Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 3672–3675

Phosphoramidite ligands for the enantioselective iridium-catalyzed asymmetric hydroboration of *meso*-bicyclic hydrazines

Alexandre Alexakis,[a,*] Damien Polet,[a] Chloée Bournaud,[b] Martine Bonin[b] and Laurent Micouin[b,*]

[a]*Department of Organic Chemistry, University of Geneva, 30 Quai Ernest Ansermet, CH-1211 Geneva, Switzerland*
[b]*Laboratoire de Chimie Thérapeutique, UMR 8638 associée au CNRS et à l'Université René Descartes, Faculté des Sciences, Pharmaceutiques et Biologiques 4, av de l'Observatoire, 75270 Paris cedex 06, France*

Received 30 July 2005; revised 14 September 2005; accepted 19 September 2005
Available online 9 November 2005

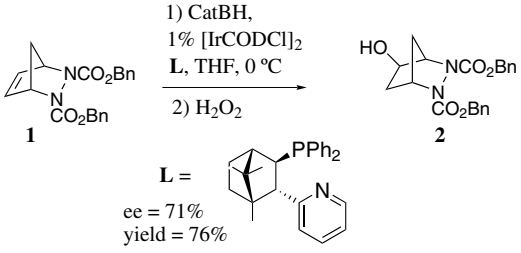
Abstract—Twenty phosphoramidites or phosphite ligands have been screened in the iridium-catalyzed hydroboration of a *meso*-bicyclic hydrazine. Enantiomeric excesses of up to 67% could be obtained with moderate to good yields. Although bidentate ligands are believed to be more efficient in transition metal-catalyzed asymmetric hydroboration, this study shows that monodentate ligands have to be investigated for further development of this type of reaction.

1. Introduction

The transition metal-catalyzed asymmetric hydroboration reaction has been intensively studied over the last two decades.[1] Excellent regio- and enantioselectivities have been achieved, mainly on styrene or substituted styrenes,[1] and more recently on prochiral cyclopropenes.[2] Despite numerous studies on the use of different metallic precatalysts and ligands, the best results are generally obtained with rhodium as the metal of choice, associated with P,P or P,N ligands. However, the scope of this asymmetric transformation is still very substrate dependent, and new reactions conditions have yet to be investigated.

We have recently described the iridium-catalyzed hydroboration of various bicyclic *meso*-hydrazines **1** with several bidentate ligands, leading to alcohol **2** with enantiomeric excesses up to 71% (Scheme 1).[3]

Phosphoramidites are now well established ligands for numerous asymmetric transformations.[4] Among them,



Scheme 1. Asymmetric hydroboration of bicyclic hydrazines.

Ir-catalyzed reactions can occur with interesting enantioselectivities with this class of ligands.[5] Since the use of monodentate ligands in asymmetric hydroboration is poorly documented,[6] we investigated the potential of chiral phosphoramidite ligands in inducing asymmetry in such a transformation. We herein report our investigations on this topic.

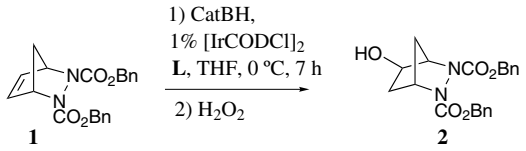
2. Results and discussion

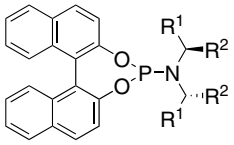
Preliminary experiments were conducted with binaphthol-based phosphoramidites **L1**–**L3** (Table 1). As most previous studies have shown that one full equivalent of a bidentate ligand is needed, we started our investigations

* Corresponding authors. Tel.: +41 22 37 96522; fax: +41 22 37 93215 (A.A.); tel.: +33 1 53 73 97 51; fax: +33 1 43 29 14 03 (L.M.); e-mail addresses: alexandre.alexakis@chiorg.unige.ch; laurent.micouin@univ-paris5.fr

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.09.023

Table 1. Screening in the binaphthol series





R^1 = H, R^2 = H, (*S*)-BINOL : **L1**
R^1 = Ph, R^2 = Me, (*R*)-BINOL : **L2**
R^1 = Ph, R^2 = Me, (*S*)-BINOL : **L3**

Entry[a]	Ligand	L/Ir	ee (%)[b]	Yield (%)[c]
1	**L1**	2	2	57
2	**L2**	2	−9[d]	25
3	**L3**	2	18	32

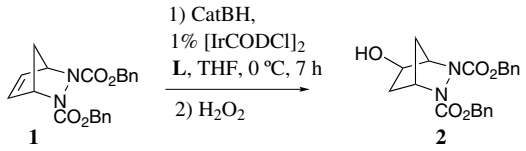
[a] Experimental conditions: see Section 4.
[b] Determined by chiral HPLC.
[c] Isolated yield of pure compound.
[d] *ent*-**2** was the major enantiomer.

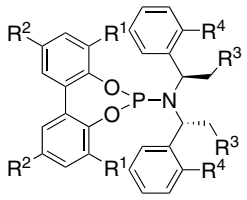
with 2 equiv of a monodentate ligand. In all cases, good conversion was obtained, although with little, if any, enantioselectivity. A small match–mismatch effect could be observed with ligands bearing two stereogenic elements (entries 2 and 3).

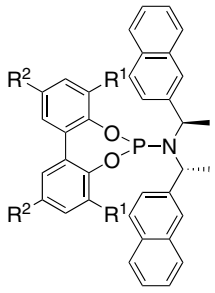
We then turned our attention to biphenol-based ligands **L4**–**L13** (Table 2).[7] The first experiments, conducted with ligand **L4**,[7a] clearly showed the influence of the chirality of the amine part of the ligand in the enantioselectivity of the hydroboration, since ees up to 48% could be obtained with these phosphoramidites devoid of axial chirality. Changing the ligand/metal ratio (entries 1–3) had a strong influence on the enantioselectivity. As expected, the best results were usually obtained with two ligands for every metallic center.[8] The only exception is **L7**, which could be considered as a bidentate ligand (entries 7 and 8). The other potential bidentate ligand **L8** also led to low selectivity (entry 9). The introduction of larger alkyl groups on the amine part (**L5**, entry 4) or increasing the steric hindrance of the biphenol moiety (**L6**, entries 5 and 6) did not lead to a significant improvement on enantioselectivity. However, the electronic properties seemed to play an important role, since a dramatic improvement was observed with chloro-substituted biphenols[7b] (**L9**, entries 10 and 11). The replacement of the usual bis (1-phenyl-ethyl)-amine by the corresponding 2-naphthalenyl derivatives[7c] also had some positive effect on the enantioselectivity (**L12** and **L13**, entries 14, 15).

Since the best enantioselectivities were generally obtained with 2 equiv of ligand per metallic center, other potentially bidentate ligands were investigated (Table 3). Once again, very different results were obtained when varying the substitution pattern of the amine moiety. The nature of the R^1 group seems to greatly influence the enantioselectivity of the hydroboration (**L18** and **L19**, entries 5 and 6). Finally, interesting results were obtained with amino-phosphite ligand **L20**,[9] leading to

Table 2. Screening in the biphenol series







R^1 = R^2 = R^3 = R^4 = H, : **L4**
R^1 = R^2 = R^3 = H, R^4 = Et : **L5**
R^1 = R^2 =Me, R^3 = R^4 = H : **L6**
R^1 = R^2 = R^3 = H, R^4 = OMe : **L7**
R^1 = OMe, R^2 = Me, R^3 = R^4 = H : **L8**
R^1 = R^2 = Cl, R^3 = R^4 = H : **L9**
R^1 = TMS, R^2 = H, R^3 = R^4 = H : **L10**
R^1 = R^2 =Br, R^3 = R^4 = H : **L11**

R^1 = R^2 = Cl : **L12**
R^1 = R^2 = Me : **L13**

Entry[a]	Ligand	L/Ir	ee (%)[b]	Yield (%)[c]
1	**L4**	1	−4[d]	55
2	**L4**	2	36	53
3	**L4**	3	48	54
4	**L5**	2	31	46
5	**L6**	1	7	24
6	**L6**	2	25	17
7	**L7**	1	34	62
8	**L7**	2	0	41
9	**L8**	1	12	42
10	**L9**	2	**50**	**48**
11	**L9**	3	**59**	**40**
12	**L10**	2	20	17
13	**L11**	2	46	45
14	**L12**	2	**55**	**75**
15	**L13**	2	40	41

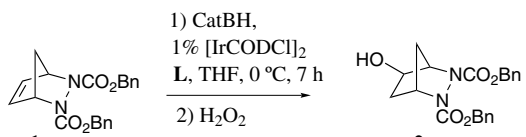
[a] Experimental conditions: see Experimental.
[b] Determined by chiral HPLC.
[c] Isolated yield of pure compound.
[d] *ent*-**2** was the major enantiomer.

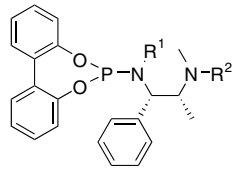
the hydrazine-alcohol in 64% yield with a 67% enantiomeric excess (entry 7).[10] Changing to a cationic iridium precatalyst led to similar results (entry 8), whereas no reaction occurred at lower temperature or with $[Rh(COD)Cl]_2$ as a rhodium precatalyst.

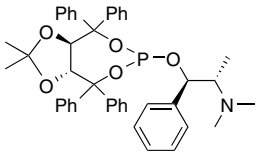
3. Conclusion

We have shown in this work that various chiral non-racemic phosphoramidites or phosphite ligands are efficient in the Ir-catalyzed asymmetric hydroboration of *meso*-hydrazines. Although promising ees up to 67% could be obtained with bidentate amino-phosphinites ligands, the use of phosphoramidite ligands in such a transformation can deliver the final compound with enantiomeric excesses between 50% and 60% with chemical yields up to 75%. These results clearly indicate that chiral non-racemic monodentate ligands have to be

Table 3. Screening of bidentate ligands

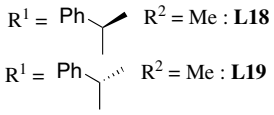






L20

$R^1 = R^2 = Me$: **L14**
$R^1 = Me$, $R^2 = Bn$: **L15**
$R^1 = Bn$, $R^2 = Me$: **L16**
$R^1 = cHex$, $R^2 = Me$: **L17**



Entry[a]	Ligand	L/Ir	ee (%)[b]	Yield (%)[c]
1	**L14**	1	18	54
2	**L15**	1	1	31
3	**L16**	1	23	68
4	**L17**	1	62	11
5	**L18**	1	7	8
6	**L19**	1	55	11
7	**L20**	1	**67**	**64**
8	**L20**	1	**64**[d]	**71**

[a] Experimental conditions: see Section 4.
[b] Determined by chiral HPLC.
[c] Isolated yield of pure compound.
[d] $Ir(COD)BF_4$ was used in this study.

investigated in the search for the further development of transition metal-catalyzed asymmetric hydro-boration.

4. Experimental

Ligands were synthesized according to reported procedures.[7,10] All the hydroborations were performed using the following procedure: $[Ir(COD)Cl]_2$ (3.4 mg, 0.005 mmol), L (0.01 mmol) and **1** (0.5 mmol) were placed under Ar atmosphere in a flame-dried Schlenk tube. THF (2 mL) was degassed at −50 °C and added to the mixture at this temperature. The reaction was then placed in a cooling bath at 0 °C and stirred for 30 min, to obtain a turbid, light yellow-orange mixture. Catecholborane (0.11 mL, 1 mmol) was added and the mixture became clear. The reaction was kept at 0 °C for an additional 7 h. Ethanol (0.5 mL) was then added and the cooling bath removed. Hydrogen peroxide (30% in water, 0.5 mL) and aqueous sodium hydroxide (3 M, 0.85 mL) were added, turning the solution to black. After 15 h of stirring, aqueous sodium hydroxide (1 M, 5 mL) was added and the mixture extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with sodium hydroxide (1 M, 2 × 10 mL), water (10 mL), brine (10 mL), and concentrated. Purification by flash chromatography (cyclohexane/ethyl acetate = 50:50) afforded **2** as a colorless oil. **5-Hydroxy-2,3-diaza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid dibenzyl ester 2**. ^1H NMR (300 MHz, DMSO-d_6, 70 °C) δ 1.46 (dt, $J = 13.7$, 2.5 Hz, 1H), 1.54 (d, $J = 10.5$ Hz, 1H), 1.98 (d, $J = 10.5$ Hz, 1H), 1.98–2.04 (m, 1H), 4.28 (s, 1H), 4.52 (s, 1H), 4.68 (s, 1H), 5.16 (m, 4H), 7.35 (m, 10H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.0, 38.0 (br), 59.6, 64.3, 68.1, 68.2, 70.4, 128.0, 128.3, 135.8, 135.9, 155.0 (br) IR (neat) 3453, 3063, 3032, 2952, 1760, 1633, 1496. MS: 400 (M+18), 383 (MH^+), 339, 249. Anal. Calcd for $C_{21}H_{22}N_2O_5$: C 65.96; H 5.80; N 7.33. Found C 65.79, H 5.96, N 7.33. $[\alpha]_D = -7.55$ (*c* 1.06, CH_2Cl_2).

Enantioselectivities were determined by chiral HPLC: Chiralpack AD column (0.46 cm I.D. × 25 cm), equipped with a Chiralpack AD pre-column (0.46 cm I.D. × 5 cm). Flow: 0.8 mL min^{-1}, detection: $\lambda = 220$ nm. Samples were injected at a 0.1 g L^{-1} concentration with a 20 μL inlet. hexane/*i*PrOH = 80/20, retention times = 15.98 min (1*S*,4*R*,5*R*), 17.82 min (1*R*,4*S*,5*S*).

Acknowledgements

This work was supported by a French-Swiss 'Germaine de Staels' program. C.B. thanks the MRT for a grant, and A.A. and D.P. thank the Swiss National Science Foundation (grant No. 200020-105368) for financial support.

References

1. For an excellent recent review, see: Carroll, A.-M.; O'Sullivan, T. P.; Guiry, P. J. *Adv. Synth. Catal.* **2005**, *347*, 609–631.
2. Rubina, R.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198–7199.
3. (a) Pérez Luna, A.; Bonin, M.; Micouin, L.; Husson, H.-P. *J. Am. Chem. Soc.* **2002**, *124*, 12098–12099; (b) Bunlaksananusorn, T.; Pérez Luna, A.; Bonin, M.; Micouin, L.; Knochel, P. *Synlett* **2003**, 2240–2242.
4. (a) Ansell, J.; Wills, M. *Chem. Soc. Rev.* **2002**, *31*, 259–268; (b) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353.
5. (a) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164–15165; (b) Bartels, B.; Helmchen, G.; Garcia-Yebra, C. *Eur. J. Org. Chem.* **2003**, 1097–1103; (c) Alexakis, A.; Polet, D. *Org. Lett.* **2004**, *20*, 3529–3532.
6. The use of TADDOL-derived cyclic phosphonites is the only example of styrene asymmetric hydroboration with monodentate ligands, with ee <30%: Sakaki, J.-I.; Schweitzer, W. B.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 2654–2665.
7. (a) Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, 1375–1378; (b) Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* **2004**, *69*, 5660–5667; (c) Alexakis, A.; Polet, D.; Benhaim, C.; Rosset, S. *Tetrahedron: Asymmetry* **2004**, *15*, 2199–2203.
8. A background hydroboration in the absence of ligand has been observed. The slight enantioselectivity improvement

with 3 equiv of ligands can be explained by the lowering of this competitive racemic pathway.
9. Alexakis, A.; Malan, C.; Lea, L.; Benhaim, C.; Fournioux, X. *Synlett* **2001**, 927–930.
10. The use of TADDOL-derived bidentates ligands in the styrene hydroboration has been reported: Blume, F.; Zemolka, S.; Fey, T.; Kranich, R.; Schmalz, H.-G. *Adv. Synth. Catal.* **2002**, *344*, 868–883.