Improved catalytic asymmetric carbon-carbon bond formation using combinations of chiral and achiral monodentate ligands

Duursma, A; Pena, D; Minnaard, Adriaan; Feringa, B.L.; Feringa, B.L.

Published in:
Tetrahedron-Asymmetry

DOI:
10.1016/j.tetasy.2005.05.006

Publication date:
2005

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: *Asymmetry* 16 (2005) 1901–1904
Tetrahedron: *Asymmetry*

Improved catalytic asymmetric carbon–carbon bond formation using combinations of chiral and achiral monodentate ligands

Ate Duursma, Diego Peña, Adriaan J. Minnaard* and Ben L. Feringa*

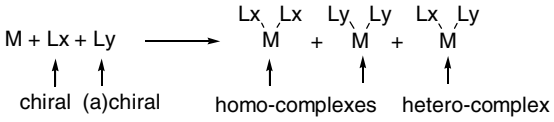
Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

Received 6 April 2005; accepted 5 May 2005

Abstract—Mixtures of chiral and achiral monodentate phosphoramidite ligands lead to improved enantioselectivity in the rhodium-catalyzed boronic acid addition.

1. Introduction

The monodentate ligand combination approach is a new concept in asymmetric catalysis, in which a catalyst, based on a combination of two different monodentate ligands (hetero-complex), leads to improved results compared to catalysts based on only one of the two ligands (homo-complexes) (Scheme 1).[1] The hetero-complexes are formed in situ by mixing the metal precursor with the ligands. This means that the overall activity and selectivity of the reaction depends on the ratio of the complexes and their corresponding activities and selectivities.



Scheme 1. The monodentate ligand combination approach.

The success of this concept has been shown for asymmetric carbon–hydrogen[2] as well as carbon–carbon bond formation[3] employing a combination of two chiral monodentate ligands, such as phosphoramidites, phosphites and phosphonites. In addition, the combination of chiral and achiral monodentate ligands has been shown by Reetz and Mehler to lead in some cases to a reversal of enantioselectivity.[4]

Herein, we report the first case of improved enantioselectivity in asymmetric C–C bond formation by the use of a combination of a chiral and an achiral monodentate ligand compared to catalysts based solely on the chiral ligand.

2. Results and discussion

A set of six monodentate ligands, consisting of three achiral ligands **L1–3** with different electronic properties and three chiral phosphoramidite ligands **L4–6**, was used as a basis for the ligand combinations (Fig. 1).[5]

The monodentate ligand combination approach was applied in the rhodium-catalyzed asymmetric conjugate addition of phenylboronic acid.[6] We have shown that in addition to BINAP as the most commonly used ligand, also monodentate phosphoramidites are also very effective ligands in this type of C–C bond formation.[7]

p-Methylnitrostyrene **1** was chosen as a substrate (Table 1).[3a] The product of this reaction, containing a benzhydrylic stereocentre, is important from a synthetic point of view, in particular due to the presence of this structural unit in a number of pharmaceutical intermediates. Nevertheless, nitrostyrenes are challenging substrates for this reaction and high ees have not yet been reported. The reaction conditions, in which phenylboronic acid is formed in situ from phenyl boroxine **2** and 1 equiv of water per boron, results in this case in higher conversions than the commonly used Hayashi–Miyaura conditions with phenylboronic acid and water as a cosolvent.

* Corresponding authors. Tel.: +31 50 3634258; fax: +31 50 3634296; e-mail addresses: a.j.minnaard@rug.nl; b.l.feringa@rug.nl

0957-4166/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2005.05.006

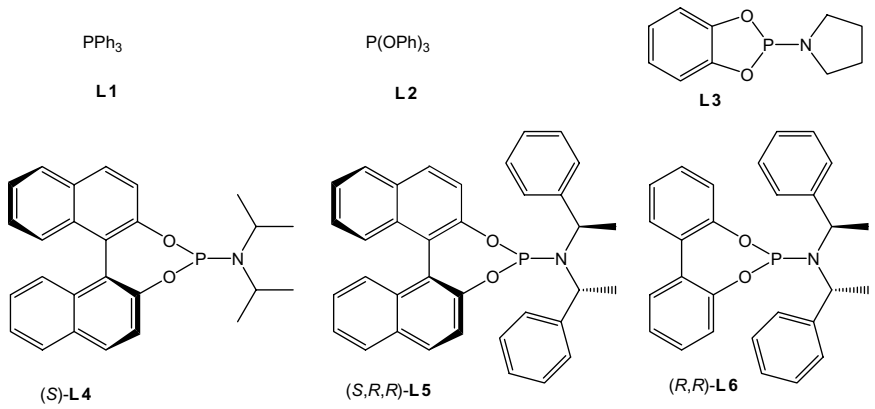
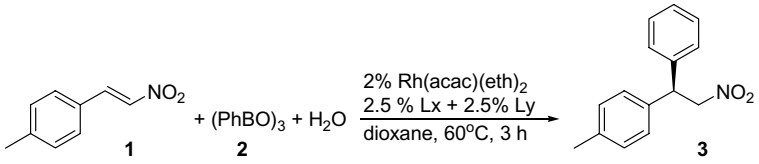


Figure 1. Monodentate ligands used for the ligand combination approach.

Table 1. Rh-catalyzed asymmetric conjugate addition to *p*-methylnitrostyrene[8]



Lx/Lx	Conv. (%)	ee (%)	Lx/Ly	Conv. (%)	ee (%)
L1/L1	8	0	**L1/L5**	12	5
L2/L2	83	0	**L2/L4**	97	0
L3/L3	100	0	**L2/L5**	73	0
L4/L4	11	23	**L2/L6**	78	0
L5/L5	4	28	**L3/L4**	94	7
L6/L6	0	—	**L3/L5**	83	−30

The use of triphenylphosphine **L1** leads to catalysts with a very low activity, in the homo- as well as the hetero-combinations. The less basic triphenylphosphite **L2** is an efficient ligand for this reaction, but unfortunately the hetero-combinations with chiral phosphoramidites **L4–6** resulted in racemic products. This indicates that the homo-complex of **L2** might be the most active catalyst in the mixture. Achiral phosphoramidite **L3** proved to be the most suitable achiral ligand, resulting in complete conversion to racemic **3** in the case of the homo-combination. In contrast, the homo-combinations of the relatively bulky chiral phosphoramidites **L4–6** gave rise to catalysts with a very low activity, a trend which has been observed previously.[3a] The result of the hetero-combination of **L5** with **L3** clearly demonstrates that the hetero-complex is formed, since it leads to a drastic improvement of conversion from 4% to 83%, a reversal in absolute configuration and a slightly higher ee value of −30% for product **3**.

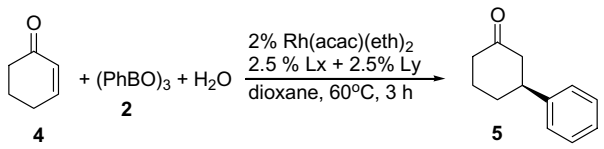
This concept of using a small achiral ligand as an activator for a more bulky chiral ligand was subsequently applied in the asymmetric conjugate addition of phenylboroxine **2** to 2-cyclohexenone **4** (Table 2).

As for *p*-methylnitrostyrene **1**, the homo-combination of the small achiral phosphoramidite **L3** led to an active catalyst for the addition to **4**, whereas the homo-combinations of the bulky phosphoramidites **L4–6** gave enantioselective catalysts, although with a very low activity. The hetero-combinations of **L3** with **L4–6** lead to catalysts that possess both positive characteristics; they are as active as the achiral catalyst based on **L3** but at the same time show enantioselectivities such as the ones based on **L4–6**. For the hetero-combinations of **L3** with **L4** and **L5**, a reversal of enantioselectivity is observed, and in the case of the latter there is even an increase in ee from 16% to 31%. The most striking results, however, were obtained with the combination of **L3** with **L6**. Whereas the homo-complex of **L6** is inactive and the homo-complex of **L3** not enantioselective, the hetero-complex of **L3** with **L6** is both an active and enantioselective catalyst.

Information about the relative amounts of the homo- and hetero-complex formed when two different phosphoramidite ligands are added to the catalyst precursor $Rh(acac)(eth)_2$, was obtained by integration of their signals in the corresponding ^{31}P NMR spectra. Whereas the homo-complexes appear as doublets ($J_{Rh-P} \approx 300$ Hz), the hetero-complexes were observed as two double doublets ($J_{Rh-P} \approx 300$ Hz, $J_{P-P} \approx 90$ Hz) (Table 3).

These data demonstrate that the lack of enantioselectivity obtained with mixtures of **L2** and **L4**, **L5** is not due to the absence of a hetero-complex, but most likely due to the fact that the homo-complex of **L2** is a much more active catalyst. This also shows that the most successful

Table 2. Rh-catalyzed asymmetric conjugate addition to 2-cyclohexenone[8]



4 5

Lx/Lx	Conv. (%)	ee (%)	Lx/Ly	Conv. (%)	ee (%)
L3/L3	100	0			
L4/L4	22	27	**L3/L4**	100	−5
L5/L5	18	16	**L3/L5**	79	−31
L6/L6	0	—	**L3/L6**	98	22

Table 3. Relative amounts of homo- and hetero-complexes based on ^{31}P NMR

Lx/Ly	$Rh(Lx)_2$	Rh(Lx)(Ly)	$Rh(Ly)_2$
L2/L4	13	49	38
L2/L5	14	61	25
L3/L4	13	69	18
L3/L5	5	92	3
L3/L6	8	86	6

combinations of ligands, **L3** with **L5** and **L6**, correspond with a high proportion of the hetero-complex.[9]

3. Conclusion

It has been shown for the first time that a catalyst based on a combination of a chiral and an achiral monodentate ligand leads to a higher enantioselectivity compared to the corresponding homo-complexes in asymmetric C–C bond formation. Reversal of enantioselectivity, improved enantioselectivity and maintenance of activity were observed when a relatively small achiral phosphoramidite ligand was combined with a bulky chiral phosphoramidite ligand. ^{31}P NMR spectra showed that the hetero-complexes are formed as the major species.

Acknowledgements

This project was funded by the National Research School Combination Catalysis (NRSCC).

References

1. (a) Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 790–793; (b) Peña, D.; Minnaard, A. J.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Biomol. Chem.* **2003**, *1*, 1087–1089; (c) Chen, W.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 8737–8740; (d) Reetz, M. T. *Chimia Oggi* **2003**, *21*, 5–8; For an early example using mixtures of *bi*dentate ligands see: Kaptein, B.; Elsenberg, H.; Minnaard, A. J.; Broxterman, Q. B.; Hulshof, L. A.; Koek, J.; Vries, T. R. *Tetrahedron: Asymmetry* **1999**, *10*, 1413–1418.
2. (a) Ref. 1; (b) Reetz, M. T.; Mehler, G. *Tetrahedron Lett.* **2003**, *44*, 4593–4596; (c) Reetz, M. T.; Mehler, G.; Meiswinkel, A. *Tetrahedron: Asymmetry* **2004**, *15*, 2165–2167; (d) Reetz, M. T.; Li, X. *Tetrahedron Lett.* **2004**, *45*, 9709–9714; For an extension of this concept using a dynamic library, see: (e) Monti, C.; Gennari, C.; Piarulli, U. *Tetrahedron Lett.* **2004**, *45*, 6859–6862.
3. (a) Duursma, A.; Hoen, R.; Schuppan, J.; Hulst, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 3111–3113; (b) Duursma, A.; Boiteau, J. G.; Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2004**, *69*, 8045–8052.
4. Ref. 2b.
5. Phosphoramidite ligand **L3** was prepared as follows: To a solution of 1.74 g (10 mmol) of 1,2-phenylene phosphorochloridite in 10 mL of anhydrous THF at 0 °C was added a solution of 711 mg (10 mmol) of pyrrolidine and 1.01 g (10 mmol) of triethylamine in 5 mL of anhydrous THF. The resulting white turbid mixture was stirred at 0 °C for 1 h. The solvent was removed under reduced pressure and the product purified by column chromatography (pentanes–diethyl ether 10/1, R_f 0.9) to give 82 mg (0.4 mmol, 4% yield) of **L3** as a colourless oil. ^{1}H NMR δ: 6.93 (m, 4H), 3.06 (m, 4H), 1.73 (m, 4H); ^{13}C NMR δ: 144.7 (d, J = 8 Hz), 120.1 (s), 109.5 (s), 43.5 (d, J = 15 Hz), 24.5 (d, J = 3 Hz); ^{31}P NMR δ: 141.5. HRMS calcd for $C_{10}H_{12}NO_2P$ 209.060. Found 209.060. Phosphoramidite ligands **L4** and **L5** have been reported before, see: Arnold, L. A.; Imbos, R.; Mandoli, A.; De Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865–2878, and were prepared according to a recently reported procedure: Boiteau, J. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2003**, *68*, 9481–9484; Ligand **L6** has been reported before, see: Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, 1375–1378.
6. (a) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229–4231; (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Saskai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580; (c) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591–11592; (d) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844.
7. (a) Boiteau, J. G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 681–684, and 1385; (b) Boiteau, J. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2003**, *68*, 9481–9484.
8. General procedure: In a Schlenk tube 2.58 mg (0.01 mmol, 2 mol %) of $Rh(acac)(eth)_2$ and two 0.012 mmol (2.5 mol %) portions of ligand were dissolved in 1 mL of anhydrous dioxane and stirred at room temperature for 15 min. Then, 0.5 mmol of the Michael acceptor, 0.67 mmol of phenylboroxine and 10 μL of *n*-tridecane (internal standard for GC) were added and the resulting mixture stirred for 2 min. An initial sample was taken before the addition of 0.1 mL of water after which the mixture was degassed and stirred for 3 h at 60 °C. During the reaction, samples of 0.1 mL were taken from the reaction mixture with a glass pipette and added to 1 mL of a stirred mixture of diethyl ether–saturated

aqueous $NaHCO_3$ (1/1). After a few minutes, the organic layer was decanted, filtered over Na_2SO_4, and subjected to GC and HPLC analysis. For **3**: enantiomer separation by HPLC on a Chiralpak OD column, heptanes–isopropanol 99/1, 210 nm, 12.7/14.3 min. For **5**: Enantiomer separation by GC on a Chiraldex A-TA column, 30 m × 0.25 mm × 0.12 μm, 120 °C isothermic, 58.0/60.1 min. For spectroscopic data of **3** and **5** see Ref. 7a.

9. Imbalance in homo-complex ratios is due to errors in weighing.