# UREAphos: supramolecular bidentate ligands for asymmetric hydrogenation†

**Albertus J. Sandee, Alida M. van der Burg and Joost N. H. Reek***

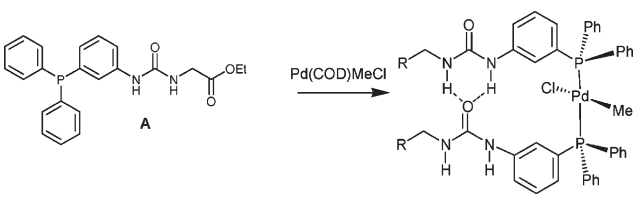
*Received (in Cambridge, UK) 6th October 2006, Accepted 6th November 2006*
*First published as an Advance Article on the web 24th November 2006*
**DOI: 10.1039/b614571j**

**Supramolecular bidentate phosphite ligands are presented as a new class of ligands for rhodium catalysed asymmetric hydrogenation.**

Chiral bidentate ligands[1] have dominated the field of asymmetric transition metal catalysis for more than 30 years. However, since the recent breakthrough by Feringa and de Vries,[2] Reetz[3] and Pringle,[4] showing that metal complexes based on monodentate ligands can provide highly enantioselective catalysts, many examples using monodentate ligands have appeared in the literature.[5] The main reason for the preference for monodentate over bidentate ligands is their relative ease of preparation, facilitating the preparation of large catalyst libraries. Recently, we[6] and others[7] have introduced a new class of bidentate ligands that form by a self-assembly process of two monodentate ligands.[8] After the successful exploration of our SUPRAphos[6c,d,e] library based on porphyrin appended ligands we decided to extend our recently introduced nonchiral urea-based homo-bidentate ligands[9] to chiral analogues for use in asymmetric conversions.[10] This class should lead to a novel class of supramolecular bidentate ligands that is easily accessible. Here we report the synthesis of urea appended chiral phosphite building blocks and their successful use in rhodium catalysed hydrogenation of various substrates.

We, and the group of Love[7f] have independently introduced novel phosphine ligands containing appended urea groups. These self-complementary hydrogen bond motifs enable the formation of supramolecular bidentate ligands.[9] We showed that bidentate ligands form *in situ* by just mixing two equivalents of ligand **A** in the presence of a palladium precursor to provide [Pd(**A**)$_2$MeCl] (Scheme 1).

The current ligand building blocks (Chart 1, **B**–**G**)† consist of a similar urea-type hydrogen bond motif, a chiral phosphite ligand




**Scheme 1** Formation of a palladium complex based on a supramolecular bidentate ligand (**A**).

*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)20-525-6422; Tel: (+31)20-525-6437*

† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b614571j

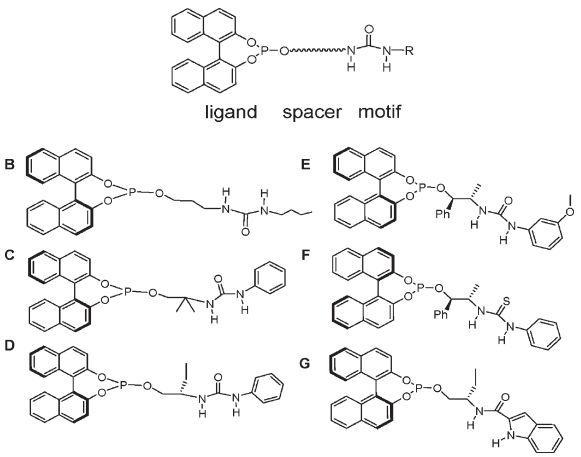



**Chart 1**

based on the bisnaphthol backbone, and a (chiral) spacer to connect these functions (Chart 1, top). Small differences in spacer and motif were applied to create a small series of ligand building blocks.† **F** is the only ligand containing an *R*-bisnaphthol backbone; all the others contain the *S*-bisnaphthol backbone. The spacers of building blocks **D**, **E**, **F** and **G** contain additional chirality (see Chart 1 for details). **F** is the only ligand that contains a thiourea motif, **G** is utilised with an indole-amide binding motif whereas all other systems are functionalised with the urea binding motif.

It is important to note that all ligand building blocks are easily accessible and amenable to simple variation to facilitate the preparation of large, diverse libraries at a later stage. Indeed, all compounds were obtained *via* a simple two-step synthetic procedure, consisting of a coupling of an amino-alcohol with an iso(thio)cyanate to obtain the urea-alcohol that is subsequently reacted with 2,2′-bisnaphthol phosphorochloridite to obtain the urea containing phosphites. These ligands were characterised and [Rh(**D**)$_2$(NBD)](BF$_4$) was investigated as an archetypal complex by NMR and IR to study the structure of this type of complexes and support the presence of intramolecular H-bonding between the two ligands attached to the metal centre (see ESI). In analogy to **A** (and complexes thereof) studied previously,[9] it was observed that at low concentration (5 mM) the Ar–NH moiety of ligand **D** is predominantly in the non-associated state (N–H stretch at 3430 cm$^{-1}$). In contrast, in [Rh(**D**)$_2$(NBD)](BF$_4$) the majority of the N–H is found to be in the hydrogen bonded form (N–H stretch at 3360 cm$^{-1}$). As expected, the Ar–NH-signal in the $^1$H-NMR spectrum varies with the ligand concentration (from 5 mM to 40 mM), indicating the formation of intermolecular hydrogen bonds. In the complex [Rh(**D**)$_2$(NBD)](BF$_4$), this signal does not

shift in this concentration range, since it is involved in an intramolecular hydrogen bond (see ESI).[11] These experiments clearly demonstrate that these phosphite ligands behave similarly to **A**; they self-aggregate at high concentrations in solution or form intramolecular hydrogen bonds when coordinated to a transition metal. In contrast to what is observed for [Pd(**A**)$_2$MeCl] and in agreement with what is generally observed for rhodium–phosphite complexes,[12a] the ligands are coordinated in a *cis*-configuration about the metal centre in [Rh(**D**)$_2$(NBD)](BF$_4$) as evidenced by $^{31}$P NMR.[12b]

Next, the ligands were explored as supramolecular bidentate ligands in rhodium catalysed asymmetric hydrogenation reactions (Table 1).‡ Two of the six ligands provided rhodium complexes that hydrogenated dimethyl itaconate in more than 90% ee, and most catalysts gave 100% conversion of this substrate. The most selective catalyst was [Rh(**G**)$_2$] (Table 1 entry 7). It provided an enantioselectivity of 95.8% to the *S*-product at 100% conversion after a reaction of 18 hours at room temperature.

The huge difference in catalyst performance between metal complexes based on **E** and **F** (entries 5 and 6) must be caused by the thio-urea functional group since this is the main difference between the ligands. An explanation for this is that the sulfur of the thio-urea can also coordinate to rhodium, potentially giving rise to PS-coordination complexes.[14] In addition, thio-ureas show much weaker self-association behaviour than oxygen based ureas.[13] The current results suggest that the thio-urea is not a suitable binding motif for the formation of supramolecular ligands for rhodium catalysed hydrogenation.

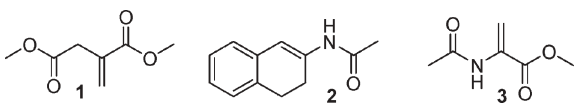
The absolute chirality of the product is clearly determined by the nature of the bisnaphthol since all catalysts yielded the *S*-product except that based on **F**, which was the only building block prepared from the *R*-bisnaphthol. The difference in ee obtained with the catalysts based on **E** and **C** (entries 5 and 3) (92.7, 16.6% ee, respectively) indicates that the introduction of chirality in the spacer can result in huge improvements of the selectivity. Comparison of the selectivity induced by [Rh(**G**)$_2$] and [Rh(**D**)$_2$] (95.8% *vs.* 46%) (entries 7 and 4) shows that a change in binding motif can also have major consequences. The reason for the large effect is currently not clear, but it is likely that the increased acidity of one of the N–H moieties in ligand **G** increases the affinity between the building blocks, thereby making the complex more rigid. At this stage we cannot rule out the possibility that steric effects introduced by the indole, although it is positioned remotely, are the origin of the effect observed. Surprisingly, the rhodium complex formed from ligand **B**, which contains a simple C$_3$ amino-alcohol spacer and an n-butyl urea binding motif, did not give any conversion in this catalytic process. Since this ligand has the most flexible spacer (C3 and no substituents) between the ligand and the urea, it is likely that intramolecular urea coordination to rhodium metal reduces the catalytic activity of the complex.

In general, large differences are observed, making the current approach and building blocks very interesting since extension of the library is straightforward due to the availability of chiral amino-alcohols and isocyanides.

After these interesting initial results we also studied the hydrogenation of *N*-(3,4-dihydro-2-naphthalenyl)-acetamide (**2**), which is a much more challenging substrate both in terms of conversion and selectivity.[15] Upon applying rhodium catalysts based on **A**–**G**, conversions were obtained between 0.4 to 100% and the selectivity ranged from 37.9% for the *S*-enantiomer to 76.5% for the *R*-enantiomer. Also in the hydrogenation of **2** the enantioselective outcome of the catalysis is determined by the chirality of the bisnaphthol backbone; only [Rh(**F**)$_2$] resulted in preference for the formation of the *S*-product (entry 13). The difference in results for catalysts based on **C**, **D** and **E** in this conversion (providing 76.5, 60.7% and 52.5 ee, respectively) (entries 10, 11 and 12) shows the influence of the nature of the amino-alcohol spacer on the enantioselectivity. The nature of the binding motif also appeared important in the hydrogenation of **2**. The thio-urea motif again slows down the catalysis; [Rh(**F**)$_2$] only gave 0.4% conversion (entry 13). Remarkably, the amide-indole functionalised ligand **G** provides a catalyst [Rh(**G**)$_2$] that gives an almost racemic product mixture (1.5% ee only) (entry 14), whereas in the hydrogenation of **1** this ligand was found to provide the most selective catalyst. Similar to the hydrogenation of **1**, the ability to vary the amino-alcohol spacer as well as the binding motif provides new handles for catalyst fine-tuning. The most selective catalyst, [Rh(**C**)$_2$], provided 76.5% ee towards the *R*-product (entry 10), which makes this the second best rhodium catalyst in terms of selectivity (obtained at conversion of 12.3%).[6e,15] The application of monodentate phosphoramidite ligands results only in very low ee (up to 34%) in this reaction as was previously reported.[15b]

In the hydrogenation of methyl 2-acetamidoacrylate (**3**) we found similar trends. Four catalysts provided full conversion while [Rh(**F**)$_2$] (entry 20) and [Rh(**B**)$_2$] (entry 16) showed low and no conversion respectively. The chirality of the bisnaphthol determines the chirality of the product while fine-tuning is established by the choice of the amino-alcohol spacer. Both [Rh(**C**)$_2$] and [Rh(**D**)$_2$] provided the product in high selectivity; 93.6% and 92.3%

**Table 1** Rhodium catalysed asymmetric hydrogenation of various substrates using UREA-phos ligands



| Entry | Ligand[a] | Substrate | Conversion [%] | Ee [%] (config) |
|---|---|---|---|---|
| 1 | **A** | **1** | 100 | 0 |
| 2 | **B** | **1** | 0 | 0 |
| 3 | **C** | **1** | 100 | 16.6 (*S*) |
| 4 | **D** | **1** | 100 | 46 (*S*) |
| 5 | **E** | **1** | 100 | 92.7 (*S*) |
| 6 | **F(R)** | **1** | 100 | 13.8 (*R*) |
| 7 | **G** | **1** | 100 | 95.8 (*S*) |
| 8 | **A** | **2** | 100 | 0 |
| 9 | **B** | **2** | 4 | 4 (*R*) |
| 10 | **C** | **2** | 12.3 | 76.5 (*R*) |
| 11 | **D** | **2** | 4.1 | 60.7 (*R*) |
| 12 | **E** | **2** | 34.1 | 52.5 (*R*) |
| 13 | **F(R)** | **2** | 0.4 | 37.9 (*S*) |
| 14 | **G** | **2** | 26.1 | 1.5 (*R*) |
| 15 | **A** | **3** | 100 | 0 |
| 16 | **B** | **3** | 0 | 0 |
| 17 | **C** | **3** | 100 | 93.6 (*R*) |
| 18 | **D** | **3** | 100 | 92.3 (*R*) |
| 19 | **E** | **3** | 100 | 82.1 (*R*) |
| 20 | **F(R)** | **3** | 36.9 | 44.6 (*S*) |

[a] All ligands based on *S*-bisnaphthol phosphite backbone, unless noted differently.

ee respectively (entries 17 and 18). In this process a large phenyl-group on the α-position in the spacer (in **E**) appeared to have a negative effect on the selectivity.

In conclusion, we have introduced a new class of supramolecular bidentate phosphite ligands that was successfully applied in the rhodium catalysed asymmetric hydrogenation of various substrates. The small series employed in this contribution have already provided hydrogenation catalysts that are highly selective. The easy accessibility of these ligands and the huge potential for catalyst tuning make them highly suitable for combinatorial approaches and high throughput screening experimentation. We are currently developing a fully automated preparation protocol for this new class of ligands and these results will be reported in due course.

Engelhard De Meern B.V. and the Ministry of Economic Affairs are gratefully acknowledged for financial support.

## Notes and references

‡ All reactions were performed in $CH_2Cl_2$, Rh : L = 1 : 2.4, Rh : substrate = 1 : 100, 10 bar of $H_2$, 18 h at room temperature.


1 For a recent review on bidentate ligands in asymmetric hydrogenation, see: W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029 and references cited therein.

2 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.

3 M. T. Reetz and G. Mehler, *Angew. Chem., Int. Ed.*, 2000, **39**, 3889.

4 C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen and P. G. Pringle, *Chem. Commun.*, 2000, 961.

5 For a recent review on monodentate ligands, see: (*a*) T. Jerphagnon, J.-L. Renaud and C. Bruneau, *Tetrahedron: Asymmetry*, 2004, **15**, 2101 and references cited therein; (*b*) J. G. de Vries, in *Handbook of Chiral Chemicals*, ed. D. Ager, S. Laneman, CRC Press, New York, 2nd edn, 2005.

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.

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 recent reviews on this subject see: (*a*) M. J. Wilkinson, P. W. N. M. van Leeuwen and J. N. H. Reek, *Org. Biomol. Chem.*, 2005, **3**, 2371; (*b*) B. Breit, *Angew. Chem., Int. Ed.*, 2005, **44**, 6816; (*c*) A. J. Sandee and J. N. H. Reek, *Dalton Trans.*, 2006, 3385.

9 L. K. Knight, Z. Freixa, P. W. N. M. van Leeuwen and J. N. H. Reek, *Organometallics*, 2006, **25**, 954.

10 During the preparation of this manuscript an example of asymmetric hydrogenation using self-assembled ligands by means of hydrogen bonds was reported: M. Weis, C. Waloch, W. Seiche and B. Breit, *J. Am. Chem. Soc.*, 2006, **128**, 4188.

11 Upon increasing the concentration further, higher order aggregates are observed. These are, however, of no significance to catalysis since that is typically performed at lower concentrations.

12 Observed $^{31}P$ NMR signal for [Rh(**D**)$_2$(NBD)](BF$_4$): $^{31}P$ NMR ($CDCl_3$, 162.0 MHz) $\delta$ 164.4 (d, $J_{RhP}$ = 220 Hz) which is typical for *cis*-bisphosphite complexes, see: P. C. J. Kamer, J. N. H. Reek and P. W. N. M. van Leeuwen, Rhodium Phosphite Catalysts, *Catal. Met. Complexes*, 2000, **22**, 35.

13 P. Bühlmann, S. Nishizawa, K. P. Xiao and Y. Umezawa, *Tetrahedron*, 1997, **53**, 1647.

14 Hydrogenation catalysis using PS-coordinating ligands including thiourea functional groups has been previously reported by Tiripicchio *et al.*: D. Cauzzi, M. Costa, N. Cucci, C. Graiff, F. Grandi, G. Predieri, A. Tiripicchio and R. Zanoni, *J. Organomet. Chem.*, 2000, **593**, 431.

15 (*a*) Z. Zhang, G. Zhu, Q. Jiang, D. Xiao and X. Zhang, *J. Org. Chem.*, 1999, **64**, 1774; (*b*) H. Bernsmann, M. van den Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. de Vries and B. L. Feringa, *J. Org. Chem.*, 2005, **70**, 943.