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Study of incidence of DiPAMP ligand modification on the rhodium(I)-catalyzed asymmetric hydrogenation of α-acetamidostyrene

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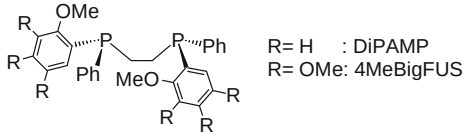
ABSTRACT

A series of *P*-stereogenic enantiopure 1,2-bis[(aryl)(phenyl)phosphino]ethane ligands was prepared through an extensive systematic incorporation of various substituents onto the *P*-*o*-anisyl rings of Knowles' DiPAMP (DiPAMP = 1,2-bis[(*o*-anisyl)(phenyl)phosphino]ethane). The study of incidence of such modification on the Rh(I)-catalyzed hydrogenation of α-acetamidostyrene is reported revealing that substitution on position 3 is detrimental, while it is beneficial on position 5. Namely, a 2.5-fold increased catalyst activity coupled with a higher enantioselectivity (90% ee) was attained with the *P*-(2-MeO-3-naphthyl)-substituted ligand under mild conditions (1 bar H_2, rt in MeOH).

In their *P*-stereogenic phosphine ligand optimization for the Rh(I)-catalyzed L-DOPA process, Knowles and co-workers' chelating DiPAMP ligand (DiPAMP = 1,2-bis[(*o*-anisyl)(phenyl)phosphino]-ethane) proved to be less sensitive to impurities and reaction variables compared to monophosphines.[1] Since their pioneering research, a relatively small group of *P*-stereogenic diphosphines emerged compared to the plethora of stereogenic backbone ones.[2] Design of *P*-stereogenic bis(diarylphosphino)-containing ligands has been sporadic,[3] while the interest in *P*-stereogenic phosphine ligands has been progressively revitalized due to advances in efficient synthetic strategies towards them.[3c–e,m,4] In particular, the milestone contribution to Rh(I)-catalyzed asymmetric hydrogenation by Zhang[5] and Imamoto[6] groups was highlighted by the introduction of the aliphatic TangPhos, BisP*, and MiniPHOS diphosphines. Interestingly, by contrast to the early explored and commonly accepted unsaturate Rh-DiPAMP hydrogenation route of α-acetamidocinnamates,[7] an extensive mechanistic study by Gridnev et al. pointed out an underlying solvate dihydride pathway using the electron-rich BisP* with α-substituted acetamidoethylenes.[6b]

Moreover, we have recently shown that mutant DiPAMP-type ligands, particularly our 4MeBigFUS ligand (4MeBigFUS = 1,2-bis[(phenyl)(2,3,4,5-tetramethoxyphenyl)phosphino]ethane), boosted the Rh(I)-catalyzed hydrogenation of a variety of olefins compared to the original Knowles' mid-70s design.[8]



Rh(I)-Catalyzed asymmetric hydrogenation of α-acetamidostyrenes is a powerful method to prepare a variety of chiral α-aryl amines.[4b,5a,6d,9] To our knowledge, sparse study-cases exist that are targeted to understanding the effect of variations brought to a ligand structure on hydrogenation.[4b,9i] *P*-Stereogenic tetraarylic diphosphines are easy to prepare, handle, and store, less capricious to reaction parameters (solvent, temperature, pressure, etc.), and could be readily accessible in both enantiomeric forms. Furthermore, few *P*-stereogenic tetraarylic diphosphines were prepared wherein the substituted phenyl rings were devoid of *o*-substituents (as for example *P*-β-naphthyl), and to a lesser extent their testing in Rh-catalyzed hydrogenation was reported.[3c–e] In the present work, we aimed to study the impact of a systematic incorporation of various substituents onto the *P*-*o*-anisyl groups of DiPAMP, in addition to the effect on hydrogenation of *meta*- and/or *para*-MeO substituents of its analogs.

In our ongoing research program on stereogenic phosphines,[3m,p,4c] we present hereafter our in-depth study of the Rh(I)-catalyzed hydrogenation of the model substrate α-acetamidostyrene employing a large series of *P*-stereogenic 1,2-bis(diphenylphosphino)ethane derivatives.

By analogy to our previously disclosed library of DiPAMP derivatives,[3p] the screened new enantiopure *P*-stereogenic ligands were readily prepared in high overall yields via the Jugé–Stephan

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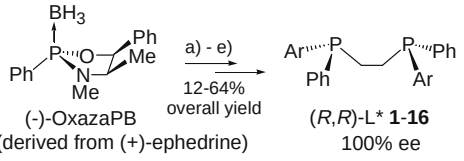
phosphine-*P*-borane asymmetric route.[3c] This expedient route relies upon the sequential displacement of the ephedrine auxiliary from the 1,3,2-oxazaphospholidine-2-borane complex (oxazaPB) with organolithium reagents and both enantiomers can be attained starting from either (+)- or (−)-ephedrine (Scheme 1).

The preliminary screening results of the Rh(I)-catalyzed hydrogenation of α-acetamidostyrene using diphosphines L* **1**–**16** are compiled in Table 1 and correspond to un-optimized reaction conditions. The observed sense of enantioselection is the same as with DiPAMP.

The ligands **11** (Ar = 2-MeO-3-TMS-Ph) and **12** (Ar = 2-MeO-3,5-di(*t*Bu)Ph) yielded 83 and 80% ee, respectively, which is in the same range as obtained with DiPAMP (83% ee) but with faster reaction rates. Also, the *o*-unsubstituted ligands **1**–**4** exhibited twofold faster reaction rates compared to DiPAMP, with the best ee of up to 27% being attained with ligand **3** bearing *P*-[3,4-di(MeO)Ph] groups. Thus, albeit low, still a perceptible level of asymmetric bias was reached using ligands devoid of *o*-substituents on the *P*-phenyls of *P*-stereogenic 1,2-bis(diphenylphosphino)ethane derivatives. The results transpire also that the *p*-MeO substituent has a beneficial influence compared to the *m*-MeO substituent.

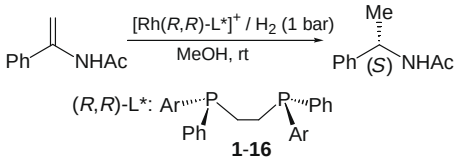
Ligand **14** possessing a phenyl substituent at position 3 of the *o*-anisyl moiety gave low ee (65%) versus 80–83% ee with ligands **11** and **12** possessing a TMS or *t*Bu group, respectively, at the same position. Ligands **5** and **6** possessing a MeO or *i*PrO group at position 3 on the one hand, and ligands **9**, **13**, and **15** possessing MeO groups or a fused cycle at positions 3 and 4 on the other hand, furnished ees in the narrow range of 69–72%. This reflects that the variations brought to DiPAMP at position 3 are to a certain extent detrimental. Conversely, ligands **7**, **8,** and **16** with no substituent at position 3 exerted a slightly higher ee (88–90%) compared to DiPAMP. It is also noticeable that ligand **7** bearing a *P*-[2,4-di(MeO)Ph] group led to a protracted reaction time, probably attributable to the nature of the electron-donating MeO group at *para*-position to the phosphorous atom; the reverse effect was encountered with the ligand **16** wherein Ar = 2-MeO-3-naphthyl. Noteworthy, the 87% ee achieved with ligand **10** (4MeBigFUS; Ar = 2,3,4,5-tetra(MeO)Ph) versus the 71% ee with ligand **5** (2MeBigFUS) or **9** (3MeBigFUS) points out the beneficial incidence of the MeO group at position 5 as also observed with ligand **8** (Ar = 2,5-di(MeO)Ph). We believe that the steric effect engaging the *ortho*-MeO group is responsible for the observed decrease in enantioselectivity in case of a substituent on position 3, and that an electronic effect on position 5 influencing the basicity of the phosphorus atom is responsible for the increase in enantioselectivity. Thus, in the *P*-(2-MeO-3-naphthyl)-substituted ligand **16**, steric and electronic effects are acting in concert in favor of a higher enantioselectivity and activity of the Rh(I)-catalyst.

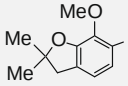
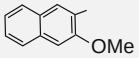
Next, we have investigated the susceptibility of [Rh(L* **16**)]$^+$-catalyzed hydrogenation to reaction parameters (Table 2). An enantiomeric excess in the range of 87–91% was maintained in various reaction media; however, protracted reaction times occurred in THF, CH_2Cl_2, and $CHCl_3$ (probably due to H_2 gas solubility[10a]), and in toluene (aromatic solvents are known to inhibit hydrogenation[10b]). Also, carrying out the reaction at 0 °C in MeOH did not affect the ee much, but a noticeable drop in enantioselectivity (85% ee) occurred at 50 °C. In general, H_2 pressure markedly affects the hydrogenation,[10c] but interestingly with L* **16** an 89% ee was maintained up to 20 bar of H_2.



Scheme 1. Synthesis of 1,2-bis[(aryl)(phenyl)phosphino]ethane ligands (*R*,*R*)-L* **1**–**16**. Reagents and conditions: (a) ArLi, THF, −20 °C to rt; (b) MeOH, H_2SO_4, rt; (c) MeLi, THF, −20 °C to rt; (d) *s*BuLi, THF, −30 °C, then $CuCl_2$, −30 °C; (e) Et_2NH, 55–60 °C.

Table 1
[Rh((*R*,*R*)-L*)(MeOH)$_2$]BF_4 catalyzed hydrogenation of α-acetamidostyrene[a]



L*	Ar	Time (min)	ee (%)
DiPAMP	2-MeO-Ph	13	83
1	3-MeO-Ph	6	1
2	4-MeO-Ph	5	15
3	3,4-di(MeO)Ph	7	27
4	3,5-di(MeO)Ph	7	5
5	2,3-di(MeO)Ph	4	71
6	2-MeO-3-*i*PrO-Ph	4	71
7	2,4-di(MeO)Ph	18	88
8	2,5-di(MeO)Ph	7	88
9	2,3,4-tri(MeO)Ph	4	71
10	2,3,4,5-tetra(MeO)Ph	4	87
11	2-MeO-3-TMS-Ph	7	83
12	2-MeO-3,5-di(*t*Bu)Ph	9	80
13		7	69
14	(2-MeO-3-Ph)Ph	8	65
15		6	72
16		5 45[b]	90 90

[a] For convenient comparison of the catalysts' activities, the induction period was eliminated by preforming the catalysts in situ. Runs were carried out with 0.5 mmol of α-acetamidostyrene in 7.5 mL MeOH with a substrate/catalyst molar ratio (S/C) of 100 at 25 °C for the time indicated (100% conversion). Conversion and ee were determined by GC on CP-Chiralsil-DEX CB column.
[b] S/C = 1000.

Table 2
Solvent and pressure dependence[a]

Solvent	pH_2 (bar)	Time (min)	ee (%)
MeOH	1	5	90
MeOH	1	12[b]	91
MeOH	1	4[c]	85
MeOH	10	5	89
MeOH	20	5	89
EtOH	1	7	90
*i*PrOH	1	8	91
EtOAc	1	8	87
Acetone	1	6	88
THF	1	17	88
CH_2Cl_2	1	12	88
$CHCl_3$	1	13	88
Toluene	1	25	87

[a] Runs were carried out under conditions of Table 1. For runs under 10 or 20 bar H_2, the reaction mixture was only analyzed after 5 min (100% conversion).
[b] Hydrogenation at 0 °C.
[c] Hydrogenation at 50 °C.

In conclusion, we have prepared a large series of enantiomerically pure *P*-stereogenic 1,2-bis[(aryl)(phenyl)phosphino]ethane ligands through a systematic modification of the *P*-*o*-anisyl rings

of DiPAMP. Their screening in the Rh(I)-catalyzed hydrogenation of α-acetamidostyrene identified the *P*-(2-MeO-3-naphthyl)-substituted ligand which led to 90% ee coupled with 2.5-fold shorter reaction time under mild conditions (1 bar H_2, rt). In addition, this study revealed that for this substrate, substitution on position 3 of the *P*-*o*-anisyl rings is detrimental while it is beneficial on position 5. It seems that an increased steric effect on position 3 has a negative effect on enantioselectivity, while substituents on position 5 can exert an increase in enantioselectivity due to electronic reasons. Catalysis continues to be a very sensitive function of ligand structure and key challenges remain associated with the complexity of rational design of an optimum ligand. The *P*-(2-MeO-3-naphthyl) groups of the ligand increase its overall steric requirements and we believe that they induce a favored conformation of its Rh(I) complex which may facilitate the turnover-limiting and enantiodetermining H_2 oxidative-addition step. Nevertheless, caution should be exercised in extrapolation of these results to other α-acetamidostyrenes as changes in a substrate structure could necessitate other requirements/matching for the catalyst.[11] Ongoing progress in our group in this area shall be communicated in due time.

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Supplementary data

Supplementary data (experimental procedures and characterization data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.088.

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