Enantioselective conjugate addition of phenylboronic acid to enones catalysed by a chiral tropos/atropos rhodium complex at the coalescence temperature†

Chiara Monti,[a] Cesare Gennari*[a] and Umberto Piarulli*[b]

Received (in Cambridge, UK) 22nd June 2005, Accepted 31st August 2005
First published as an Advance Article on the web 21st September 2005
DOI: 10.1039/b508832a

A highly enantioselective rhodium-catalysed conjugate addition of phenylboronic acid to cyclic enones has been achieved using a dynamic library of chiral phosphorus ligands; the tropos/atropos nature of the ligands in the rhodium complex has been characterised *via* ^{31}P-NMR.

The asymmetric rhodium-catalysed conjugate addition of aryl- and vinylboronic acids, originally reported by Miyaura and Hayashi, has become the method of choice for the stereoselective introduction of an aryl or a vinyl group in the β position of a variety of electron-deficient olefins.[1] Excellent enantioselectivities were obtained using both bidentate (binap, segphos, chiraphos, diphosphonites, diphosphites, amidomonophosphines, chiral dienes) and more recently monodentate ligands (binaphtholic phosphoramidites).[2]

In this paper we report a highly enantioselective rhodium-catalysed conjugate addition of phenylboronic acid to cyclic enones using a dynamic library of chiral phosphorus ligands, and characterise the tropos/atropos nature of the ligands in the rhodium complex *via* ^{31}P-NMR.

A library of nineteen chiral tropos phosphorus ligands, based on a flexible (tropos) biphenol unit and a chiral P-bound alcohol (eleven phosphites) or secondary amine (eight phosphoramidites), was recently synthesised and used in the rhodium-catalysed asymmetric hydrogenation of prochiral olefins.[3] These ligands exist as a mixture of two rapidly interconverting diastereomers, L^a and $L^{a'}$, differing in the conformation of the biphenol unit and not discernible on the NMR time scale (Fig. 1). Upon complexation with Rh, the ligand (L^a in equilibrium with $L^{a'}$) should give rise to three different species, namely RhL^aL^a, $RhL^aL^{a'}$, $RhL^{a'}L^{a'}$. These three diastereomeric species, which might be interconverting, are generated in proportions which most likely differ from the statistical value (1 : 2 : 1). Following the lead of Reetz and co-workers[4] and Feringa and co-workers,[5] we used a combination of two of these ligands (L^a in equilibrium with $L^{a'}$ and L^b in equilibrium with $L^{b'}$) and generated a dynamic *in situ* library, with up to ten different species theoretically present in solution:

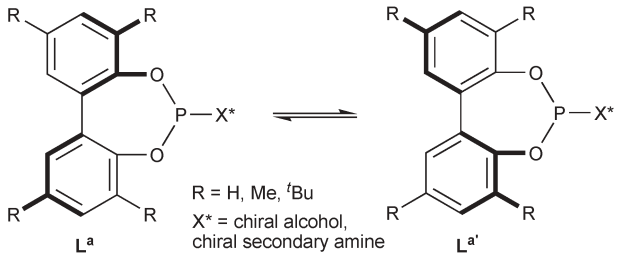


Fig. 1 Chiral phosphorus ligands based on a chiral P-bound alcohol or secondary amine and a flexible (tropos) P-bound biphenol unit.

RhL^aL^a, $RhL^aL^{a'}$, $RhL^{a'}L^{a'}$, RhL^bL^b, $RhL^bL^{b'}$, $RhL^{b'}L^{b'}$, RhL^aL^b, $RhL^aL^{b'}$, $RhL^{a'}L^b$, $RhL^{a'}L^{b'}$. Although each species could, in principle, be present and catalyse the reaction, one of them could overcome the others, determining the direction and the extent of the enantioselectivity.

The library of eleven biphenolic phosphites and eight biphenolic phosphoramidites was screened in the conjugate addition of phenylboronic acid to 2-cyclohexenone **2**, using 1.5 mol% $[Rh(C_2H_4)_2Cl]_2$‡ and a total of 6 mol% of ligands (Rh : L = 1 : 2; see the ESI for the ligand structures and the complete screening results). The reaction was performed using KOH (1 equiv) as base,[6] in a 10 : 1 dioxane/water solution at room temperature overnight. A few selected results are presented in Table 1, and the relevant ligands are shown in Fig. 2. In general, when the chiral ligands were used individually (homocombinations) the phosphites gave more efficient catalysts and higher enantioselectivity than the phosphoramidites. However, the enantiomeric excesses were only moderate and the best ee was 70% with phosphite **7**-$P(O)_2O$ (Table 1, entry 1). Mixtures of a phosphite and a phosphoramidite (heterocombinations) gave reduced yields and ee's in comparison with the phosphite alone, in all combinations except those containing either phosphoramidite **11**-$P(O)_2N$ or **12**-$P(O)_2N$. In these heterocombinations, considerably higher ee's and quantitative yields were obtained. In particular, (*R*)-3-phenylcyclohexanone **5** was obtained in 95% ee (100% yield) with phosphoramidite **11**-$P(O)_2N$ and phosphite **7**-$P(O)_2O$ (Table 1, entry 5), and in 91% ee (100% yield) with phosphoramidite **11**-$P(O)_2N$ and phosphite **8**-$P(O)_2O$ (Table 1, entry 6). In the latter case, the synergistic effect of the heterocombination with respect to the corresponding homocombinations is worth an additional 55% ee [**8**-$P(O)_2O$ 28% ee, **11**-$P(O)_2N$ 36% ee]. The mismatched combinations gave (*S*)-3-phenylcyclohexanone **5** in 70% ee (100% yield) with phosphoramidite **12**-$P(O)_2N$ and phosphite **7**-$P(O)_2O$ (Table 1, entry 7), and 87% ee (100% yield) with phosphoramidite

[a]*Dipartimento di Chimica Organica e Industriale, Centro di Eccellenza C. I. S. I., Università degli Studi di Milano, Istituto di Scienze e Tecnologie Molecolari (ISTM) del CNR, Via G. Venezian 21, Milano, 20133, Italy. E-mail: cesare.gennari@unimi.it; Fax: +39 02 5031 4072; Tel: +39 02 5031 4091*
[b]*Dipartimento di Scienze Chimiche e Ambientali, Università dell'Insubria, via Valleggio 11, Como, 22100, Italy. E-mail: umberto.piarulli@uninsubria.it*
† Electronic supplementary information (ESI) available: Comprehensive experimental data for the library screening and ^{31}P-NMR characterisation of the rhodium complexes. See http://dx.doi.org/10.1039/b508832a

Table 1 Selected results from the screening of the library of chiral phosphites and phosphoramidites (homo- and heterocombinations) in the rhodium-catalysed conjugate addition of phenylboronic acid to cyclic enones

Entry	Enone	L^a	L^b	Yield (%)[a]	Ee (%)[b]
1	**2**	**7**-$P(O)_2O$	**7**-$P(O)_2O$	100	70 (*R*)
2	**2**	**8**-$P(O)_2O$	**8**-$P(O)_2O$	100	28 (*R*)
3	**2**	**11**-$P(O)_2N$	**11**-$P(O)_2N$	100	36 (*R*)
4	**2**	**12**-$P(O)_2N$	**12**-$P(O)_2N$	100	36 (*S*)
5	**2**	**7**-$P(O)_2O$	**11**-$P(O)_2N$	**100**	**95 (*R*)**[c]
6	**2**	**8**-$P(O)_2O$	**11**-$P(O)_2N$	100	91 (*R*)
7	**2**	**7**-$P(O)_2O$	**12**-$P(O)_2N$	100	70 (*S*)
8	**2**	**8**-$P(O)_2O$	**12**-$P(O)_2N$	100	87 (*S*)
9	**3**	**8**-$P(O)_2O$	**12**-$P(O)_2N$	100	80 (*S*)
10	**3**	**9**-$P(O)_2O$	**12**-$P(O)_2N$	80	83 (*S*)
11	**3**	**7**-$P(O)_2O$	**11**-$P(O)_2N$	**100**	**90 (*R*)**[c]
12	**3**	**8**-$P(O)_2O$	**11**-$P(O)_2N$	100	90 (*R*)
13	**1**	**10**-$P(O)_2O$	**10**-$P(O)_2O$	100	58 (*S*)
14	**1**	**7**-$P(O)_2O$	**11**-$P(O)_2N$	**100**	**73 (*R*)**[c]
15	**1**	**8**-$P(O)_2O$	**11**-$P(O)_2N$	100	68 (*R*)

[a] GC yield, using *n*-tridecane as internal standard. [b] Determined by GC. For **4**: SUPELCO γ-DEX 225, 25 m, film 0.25 μm, carrier H_2. For **5** and **6**: MEGADEX DACTBSβ, OV 1701, 25 m, film 0.25 μm, carrier H_2. [c] Using the combination of **12**-$P(O)_2N$ and *ent*-**7**-$P(O)_2O$, the opposite enantiomer (*S*) was obtained with the same yield and ee.

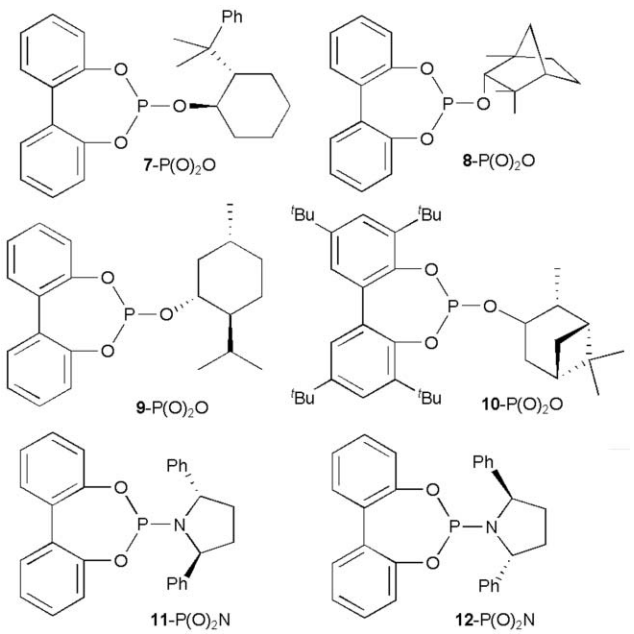
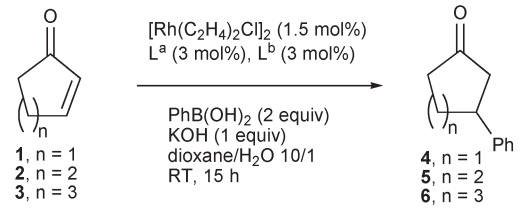


Fig. 2 Selected phosphites and phosphoramidites.

12-$P(O)_2N$ and phosphite **8**-$P(O)_2O$ (Table 1, entry 8), showing that it is the phosphoramidite which determines the absolute configuration of the reaction product. Again, the synergistic effect of the heterocombination is remarkable. The effect of the ring-size was then evaluated. 2-Cyclopentenone **1** and 2-cycloheptenone **3** were investigated using all the homocombinations and several heterocombinations (see Table 1 for selected results and the ESI for the complete screening). The best results were again obtained using the heterocombinations containing the 2,5-diphenylpyrrolidine phosphoramidites [**11**-$P(O)_2N$ or **12**-$P(O)_2N$] (Table 1, entries 9–15). The matched combination **7**-$P(O)_2O$/**11**-$P(O)_2N$ afforded (*R*)-3-phenylcycloheptanone **6** in 90% ee (100% yield) and (*R*)-3-phenylcyclopentanone **4** in 73% ee (100% yield).



The remarkable increase in ee obtained with the **7**-$P(O)_2O$/**11**-$P(O)_2N$ heterocombination compared to the single ligands, prompted us to study the tropos/atropos nature[7] of the ligands in the rhodium complex. The metal complexes containing biphenolic tropos ligands (phosphites or phosphoramidites) were defined as "induced atropisomeric" by Alexakis[8] and "fluxionally atropisomeric" by Reetz.[9] However, no proof was ever presented regarding their tropos or atropos nature. A variable-temperature ^{31}P-NMR study of the ligands **7**-$P(O)_2O$ and **11**-$P(O)_2N$ and of the rhodium complexes [Rh(acac)L_2] which originate from their homo- ($2L^a$, $2L^b$) and heterocombination (L^a + L^b) was undertaken, using Rh(acac)$(C_2H_4)_2$ as the metal source.§[10] Both ligands showed a singlet by ^{31}P-NMR spectroscopy, whose multiplicity did not change over the temperature range 230–380 K. A doublet (J_{P-Rh} = 296 Hz, toluene-d_8) was observed for the rhodium complex of phosphite **7**-$P(O)_2O$ over the temperature range 230–380 K,¶ and this demonstrates the tropos nature of the ligand in the complex even at low temperatures.‖[11] Interestingly, the spectra of the rhodium complex of phosphoramidite **11**-$P(O)_2N$ showed typical coalescence behavior (Fig. 3).**

In fact, the spectrum at 380 K (Fig. 3, upper trace) consists of a doublet (δ = 152.0 ppm, J_{P-Rh} = 294 Hz), which, upon cooling, broadens and coalesces at 320 K (Fig. 3, medium trace). Further cooling results in the generation of multiple species which at 230 K give origin to a sharp doublet (δ = 154.6 ppm, J_{P-Rh} = 290 Hz) and two doublets of doublet (δ = 152.4 ppm, J_{P-Rh} = 291.8 Hz, J_{P-P} = 95 Hz; δ = 149.5 ppm, J_{P-Rh} = 289.5 Hz, J_{P-P} = 95 Hz)

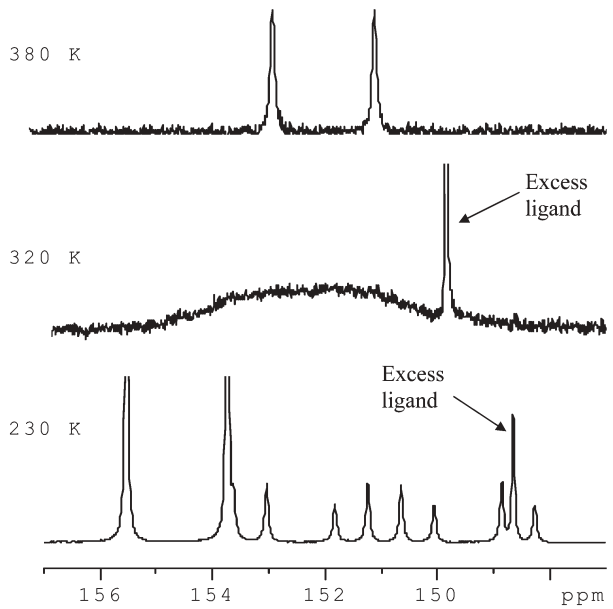


Fig. 3 Variable-temperature ^{31}P-NMR spectra (toluene-d_8) of the rhodium complex of ligand **11**-$P(O)_2N$.

(Fig. 3, lower trace). This can be interpreted in terms of the formation of three diastereomers (a*R*, a*R*; a*S*, a*S*; a*R*, a*S*) differing in the configuration at the two atropisomeric biphenols (which can be a*R* or a*S*), while the configuration of the two amine stereocenters is obviously fixed (2*S*, 5*S*). The two diastereomers (a*R*, a*R*) and (a*S*, a*S*), where the two phosphorus atoms are homotopic, give rise to two doublets (P–Rh coupling) which are accidentally isochronous. In contrast, the (a*R*, a*S*) diastereomer where the two phosphorus atoms are diastereotopic and couple with rhodium and with the other phosphorus, gives origin to two doublets of doublet (dd). The free energy barrier to the biphenol rotation was calculated from the dd signals: in toluene-d_8, $\Delta G^{\neq}$ is = 14.4 ± 0.2 kcal mol^{-1} (coalescence temperature T_C = 320 K), while in dichloromethane-d_2, $\Delta G^{\neq}$ is = 13.0 ± 0.2 kcal mol^{-1} (T_C = 290 K).

The spectra of the rhodium complexes resulting from the combination of phosphite **7**-P(O)$_2$O and phosphoramidite **11**-P(O)$_2$N account for the presence of all the signals described above (due to the L^{a}RhL^a and L^{b}RhL^b homocomplexes, *ca.* 40%) and of the new signals for the L^{a}RhL^b heterocomplex (*ca.* 60%). At 375 K (Fig. 4, upper trace), the heterocomplex L^{a}RhL^b gives origin to two doublets of doublet (each phosphorus couples with rhodium and with the other phosphorus), which can be interpreted in terms of both a tropos phosphite and a tropos phosphoramidite. The coalescence temperature (T_C) is 310 K (Fig. 4, medium trace), and by cooling to 230 K, two new doublets of doublet (total 8 lines) can be clearly observed (Fig. 4, lower trace).

This can be interpreted by the formation of one of the two possible diastereomers differing in the configuration at the phosphoramidite atropisomeric biphenol (which can be a*R* or a*S*),†† while the phosphite biphenol remains free to rotate (tropos). The free energy barrier to the biphenol rotation in the L^{a}RhL^b heterocomplex was calculated in toluene-d_8 $\Delta G^{\neq}$ = 14.5 ± 0.2 kcal mol^{-1} (coalescence temperature T_C = 310 K).††

In summary, of the ten possible different precatalysts, we detected the presence of five species: four homocomplexes (total *ca.* 40%) Rh[**7**-P(O)$_2$O]$_2$, Rh[(a*R*)-**11**-P(O)$_2$N]$_2$, Rh[(a*S*)-**11**-P(O)$_2$N]$_2$, Rh[(a*R*)-**11**-P(O)$_2$N][(a*S*)-**11**-P(O)$_2$N], and one heterocomplex (*ca.* 60%) Rh[**7**-P(O)$_2$O][(a*R*)-**11**-P(O)$_2$N] or Rh[**7**-P(O)$_2$O][(a*S*)-**11**-P(O)$_2$N]. Performing the reaction at 298 K (15 h, 100% yield, 95% ee), near the heterocomplex coalescence temperature (310 K), seems particularly important. In fact, the enantiomeric excess slightly decreased at both 353 K (15 h, 100% yield, 86% ee) and 283 K (60 h, 100% yield, 93% ee). We also prepared the (*R*)- and the (*S*)-binaphthol analogues of phosphoramidite **11**-P(O)$_2$N and tested each of them in combination with phosphite **7**-P(O)$_2$O. Surprisingly, the combinations of **7**-P(O)$_2$O with either the (*S*)-binaphthol analogue [50% yield, 46% ee, (*R*)] or the (*R*)-binaphthol analogue [70% yield, 72% ee, (*R*)] were both considerably less effective than the original biphenol-based combination (Table 1, entry 5). These experiments further emphasise the role of the tropos/atropos biphenol near the coalescence temperature in promoting high enantioselectivities.

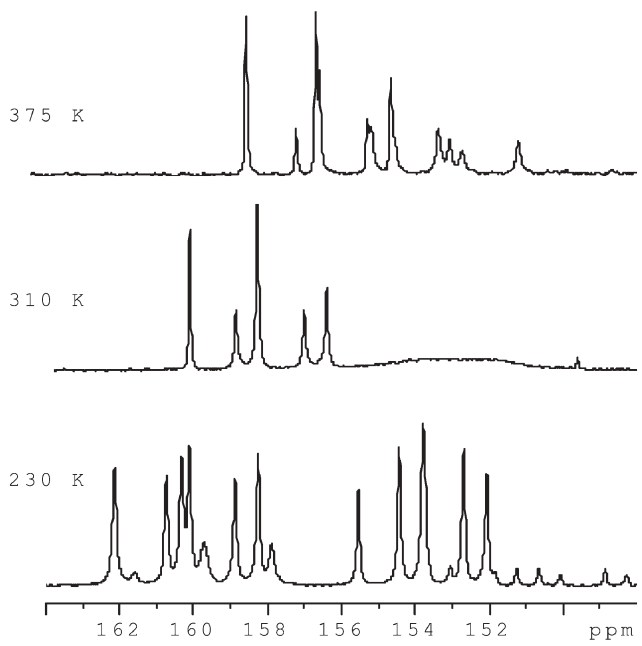


Fig. 4 Variable-temperature ^{31}P-NMR spectra of the rhodium complex resulting from the combination of **7**-P(O)$_2$O and **11**-P(O)$_2$N.

We thank the European Commission for financial support (“Enantioselective Recognition” HPRN-CT-2001-00182), Merck Research Laboratories (Merck’s Academic Development Program Award to C. Gennari) and Università di Milano for financial support and for a postdoctoral fellowship to C. Monti.

Notes and references

‡ [Rh(C$_2$H$_4$)$_2$Cl]$_2$ is cheaper than the often used Rh(acac)(C$_2$H$_4$)$_2$, and gave in our hands comparable or better conversions and enantiomeric excesses.
§ For related ^{31}P-NMR studies of L^{a}RhL^b type complexes, containing mixtures of binaphthol-derived phosphoramidites, see ref. 10.
¶ The chemical shift of this signal changed with the temperature, moving downfield as the temperature was lowered (δ = 157.3, 159.6 and 161.3 ppm at 380, 300 and 230 K, respectively).
‖ For the detection of two atropisomeric Rh(Cl)(COD)P species (where P is a chiral biphenol-based phosphite) by ^{31}P-NMR at −65 °C, see ref. 11.
** The coalescence behavior of the rhodium complex of phosphoramidite **11**-P(O)$_2$N is not ascribable to the conformational properties of the 2,5-diphenylpyrrolidine moiety. For example, the rhodium complex of the (*S*)-binaphthol analogue of phosphoramidite **11**-P(O)$_2$N gave a sharp doublet over the temperature range 230–380 K.
†† In the combination of phosphite **7**-P(O)$_2$O and phosphoramidite **12**-P(O)$_2$N, the heterocomplex L^{a}RhL^b gave origin to four doublets of doublet (total 16 lines) caused by the presence of two diastereomers Rh[**7**-P(O)$_2$O][(a*R*)-**12**-P(O)$_2$N] and Rh[**7**-P(O)$_2$O][(a*S*)-**12**-P(O)$_2$N] (ratio 85 : 15 or 15 : 85) differing for the configuration at the phosphoramidite atropisomeric biphenol. For the relevant spectra and free energy barrier calculations, see the ESI.

1 T. Hayashi and K. Yamasaki, *Chem. Rev.*, 2003, **103**, 2829.
2 J. G. Boiteau, F. Imbos, A. J. Minnaard and B. L. Feringa, *Org. Lett.*, 2003, **5**, 681 and 1385.
3 C. Monti, C. Gennari and U. Piarulli, *Tetrahedron Lett.*, 2004, **45**, 6859.
4 M. T. Reetz, T. Sell, A. Meiswinkel and G. Mehler, *Angew. Chem., Int. Ed.*, 2003, **42**, 790.
5 D. Peña, A. J. Minnaard, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries and B. L. Feringa, *Org. Biomol. Chem.*, 2003, **1**, 1087.
6 S. Sakuma and N. Miyaura, *J. Org. Chem.*, 2001, **66**, 8944.
7 K. Mikami, K. Aikawa, Y. Yusa, J. J. Jodry and M. Yamanaka, *Synlett*, 2002, 1561.
8 A. Alexakis, S. Rosset, J. Allamand, S. March, F. Guillen and C. Benhaim, *Synlett*, 2001, 1375.
9 M. T. Reetz and X. Li, *Angew. Chem., Int. Ed.*, 2005, **44**, 2959.
10 A. Duursma, R. Hoen, J. Schuppan, R. Hulst, A. J. Minnaard and B. L. Feringa, *Org. Lett.*, 2003, **5**, 3111; A. Duursma, D. Peña, A. J. Minnaard and B. L. Feringa, *Tetrahedron: Asymmetry*, 2005, **16**, 1901.
11 A. Suarez, A. Pizzano, I. Fernandez and N. Khiar, *Tetrahedron: Asymmetry*, 2001, **12**, 633.