. Organomet. Chem.*, 2005, **605**, 4505; (*e*) X.-B. Jiang, L. Lefort, P. E. Goudriaan, A. H. M. de Vries, P. W. N. M. van Leeuwen, J. G. de Vries and J. N. H. Reek, *Angew. Chem., Int. Ed.*, 2006, **45**, 1223; (*f*) A. J. Sandee, A. M. van der Burg and J. N. H. Reek, *Chem. Commun.*, 2007, 864; (*g*) M. Kuil, P. E. Goudriaan, P. W. N. M. van Leeuwen and J. N. H. Reek, *Chem. Commun.*, 2006, 4679.
7 (*a*) B. Breit and W. Seiche, *J. Am. Chem. Soc.*, 2003, **125**, 6608; (*b*) B. Breit and W. Seiche, *Angew. Chem., Int. Ed.*, 2005, **44**, 1640; (*c*) B. Breit

and W. Seiche, *J. Am. Chem. Soc.*, 2003, **125**, 6608; (*d*) F. Chevallier and B. Breit, *Angew. Chem., Int. Ed.*, 2006, **45**, 1599; (*e*) J. M. Takacs, D. S. Reddy, S. A. Moteki, D. Wu and H. Palencia, *J. Am. Chem. Soc.*, 2004, **126**, 4494; (*f*) P. A. Duckmanton, A. J. Blake and J. B. Love, *Inorg. Chem.*, 2005, **44**, 7708.

8 For other examples of hybrid phosphine-phosphoramidite ligands see: (*a*) G. Franciò, F. Faraone and W. Leitner, *Angew. Chem., Int. Ed.*, 2000, **39**, 1428; (*b*) S. Burk, G. Franciò and W. Leitner, *Chem. Commun.*, 2005, 3460; (*c*) G. Calabrò, D. Drommi, G. Bruno and F. Faraone, *Dalton Trans.*, 2004, 81; (*d*) G. Calabrò, D. Drommi, C. Graiff, F. Faraone and A. Tiripicchio, *Eur. J. Inorg. Chem.*, 2004, **7**, 1447; (*e*) S. K. Mandal, G. A. N. Gowda, S. S. Krishnamurthy, T. Stey and D. Stalke, *J. Organomet. Chem.*, 2005, **690**, 742; (*f*) Y. Yan and X. Zhang, *J. Am. Chem. Soc.*, 2006, **128**, 7198; (*g*) X.-P. Hu and Z. Zheng, *Org. Lett.*, 2004, **6**, 3585; (*h*) X.-P. Hu and Z. Zheng, *Org. Lett.*, 2005, **7**, 419; (*i*) J.-D. Huang, X.-P. Hu, Z.-C. Duan, Q.-H. Zeng, S.-B. Yu, J. Deng, D.-Y. Wang and Z. Zheng, *Org. Lett.*, 2006, **8**, 4367; (*j*) F. Boeda, D. Rix, H. Clavier, C. Crévisy and M. Mauduit, *Tetrahedron: Asymmetry*, 2006, **17**, 2726; (*k*) K. A. Vallianatou, I. D. Kostas, J. Holz and A. Börner, *Tetrahedron Lett.*, 2006, **47**, 7947.

9 A flexible two-atom bridged hybrid phosphine-phosphite bidentate has been reported by Faraone *et al.*: C. G. Arena, F. Faraone, C. Graiff and A. Tiripicchio, *Eur. J. Inorg. Chem.*, 2002, 711.

10 J. O. Yu, E. Lam, J. L. Sereda, N. C. Rampersad, A. J. Lough, C. S. Browning and D. H. Farrar, *Organometallics*, 2005, **24**, 37.

11 A. R. Katritzky and K. Akutagawa, *Synth. Commun.*, 1988, **18**, 1151.

12 A similar species has been detected for hybrid phosphine-phosphite ligands by Pizzano *et al.*: M. Rubio, S. Vargas, A. Suárez, E. Álvarez and A. Pizzano, *Chem.–Eur. J.*, 2007, **13**, 1821.

13 For a recent review on the mechanism of Rh-catalysed asymmetric hydrogenation see: I. D. Gridnev and T. Imamoto, *Acc. Chem. Res.*, 2004, **37**, 633.

14 C. Darcel, D. Moulin, J.-C. Henry, M. Lagrelette, P. Richard, P. D. Harvey and S. Jugé, *Eur. J. Org. Chem.*, 2007, 2078.

15 Y. Berens, U. Englert, S. Geyser, J. Runsink and A. Salzer, *Eur. J. Org. Chem.*, 2006, 2100.