Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 5266

www.rsc.org/obc

PAPER

Profiling the tuneable R-SMS-Phos structure in the rhodium(I)-catalyzed hydrogenation of olefins: the last stand?†

Michel Stephan,*[a,b] Damjan Šterk,[a] Borut Zupančič[a] and Barbara Mohar[a]

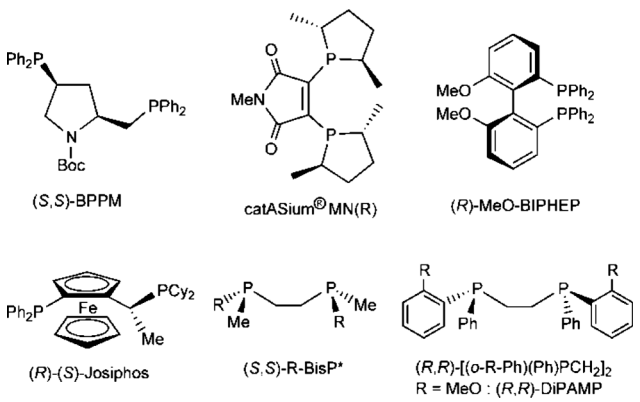
Received 8th March 2011, Accepted 21st April 2011
DOI: 10.1039/c1ob05364g

A diversified family of enantiopure *P*-stereogenic "R-SMS-Phos" {R-SMS-Phos = 1,2-bis[(*o*-RO-phenyl)(phenyl)phosphino]ethane} ligands wherein R = branched or heteroatom-substituted alkyl, aralkyl, silyl, acyl, sulfonyl, *etc.* was screened for the Rh(I)-catalyzed hydrogenation of a representative set of olefinic substrates. This systematic and detailed investigation revealed a marked beneficial impact on enantioselectivity and catalyst activity in comparison to Knowles' ultimate DiPAMP {DiPAMP = 1,2-bis[(*o*-anisyl)(phenyl)phosphino]ethane} design. Mutant ligands with highly enhanced properties possessing particular features wherein the DiPAMP structure is found embedded were identified.

Introduction

Despite milestone achievements in transition metal-catalyzed asymmetric hydrogenations since the late 1960's, a do-it-all catalyst proved to be elusive due to the structurally diverse plethora of prostereogenic olefinic targets to be reduced and to their different possible interactions with the catalyst.[1] Consequently, for an increased chance of success in R&D efforts within the constrained time-frames allocated to projects, broad ligand and catalyst libraries are indispensable screening tools for a quick evaluation of the technical feasibility of a catalyzed transformation step within a devised synthetic strategy. An added impetus to industrial production purposes is that bench-top results have to concur: short reaction times (100% conversion in <12 h) at maximum substrate-to-catalyst ratios (S/Cs) coupled with high ee values. An extra vital advantage would be to operate with high substrate concentrations and under mild conditions, *i.e.* at technically convenient pressures (<10 bar H_2) and around room temperature.[1d] A number of enantiopure phosphorus-based ligands were elaborated for those purposes but each is associated with specific drawbacks.

A comprehensive survey of the literature reveals several study-cases whereby the diversification of a given diphosphine by judicious alterations was undertaken.[2] Variations were brought forth by modifying the scaffold spanning the two phosphorus atoms and/or by exchanging the *P*-substituents. These changes were attained in such a way that the overall original structure was virtually preserved, as any radical departure from the model would probably lead to the loss of the essential features in the molecular recognition process gained with the parent ligand. This was the case for instance with DIOP, BPPM, DEGUPHOS, catASium® MN, and MeO-BIPHEP ligands wherein the peripheral remote *O*- or *N*-substituents were varied, and with the ferrocene-based diphosphines (ex. Josiphos, MandyPhos™, and Walphos) and the *P*-stereogenic BisP* where the *P*-substituents were exchanged.[3,4]



In particular, during their ligand optimization in the mid-1970's, Knowles *et al.* prepared a set of *P*-stereogenic 1,2-bis[(*o*-R-phenyl)(phenyl)phosphino]ethanes from which DiPAMP (with R = MeO) exhibited in their hands the best performance in the Rh(I)-hydrogenation of α-amidocinnamic acids.[5] Of interest, the 1,2-bis[(*o*-acetoxy-phenyl)(phenyl)phosphino]ethane ligand was prepared therein by acetylation of the corresponding *P*-*o*-(hydroxy-phenyl) intermediate (R = HO) derived from the demethylation of DiPAMP.[6] However, "since it did not crystallize, it was used without purification" and it furnished a much lower enantioselectivity than DiPAMP.[5] In 2004, Imamoto *et al.* introduced congeners of such diphosphines with R = alkyl,

[a]*National Institute of Chemistry, Hajdrihova 19, SI-1001, Ljubljana, Slovenia; Fax: +386 1 4760300; Tel: +386 1 4760250*
[b]*PhosPhoenix SARL, rue de l'Abbé Groult, 75015, Paris, France. E-mail: mstephan@phosphoenix.com; Fax: +33 1 48283011*

† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR, ^{31}P NMR, HRMS, GC) for all compounds. See DOI: 10.1039/c1ob05364g

and demonstrated that the enantioselection in hydrogenation "is induced by the spacial properties of the ligands".[7]

We have reported our in-depth and detailed study on the beneficial effect gained from incorporating substituents into DiPAMP's *P*-*o*-anisyl rings.[8] Herein, we present our extended study on the alteration of DiPAMP's methyl groups by switching to branched or substituted/functionalized chains, and its impact on the Rh(I)-catalyzed asymmetric hydrogenation of olefins.[9]

Results and discussion

Ligand synthesis

A representative spectrum of potential variety of 1,2-bis[(*o*-RO-phenyl)(phenyl)phosphino]ethanes (**2**) was targeted. In this type of series, which we have dubbed "R-SMS-Phos", R represents a branched or substituted/functionalized chain. Mutants modified at the level of the RO groups were envisaged possessing branching on the first or second carbon atom, heteroatom-substitution, or O atom-borne heteroatoms (*e.g.* Si, P).

The bulk of the selected analogues **2** were readily obtained in 85–96% yield from the crystalline precursor 1,2-bis[(*o*-hydroxy-phenyl)(phenyl)phosphino-*P*-borane]ethane (**1a**) (Scheme 1).[10] The latter was easily prepared in enantiomerically pure form with 57% overall yield *via* an adapted Jugé–Stephan asymmetric route from the enantiopure 1,3,2-oxazaphospholidine-2-borane complex (oxazaPB). *Via* this strategy, both enantiomers of the diphosphine were equally easily accessible from the commercially available (+)- and (−)-ephedrine.

The key intermediate **1a** opens a general access within 2 steps (*step a* followed by *step b* or *step b* followed by *step d*) to a very large variety of enantiopure *P*-stereogenic R-SMS-Phos ligands (**2**). This family of ligands includes the *O*-alkylated series of the demethylated-DiPAMP **2a**, as well as for instance the (*P*-*o*-*t*-BuO_2CCH_2OPh)-substituted ligand **2q** which would not survive through the classical Jugé–Stephan route. Hence, this novel approach offers an added flexibility in terms of synthesis of a wide diversity of homochiral analogues and virtually unlimited opportunities for fine-tuning the features of the ligands.

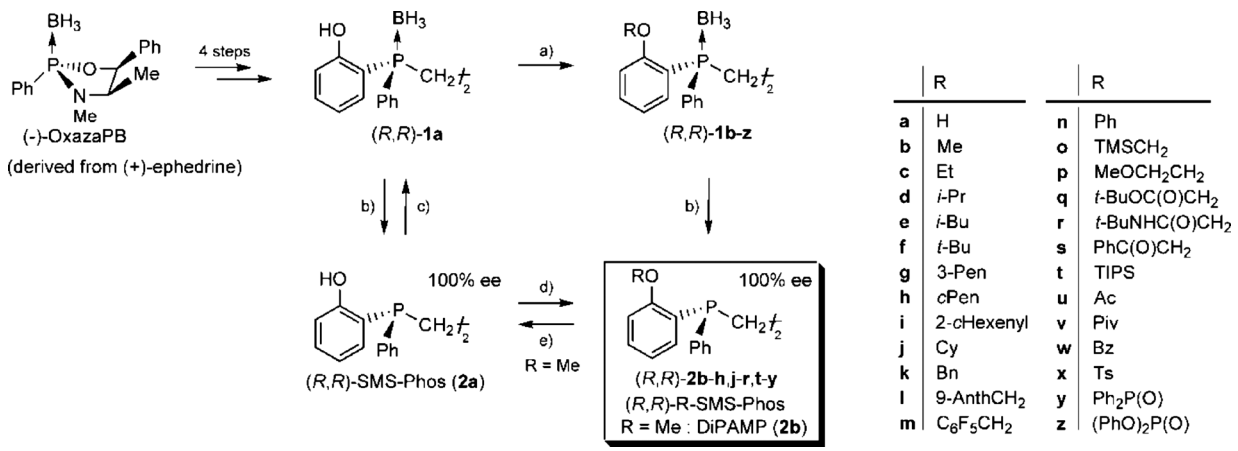
Moreover, prepared by decomplexation of **1a** (*step b*), SMS-Phos (**2a**) was also prepared from DiPAMP (**2b**) using BBr_3 (*step e*) and its complexation with borane (*step c*) retrieved **1a**. The diastereomeric purity was maintained throughout these transformations.

Hydrogenation screening results

The prepared R-SMS-Phos (**2**) were evaluated under mild conditions (1 bar of H_2 at room temperature in MeOH) in the Rh(I)-catalyzed hydrogenation of a representative reference set of olefins: methyl α-acetamidoacrylate (**S1**), methyl (*Z*)-α-acetamidocinnamate (**S2**), methyl (*Z*)-3-acetamidobut-2-enoate (**S3**), methyl (*E*)-3-acetamidobut-2-enoate (**S4**), α-acetamidostyrene (**S5**), dimethyl itaconate (**S6**), and atropic acid (**S7**) (Table 1). Our adopted systematic transmutation of the pendant R groups revealed significant variations in reactivity and enantioselectivity of the Rh(I)-(R-SMS-Phos) catalysts with a consistent sense of stereoselection per examined substrate. Both steric bulk and coordinating ability of the R substituents proved to markedly impact the catalysis, with the predominant majority of the examined ligands displaying a superior performance than that of the basic DiPAMP (**2b**).[11]

Hydrogenation of methyl α-acetamidoacrylate (S1) and methyl (*Z*)-α-acetamidocinnamate (S2)

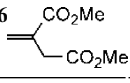
DiPAMP's saga is partially attributable to its good performance in the hydrogenation of dehydro-α-amido acids. In our initial hydrogenation screening on these probe dehydro-α-amido acid derivatives, even a subtle modification from R = Me (DiPAMP: **2b**) to R = Et (**2c**) provided an improved catalysis furnishing 99.1% ee *vs.* ~95% ee at *ca.* 3-fold reaction rate increase. The derived $MeOCH_2CH_2$-substituted ligand (**2p**) also performed comparatively well. Shifting to branched R groups such as R = *i*-Pr (**2d**), *i*-Bu (**2e**), *t*-Bu (**2f**), 3-Pen (**2g**), *c*Pen (**2h**), Cy (**2j**), or $TMSCH_2$ (**2o**), further enhanced the overall result pushing the enantioselectivity up to 99.9% ee at 9-fold faster rate. Noteworthy, even with *i*-Pr-SMS-Phos (**2d**), which is the simplest higher branched DiPAMP homolog, >99.4% ee was attained in few minutes. Within the



	R		R
a	H	**n**	Ph
b	Me	**o**	$TMSCH_2$
c	Et	**p**	$MeOCH_2CH_2$
d	*i*-Pr	**q**	*t*-BuOC(O)CH_2
e	*i*-Bu	**r**	*t*-BuNHC(O)CH_2
f	*t*-Bu	**s**	PhC(O)CH_2
g	3-Pen	**t**	TIPS
h	*c*Pen	**u**	Ac
i	2-*c*Hexenyl	**v**	Piv
j	Cy	**w**	Bz
k	Bn	**x**	Ts
l	9-AnthCH_2	**y**	$Ph_2P(O)$
m	$C_6F_5CH_2$	**z**	$(PhO)_2P(O)$

Scheme 1 Synthesis of the R-SMS-Phos series.[10] Reagents and conditions: a) for **1b–e**,**g–i**,**k–m**,**o–t**: RX (X = Br, I or OTs), K_2CO_3, acetone or DMF, r.t. to 60 °C; for **1u–z**: RCl, NaH, THF, 0 °C to r.t.; **1j** derives from hydrogenation (3 bar H_2, PtO_2, MeOH/CH_2Cl_2) of **1i** (prepared from 3-bromocyclohexene); b) Et_2NH, 55–60 °C; c) $Me_2S{\cdot}BH_3$, THF, r.t.; d) for **2t**,**u**: RCl, NaH, THF, 0 °C to r.t.; e) for R = Me: BBr_3, CH_2Cl_2, 0 °C.

Table 1 [Rh((*R*,*R*)-R-SMS-Phos)(MeOH)$_2$]BF_4-catalyzed hydrogenation of selected representative classes of olefins[a]

R-SMS-Phos (**2**)	**S1** 		**S2** 			**S3**  (*Z*)			**S4**  (*E*)			**S5** 		**S6** 		**S7**[b] 		
R =	*t* (min)	ee (%)	*t* (min)	ee (%)	Conv (%)	*t* (min)	ee (%)	Conv (%)	*t* (min)	ee (%)	Conv (%)	*t* (min)	ee (%)	*t* (min)	ee (%)	Conv (%)	*t* (min)	ee (%)	Conv (%)
a H	20[c]	94.5	70	97.8	2	24 h	17.0	0	24	—	35	84.7	30	64.2	17	3	15.1		
b Me[11]	15	93.6	18	94.9	100	5.5 h	65.8	100	5.5	87.0	11	84.0	10	85.4	100	3	48.6[d]		
c Et	6	99.1	6	99.1	100	90	66.7	100	2	91.3	10	92.1	9	96.6	70	2	78.6		
d *i*-Pr	6	99.4	4	99.7	100	20	82.1	100	1.5	93.0	3	97.8	5	98.1	100	2	88.0		
e *i*-Bu	6	99.4	4	99.7	100	30	70.2	100	1.5	93.4	5	96.9	5	98.5	78	2	86.0		
f *t*-Bu	4	99.9	2	99.8	100	7	80.1	100	1	97.3	2	99.3	2	99.8	100	2	94.7[e]		
g 3-Pen	5	99.8	4	99.4	100	15	84.4	100	1.5	94.9	4	98.5	4	98.6	100	2	92.9		
h *c*Pen	6	99.9	3	99.9	100	10	84.8	100	0.3	97.6	3	99.9	3	99.3	100	2	96.4		
j Cy	5	99.8	3	99.9	100	15	88.2	100	0.75	97.8	3	99.9	3	99.3	100	2	97.1[e]		
k Bn	12	99.2	5	99.6	100	4 h	63.9	77	21	88.0	5	95.4	15	96.9	100	3.3	76.8		
l 9-AnthCH_2	20	99.5	10	99.7	0	24 h	—	0	24	—	7	95.3	30[f]	91.2	100	3	85.2		
m $C_6F_5CH_2$	6	99.7	3	99.8	100	15	81.5	100	1.5	95.8	4	99.4	3	98.7	100	3	94.8		
n Ph	6	96.5	9	97.1	100	90	66.6	92	16	78.1	7	87.7	7	91.7	53	3.3	61.1		
o $TMSCH_2$	6	99.7	4	99.7	100	30	71.4	100	2	95.1	8	98.1	7	99.1	59	2	86.8		
p $MeOCH_2CH_2$	6	98.1	5	98.8	100	50	75.3	100	2	95.0	4	93.4	7	95.0	88	2	83.8		
q *t*-BuOC(O)CH_2	4[c]	95.8	15	98.1	100	45	75.3	100	3	91.3	7	93.7	9	84.6	72	3	26.8		
r *t*-BuNHC(O)CH_2	5[c]	93.6	10	95.8	100	60	46.4	76	16	87.3	4	88.0	17	93.3	93	3	1.6		
t TIPS	2[c]	99.7	50	99.3	100	2.5 h	12.2	70	20	65.6	9	99.9	20	98.7	39	3	90.2		
u Ac	5	98.0	4	99.2	26	24 h	50.2	0	24	—	6	90.4	40	86.2	13	3	71.1		
v Piv	5	99.6	6	99.7	84	6 h	33.7	45	16	46.8	9	98.8	1 h	86.3	63	3	90.6		
w Bz	6	99.0	3	99.3	100	90	57.5	33	16	57.9	5	95.2	18	91.2	76	3	87.6		
x Ts	5	99.2	3	99.3	100	90	70.1	69	16	79.1	5	92.1	15	86.6	60	3	80.7		
y $Ph_2P(O)$	—	—	150	98.5	—	—	—	—	—	—	4 h[g]	93.0	5 h[h]	40.0	—	—	—		

[a] The catalysts were prepared *in situ* from [Rh(nbd)$_2$]BF_4. Runs were carried out under 1 bar of H_2 (10 bar for **S7**) at room temperature in MeOH (0.5 mmol of substrate in 7.5 mL MeOH) with a S/C = 100 (S/C = 1000 for **S1**) for the time indicated (100% conversion) if not stated otherwise and are unoptimized. Typical isolated yields were >90%. Ee's were determined by chiral GC (Lipodex-E column for hydrogenation products of **S1** and **S6**, Chiralsil-L-Val for **S2** and CP-Chiralsil-DEX CB for **S3**, **S4**, **S5** and **S7**; prior to analysis, the carboxylic group of hydrogenation product of **S7** was esterified with $TMSCHN_2$); for this, see the ESI.† With (*R*,*R*)-R-SMS-Phos, *S*-configured products were obtained except with **S6**. [b] In the presence of Et_3N (1.1 equiv). [c] S/C = 100. For **2t** with S/C = 1000, a 99.8% ee was obtained in 18 min. [d] 7% ee in the absence of Et_3N. [e] Identical result was obtained in the presence of 0.05 equiv. Et_3N. In the presence of 0.05 equiv. Cy_2NH, 95.6% ee obtained with **2f** and 97.4% ee with **2j**. [f] 60% conversion. [g] 35% conversion. [h] 32% conversion.

R-SMS-Phos series wherein R = Bn (**2k**), 9-AnthCH_2 (**2l**), $C_6F_5CH_2$ (**2m**), or Ph (**2n**), it is interesting to notice that **2n** and **2l** exhibited the least good performance regarding enantioselectivity and activity, respectively, and with the use of $C_6F_5CH_2$-SMS-Phos (**2m**) the situation got "renormalized" as with the other (branched R)-based ligands. In this series' case, this could stem from a possible competitive secondary interaction of an aryl unit (of the R groups) with the Rh center, particularly if taken with the Cy-SMS-Phos (**2j**) results. The interplay of steric and electronic factors is evident by the advantage of the isosteric $C_6F_5CH_2$ group over Bn due to its electron-poorer ring hence precluding the likelihood of its coordinative deleterious interference with the metal. Also, it seems that a borderline magnitude of the R substituent bulk is required for an optimal performance, especially if one takes into consideration the runs with the highly-hindered TIPS-SMS-Phos (**2t**) and the other (branched R)-substituted ligands as well.

Besides, the enantioselectivity and rate penalties derived from the (carbonylmethyl fragment)-containing ligands **2q** (R = *t*-BuOC(O)CH_2) and **2r** (R = *t*-BuNHC(O)CH_2), clearly demonstrate a competitive coordination during catalysis to the Rh core between these functionalities (amplified in the latter ligand's case) and the amide oxygen of the substrates.

Most surprisingly, we have obtained a 97.8% ee (within 70 min) and 99.2% ee (within 4 min) for the reduction of **S2** applying our pure SMS-Phos (**2a**) and Ac-SMS-Phos (**2u**), respectively, compared to the 84% ee and 63% ee respectively reported for the reduction of (*E*/*Z*)-α-benzamidocinnamic acid by Knowles and co-workers using the same ligands (*vide supra*).[5] Regardless of the bulk or nature of the ligand's phenolic ester functionality (with Ac (**2u**), Piv (**2v**), Bz (**2w**), or Ts (**2x**)) a >99% ee was maintained with a fast reaction rate, however with the $Ph_2P(O)$-substituted ligand (**2y**) leading to a dramatically protracted reaction time.

Hydrogenation of methyl (*Z*)-3-acetamidobut-2-enoate (S3) and methyl (*E*)-3-acetamidobut-2-enoate (S4)

Rh(I)-catalyzed hydrogenation of these substrates (the *Z*-isomer in particular) proved to be somewhat more challenging using the prepared R-SMS-Phos series under our standard test conditions (reaction variables were not optimized in this study). Analyzed as a whole in order to identify any trends in those two cases, the least useful results were clearly obtained with the ligands possessing pendant R groups having a good coordinating nature (*e.g.* H (**2a**), *t*-BuNHC(O)CH_2 (**2r**), Ac (**2u**), Piv (**2v**)) or with quite bulky character (*e.g.* TIPS (**2t**), Piv (**2v**)), reflecting a special coordinative binding of these substrates to the Rh center. In particular, the Ac-SMS-Phos (**2u**) furnished a low ee (50.2%) and conversion (26%) in the hydrogenation of the *Z*-isomer, while it was inactive against

the *E*-isomer. An identical polar case was encountered with SMS-Phos (**2a**). Noteworthy, the 9-AnthCH_2-substituted ligand (**2l**) was ineffective with both isomers.

Nonetheless, recoursing to Cy-SMS-Phos ligand (**2j**), up to 88.2% ee (within 15 min) and 97.8% ee (within 45 min) were attained for the *Z*- and *E*-geometric isomers, respectively, with a convergent predominant preference for the (*S*)-product. Also, there exist strong parallels together with *c*Pen-SMS-Phos (**2h**) and 3-Pen-SMS-Phos (**2g**). Finally, comparison of the hydrogenation outcome of the family members with R = Et (**2c**), *i*-Pr (**2d**), *i*-Bu (**2e**), *t*-Bu (**2f**), and $TMSCH_2$ (**2o**), implies that a close proximity of the R branching is beneficial especially in the case of the *Z*-isomer.

Hydrogenation of α-acetamidostyrene (S5) and dimethyl itaconate (S6)

Inspection of the screening data transpires that essentially similar trends can be drawn for these substrates as with dehydro-α-amido acid derivatives **S1** and **S2**. However, the hydrogenation of **S6** was overall more influenced by the nature of the R groups compared to the hydrogenation of **S5**. This can be attributed to the stronger binding affinity of enamides to the Rh. If one compares on one hand the results obtained with the ligands where R = *t*-$BuOC(O)CH_2$ (**2q**), *t*-$BuNHC(O)CH_2$ (**2r**), and DiPAMP (**2b**) in the case of **S5**, and on the other hand the ones obtained with the same ligands in the case of **S6**, the influence of the amide/ester functionality of the ligand in presence of either the corresponding amide or ester functionality of the substrate, is perceptible albeit limited.

Apart from SMS-Phos (**2a**) and $Ph_2P(O)$-SMS-Phos (**2y**), virtually any changes to DiPAMP's Me groups had a positive effect on enantioselectivity culminating with the best performing (with respect to enantioselectivity allied with kinetics) R-SMS-Phos ligands wherein R = *t*-Bu (**2f**), 3-Pen (**2g**), *c*Pen (**2h**), Cy (**2j**), and $C_6F_5CH_2$ (**2m**), followed closely (depending on the substrate) by *i*-Pr (**2d**), $TMSCH_2$ (**2o**), TIPS (**2t**), and Piv (**2v**). Up to 99.9% ee was reached within 2–3 min (S/C = 100) in the hydrogenation of both **S5** and **S6**.

Hydrogenation of atropic acid (S7)

Since the early development of metal-catalyzed asymmetric hydrogenations, interest in non-steroidal anti-inflammatory drugs and analgesics has incited research on **S7** reduction which proved to be a major challenging goal.[12] Some mechanistic studies have been conducted in order to elucidate the binding mode to the Rh core of this substrate and its derivatives (ester, amide, salt, *etc.*) which in turn profoundly affects the hydrogenation result. The beneficial effect on its hydrogenation by an added base (such as Et_3N, Cy_2NH) in equimolar or catalytic (~5 mol%) amounts has been communicated.[9] With this substrate, the best enantioselectivity inducing R-SMS-Phos ligands possess R = *t*-Bu (**2f**), *c*Pen (**2h**), or Cy (**2j**), followed very closely by 3-Pen (**2g**) and $C_6F_5CH_2$ (**2m**). In fact, up to 97.1% ee was reached under 10 bar H_2 within 2 h (S/C = 100) using Cy-SMS-Phos (**2j**) in the presence of Et_3N (0.05 equiv) at room temperature, and 97.4% ee in the presence of Cy_2NH (0.05 equiv).[9d] Apart from SMS-Phos (**2a**), the hydrogenation outcome using the R-SMS-Phos ligands with R = *t*-$BuOC(O)CH_2$ (**2q**) or *t*-$BuNHC(O)CH_2$ (**2r**) led to a pronounced attenuation of the enantioselectivity reflecting a strong interference of such neighbouring substituents during catalysis.

This investigation clearly demonstrates that under given reaction conditions, the level of enantioselectivity and the reaction rate continue to be intrinsically dependent on the nature (bulkiness, electronic properties, coordination strength) of the various coordinating groups present in the medium (*i.e.* pendant groups of the ligand, functional groups of the olefinic substrate/hydrogenation product and the solvent) and on the reactivity of the olefin. Compared to relevant studies with Rh-DiPAMP, our published X-ray crystal structure analysis of [Rh(*i*-Pr-SMS-Phos)(nbd)]BF_4 revealed its pronounced dissymmetry and the ^{31}P NMR study of [Rh(*i*-Pr-SMS-Phos)(**S2**)]BF_4 showed the occurrence of different dynamics during hydrogenation.[9b] Here, coordinating functional groups of the pendant R (R = H, Bn, *t*-$BuOC(O)CH_2$, *t*-$BuNHC(O)CH_2$, $Ph_2P(O)$, *etc.*) proved to interfere with catalysis. Thus, a correlation between the catalyst activity–enantioselectivity and the various R groups of the R-SMS-Phos series is not straightforward to establish. However, projected mechanistic studies with the R-SMS-Phos ligands wherein R represents branched alkyls, may shed some light on the origin of influence of such variation on the catalyst performance. Despite the need for rationally modelling the optimum catalyst for a given substrate, still guesswork and empirical design of ligands and catalysts are definitely unavoidable.

In a broad sense, Rh-(R-SMS-Phos) catalytic profile as a function of pendant R length or nature shows that spacial mapping in proximity of the Rh center of catalysis through replacement of DiPAMP's suitably-placed methyl groups may further result in catalysts with potentially improved efficiency for a given substrate. The 1,2-bis[(*o*-hydroxy-phenyl)(phenyl)phosphino-*P*-borane]ethane (**1a**) can be regarded as a user-adjustable precursor of an assortment of do-it-yourself ethane-bridged diphosphines which may be targeted for a special application in, *inter alia*, biphasic- or supported-catalysis.

Conclusions

In summary, a very wide variety of enantiopure R-SMS-Phos-type ligands of DiPAMP lineage was readily prepared and assessed in the Rh(I)-catalyzed asymmetric hydrogenation of various classes of olefins (dehydroamido acids, enamides, itaconates, and acrylates). Far from being a gimmick, this meticulous and exhaustive alteration of the R groups was a rewarding enterprise culminating in advantageous ligands which sharply boosted reaction rates by several times and increased enantioselectivities. In hindsight, had such a study been carried out at an early development stage of asymmetric hydrogenation, it would have undoubtedly guided the design of the ensuant phosphines.

Our library of non-exotic ligands with enhanced efficiency over the DiPAMP archetype, possesses the prerequisite criterion of compatibility for the elaboration of industrial processes. The presented concept of modular structure is being extended in our group to other phosphine skeletons and the advances will be communicated in due course.

Experimental

General procedures for the preparation of 1b,c,l,p–z by derivatization of 1a[10a] (Scheme 1, *step a*)[13]

(A) A mixture of **1a** (458 mg, 1 mmol), K_2CO_3 (553 mg, 4 mmol), and the appropriate (substituted)alkyl halide or tosylate (2.5–3 mmol) in acetone (10 mL) was stirred at r.t. or refluxed until TLC showed complete conversion. The mixture was concentrated, filtered through a pad of silica gel eluting with CH_2Cl_2. The product was recrystallized from hexane/CH_2Cl_2.

(B) A mixture of **1a** (458 mg, 1 mmol), K_2CO_3 (553 mg, 4 mmol), and the appropriate (substituted)alkyl halide or tosylate (2.5–3 mmol) in DMF (5 mL) was stirred at 40 °C until TLC showed complete conversion. The mixture was concentrated, filtered through a pad of silica gel eluting with CH_2Cl_2. The product was recrystallized from hexane/CH_2Cl_2.

(C) To a stirred solution of **1a** (458 mg, 1 mmol) in THF (10 mL) was added NaH (60 mg, 2.5 mmol) at 0 °C. After 15 min the appropriate acid chloride (2.5 mmol) was added and left to stir at r.t. for 1 h. The mixture was quenched with H_2O (0.1 mL), concentrated, and the residue was filtered through a pad of silica gel eluting with CH_2Cl_2. The product was recrystallized from hexane/CH_2Cl_2.

General procedures for the synthesis of (R_P,R_P)-1,2-bis[(*o*-RO-phenyl)(phenyl)phosphino]ethane "(R_P,R_P)-R-SMS-Phos" (2c,l,p–r,t–y) - Scheme 1, *step b*[13]

(R_P,R_P)-1,2-Bis[(*o*-RO-phenyl)(phenyl)phosphino-*P*-borane]-ethane in Et_2NH (10 mL/1 mmol of (R_P,R_P)-**1**) was refluxed for 2–3 h under inert atmosphere. After concentration, purification on silica gel and/or recrystallization under inert atmosphere, the title compound (R_P,R_P)-**2** was obtained.

"(R_P,R_P)-R-SMS-Phos" (2t,u) - Scheme 1, *step d*

To a stirred solution of (R_P,R_P)-SMS-Phos (**2a**) (1 mmol) in THF (10 mL) was added NaH (60 mg, 2.5 mmol) at 0 °C. After 15 min, TIPSCl or AcCl (2.5 mmol) was added and left to stir at r.t. for 1 h under inert atmosphere. The mixture was quenched with H_2O (0.1 mL), concentrated, and the residue was filtered through a pad of silica gel and the product was recrystallized under inert atmosphere.

In situ preparation of [Rh((R_P,R_P)-R-SMS-Phos)(MeOH)$_2$]BF_4 complex

To a solution of [Rh(nbd)$_2$]BF_4 (2.3 mg, 6.3 μmol) in MeOH (0.5 mL), a solution of the (R_P,R_P)-R-SMS-Phos (**2**) ligand (0.8 equiv. to Rh-atom) in MeOH (0.5 mL) was added dropwise at r.t. The resulting solution was hydrogenated under 1 bar of H_2 for *ca.* 15 min. Elimination of metallic rhodium by filtration through a No. 3 sintered-glass filter afforded a clear brown solution of the title complex.

Hydrogenation procedure for the substrates in Table 1

To a solution of the substrate in MeOH, three freeze-pump-thaw cycles were applied and the system was filled with Ar. Then to this solution was added under Ar a solution of the preformed [Rh((R_P,R_P)-R-SMS-Phos)(MeOH)$_2$]BF_4 complex in MeOH. A vacuum was applied to this system then it was backfilled with H_2. The mixture was stirred at r.t. and H_2 pressure as indicated. Progress of the hydrogenation was monitored by the diminution of the volume of the closed reaction system at 1 bar (until H_2 uptake ceased and a colour change of the solution occurred); for reactions at 10 bar (**S7**) analyses were carried out at the indicated times.

The reaction mixture was analyzed by chiral GC (prior to analysis carboxylic groups were esterified with $TMSCHN_2$ in hexanes). Absolute configurations were assigned by comparison with the literature data of optical rotation of isolated products (90–98% yield) and/or of the t_R on chiral GC.

Acknowledgements

This work was supported by the Ministry of Higher Education, Science, and Technology of the Republic of Slovenia (Grants No. P1-242 and J1-9806). M. S. acknowledges the innovation stimulation (No. 00P141 to PhosPhoenix SARL) by the Ministry of National Education, Research, and Technology of France.

Notes and references

1 (*a*) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, New York, 1994; (*b*) *Comprehensive Asymmetric Catalysis*, Vol. 1–3 (ed., E. N. Jacobsen, A. Pfaltz and H. Yamamoto), Springer, Berlin, 1999; (*c*) *Catalytic Asymmetric Synthesis*, (Ed., I. Ojima), Wiley-VCH, Weinheim, 2000; (*d*) *Asymmetric Catalysis on Industrial Scale*, (ed., (H.-U. Blaser and E. Schmidt), Wiley-VCH, Weinheim, 2004; (*e*) *Handbook of Homogeneous Hydrogenation*, *Vol. 1–3* (ed., J. G. de Vries and C. J. Elsevier), Wiley-VCH, Weinheim, 2006.

2 (*a*) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029–3069; (*b*) A. Grabulosa, J. Granell and G. Muller, *Coord. Chem. Rev.*, 2007, **251**, 25–90; (*c*) *Phosphorus Ligands in Asymmetric Catalysis*, *Vol. 1–3* (Ed., A. Börner), Wiley-VCH, Weinheim, 2008.

3 For DIOP [2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane], see: (*a*) C. F. Hobbs and W. S. Knowles, *J. Org. Chem.*, 1981, **46**, 4422–4427; (*b*) K. Tamao, K. Nakamura, H. Ishii, S. Yamaguchi and M. Shiro, *J. Am. Chem. Soc.*, 1996, **118**, 12469–12470. For BPPM (*N-tert*-butoxycarbonyl-2-diphenylphosphinomethyl-4-diphenylphosphino-pyrrolidine), see: (*c*) H. Takeda, T. Tachinami, S. Hosokawa, M. Aburatani, K. Inoguchi and K. Achiwa, *Chem. Pharm. Bull.*, 1991, **39**, 2706–2708; (*d*) K. Achiwa and T. Soga, *Tetrahedron Lett.*, 1978, **19**, 1119–1120. For DEGUPHOS [DEGUPHOS = catASium® D(R) = (3*R*,4*R*)-bis(diphenylphosphino)-*N*-benzyl-pyrrolidine], see: (*e*) H. Jendralla, *Synthesis*, 1994, (05), 494–498; (*f*) U. Nagel and E. Kinzel, *Chem. Ber.*, 1986, **119**, 3326–3343; (*g*) For catASium® MN series [2,3-bis(2,5-dimethylphospholanyl)-pyrrole-2,5-diones], see: A. Börner, J. Holz, A. Monsees, T. Riermeier, R. Kadyrov, C. A. Schneider, U. Dingerdissen and K. Drauz, (Evonic Degussa GmbH), US2005/0209455, 2005. For MeO-BIPHEP [2,2′-bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl], see: (*h*) R. Schmid, J. Foricher, M. Cereghetti and P. Schönholzer, *Helv. Chim. Acta*, 1991, **74**, 370–389; (*i*) For SONIPHOS series [2,2′-bis(diphenylphosphino)-6,6′-diacyloxy-1,1′-biphenyls], see: M. Bulliard, B. Laboue and S. Roussiasse, (PPG-SIPSY), WO2002012253, 2002. For C_nTunaPhos series and analogues {C_3-TunaPhos = C_3-TunePhos = 1,13-bis(diphenylphosphino)-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonin}, see: (*j*) Z. Zhang, H. Qian, J. Longmire and X. Zhang, *J. Org. Chem.*, 2000, **65**, 6223–6226; (*k*) L. Qiu, J. Wu, S. Chan, T. T.-L. Au-Yeung, J.-X. Ji, R. Guo, C.-C. Pai, Z. Zhou, X. Li, Q.-H. Fan and A. S. C. Chan, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5815–2820. For similarly modified group of atropoisomeric diphosphines, see: for SEGPHOS [5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole]: (*l*) T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura and H. Kumobayashi, *Adv. Synth. Catal.*, 2001, **343**, 264–267. For SYNPHOS ®[6,6′-bis(diphenylphosphino)-2,2′,3,3′-tetrahydro-5,5′-bi-1,4-benzodioxin] and DIFLUORPHOS

®[5,5′-bis(diphenylphosphino)-2,2,2′,2′-tetrafluoro-4,4′-bi-1,3-benzodioxole]: (*m*) S. Jeulin, S. D. de Paule, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion and P. Dellis, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5799–5804; (*n*) Y. Sun, X. Wan, M. Guo, D. Wang, X. Dong, Y. Pan and Z. Zhang, *Tetrahedron: Asymmetry*, 2004, **15**, 2185–2188; (*o*) For SOLPHOS, see: B. Pugin, P. Martin, M. Mueller,F. Naud, F. Spindler, M. Thommen, G. Melone and M. Kesselgruber, (Solvias AG), WO2004089920, 2004. For ferrocene-based ligands, see: (*p*) F. Spindler, C. Malan, M. Lotz, M. Kesselgruber, U. Pittelkow, A. Rivas-Nass, O. Briel and H.-U. Blaser, *Tetrahedron: Asymmetry*, 2004, **15**, 2299–2306; (*q*) P. Barbaro, C. Bianchini, G. Giambastiani and S. L. Parisel, *Coord. Chem. Rev.*, 2004, **248**, 2131–2150; (*r*) R. G. Arrayás, J. Adrio and J. C. Carretero, *Angew. Chem., Int. Ed.*, 2006, **45**, 7674–7715. For (*S*,*S*)-R-BisP* [(*S*,*S*)-1,2-bis(alkylmethylphosphino)ethanes] and (*R*,*R*)-R-MiniPHOS [(*R*,*R*)-1,2-bis(alkylmethylphosphino)methanes] series, see: (*s*) I. D. Gridnev, Y. Yamanoi, N. Higashi, H. Tsuruta, M. Yasutake and T. Imamoto, *Adv. Synth. Catal.*, 2001, **343**, 118–136.

4 For examples of modifications of *O*- and *N*-substituted monophosphines, phosphoramidites, phosphonites and phosphites, see: (*a*) Y. Uozumi, A. Tanahashi, S.-Y. Lee and T. Hayashi, *J. Org. Chem.*, 1993, **58**, 1945–1948; (*b*) M. Peer, J. C. de Jong, M. Kiefer, T. Langer, H. Rieck, H. Schell, P. Sennhenn, J. Sprinz, H. Steinhagen, B. Wiese and G. Helmchen, *Tetrahedron*, 1996, **52**, 7547–7583; (*c*) K. Nozaki, N. Sakai, T. Nanno, T. Higashijima, S. Mano, T. Horiuchi and H. Takaya, *J. Am. Chem. Soc.*, 1997, **119**, 4413–4423; (*d*) C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen and P. G. Pringle, *Chem. Commun.*, 2000, 961–962; (*e*) M. T. Reetz and G. Mehler, *Angew. Chem., Int. Ed.*, 2000, **39**, 3889–3890; (*f*) M. van der Berg, A. J. Minnard, 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**, 11539–11540; (*g*) M. T. Reetz and T. Sell, *Tetrahedron Lett.*, 2000, **41**, 6333–6336; (*h*) A. Suárez and A. Pizzano, *Tetrahedron: Asymmetry*, 2001, **12**, 2501–2504; (*i*) D. M. Tellers, M. Bio, Z. J. Song, J. C. McWilliam and Y. Sun, *Tetrahedron: Asymmetry*, 2006, **17**, 550–553. For MonoPhos™, see: (*j*) J. G. de Vries and L. Lefort, *Chem.–Eur. J.*, 2006, **12**, 4722–4734; (*k*) C. Darcel, D. Moulin, J.-C. Henry, M. Lagrelette, P. Richard, P. D. Harvey and S. Jugé, *Eur. J. Org. Chem.*, 2007, **13**, 2078–2090.

5 W. S. Knowles, W. C. Christopfel, K. E. Koenig and C. F. Hobbs, *Adv. Chem. Ser.*, 1982, **196**, 325–336. Therein, Knowles *et al.* have reported their results of study for the Rh(I)-catalyzed hydrogenation of (*Z*)-α-acetamido- or (*E*/*Z*)-α-benzamidocinnamic acids with various [Rh((*R*,*R*)-1,2-bis{(*o*-R-phenyl)(phenyl)phosphino}ethane)] catalysts (conditions: S/C = 1000 under 3 atm of H_2 in *i*PrOH (88%) at 50 °C for 0.8–1 h): 96% ee (*S*) with *o*-R-Ph = *o*-MeO-Ph (DiPAMP), 84% ee with *o*-HO-Ph, 63% ee with *o*-AcO-Ph, 73% ee with *o*-$MeSO_2$-Ph, 60% ee with *o*-F-Ph, while no reaction occurred with *o*-MeS-Ph.

6 Prepared *via* resolution of *l*-menthyl (RS_P)-(*o*-anisyl)(methyl)phosphinate, (*R*,*R*)-DiPAMP was demethylated using Ph_2PLi. For this, see ref. 5.

7 Y. Wada, T. Imamoto, H. Tsuruta, K. Yamaguchi and I. D. Gridnev, *Adv. Synth. Catal.*, 2004, **346**, 777–788.

8 (*a*) B. Zupančič, B. Mohar and M. Stephan, *Adv. Synth. Catal.*, 2008, **350**, 2024–2032; (*b*) B. Zupančič, B. Mohar and M. Stephan, *Tetrahedron Lett.*, 2009, **50**, 7382–7384.

9 (*a*) M. Stephan and B. Mohar, (PhosPhoenix SARL; Nat. Inst. of Chem. of Slovenia), FR2887253, 2005; WO2006136695, 2006 (http://www.cas.org/spotlight/rlist1q07p/rlist1q07p.html); (*b*) M. Stephan, D. Šterk and B. Mohar, *Adv. Synth. Catal.*, 2009, **351**, 2779–2786; (*c*) B. Zupančič, B. Mohar and M. Stephan, *Org. Lett.*, 2010, **12**, 1296–1299; (*d*) B. Zupančič, B. Mohar and M. Stephan, *Org. Lett.*, 2010, **12**, 3022–3025.

10 For the preparation of SMS-Phos precursor **1a** (this acronym derives from the initials of the authors Stephan, Mohar, Sterk; ref. 9*b*), see: (*a*) M. Stephan, B. Modec and B. Mohar, *Tetrahedron Lett.*, 2011, **52**, 1086–1089. The preparation of *t*-Bu-SMS-Phos[9c] and Ph-SMS-Phos[9d] was carried out following the general asymmetric strategy of Jugé-Stephan. For the latter, see: (*b*) S. Jugé, M. Stephan, J. A. Laffitte and J.-P. Genêt, *Tetrahedron Lett.*, 1990, **31**, 6357–6360; (*c*) Ligands **2s** and **2z** were not prepared in sufficiently pure form to be used in testing.

11 For (Rh-DiPAMP)-catalyzed hydrogenations, see ref. 9*b* and for **S1**: (*a*) B. D. Vineyard, W. S. Knowles and M. J. Sabacky, *J. Mol. Catal.*, 1983, **19**, 159–169; (*b*) J. W. Scott, D. D. Keith, G. Nix Jr., D. R. Parrish, S. Remington, G. P. Roth, J. M. Townsend, D. Valentine Jr. and R. Yang, *J. Org. Chem.*, 1981, **46**, 5086–5093 for **S2**: (*c*) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman and D. J. Weinkauf, *J. Am. Chem. Soc.*, 1977, **99**, 5946–5952 **S3** and **S4**: (*d*) D. Heller, H.-J. Drexler, J. You, W. Baumann, K. Drauz, H.-P. Krimmer and A. Börner, *Chem.–Eur. J.*, 2002, **8**, 5196–5203 for **S6**: (*e*) W. C. Christopfel and B. D. Vineyard, *J. Am. Chem. Soc.*, 1979, **101**, 4406–4408.

12 For indicative metal-catalyzed asymmetric hydrogenation of 2-arylpropenoic acids, see: with Rh: (*a*) R. Deschenaux and J. K. Stille, *J. Org. Chem.*, 1985, **50**, 2299–2302; (*b*) T. Hayashi, N. Kawamura and Y. Ito, *J. Am. Chem. Soc.*, 1987, **109**, 7876–7878; (*c*) G. Argouarch, O. Samuel and H. B. Kagan, *Eur. J. Org. Chem.*, 2000, **16**, 2885–2891; (*d*) W. S. Knowles, *Angew. Chem., Int. Ed.*, 2002, **41**, 1998–2007 with Ru: (*e*) T. Ohta, H. Takaya, M. Kitamura, K. Nagai and R. Noyori, *J. Org. Chem.*, 1987, **52**, 3174–3176; (*f*) T. Uemura, X. Zhang, K. Matsumura, N. Sayo, H. Kumobayashi, T. Ohta, K. Nozaki and H. Takaya, *J. Org. Chem.*, 1996, **61**, 5510–5516; (*g*) T. Benincori, E. Brenna, F. Sannicolò, L. Trimarco, P. Antognazza, E. Cesarotti, F. Demartin and T. Pilati, *J. Org. Chem.*, 1996, **61**, 6244–6251; (*h*) A. L. Monteiro, F. K. Zinn, R. F. de Souza and J. Dupont, *Tetrahedron: Asymmetry*, 1997, **8**, 177–179; (*i*) Y. Crameri, J. Foricher, M. Scalone and R. Schmid, *Tetrahedron: Asymmetry*, 1997, **8**, 3617–3623; (*j*) T. Benincori, E. Cesarotti, O. Piccolo and F. Sannicolò, *J. Org. Chem.*, 2000, **65**, 2043–2047; (*k*) C.-C. Pai, C.-W. Lin, C.-C. Lin, C.-C. Chen, A. S. C. Chan and W. T. Wong, *J. Am. Chem. Soc.*, 2000, **122**, 11513–11514; (*l*) G.-J. Deng, Q.-H. Fan, X.-M. Chen, D.-S. Liu and A. S. C. Chan, *Chem. Commun.*, 2002, 1570–1571; (*m*) G.-J. Deng, B. Yi, Y.-Y. Huang, W.-J. Tang and Y.-M. He, *Adv. Synth. Catal.*, 2004, **346**, 1440–1444; (*n*) H.-F. Zhou, Q.-H. Fan, W.-J. Tang, L.-J. Xu, Y.-M. He, G.-J. Deng, L.-W. Zhao, L.-Q. Gu and A. S. C. Chan, *Adv. Synth. Catal.*, 2006, **348**, 2172–2182; (*o*) X. Cheng, J.-H. Xie, S. Li and Q.-L. Zhou, *Adv. Synth. Catal.*, 2006, **348**, 1271–1276 with Ir: (*p*) R. Hoen, J. A. F. Boogers, H. Bernsmann, A. J. Minnaard, A. Meetsma, T. D. Tiemersma-Wegman, A. H. M. de Vries, J. G. de Vries and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2005, **44**, 4209–4212; (*q*) S. Li, S.-F. Zhu, C.-M. Zhang, S. Song and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2008, **130**, 8584–8585; (*r*) Y. Zhang, Z. Han, F. Li, K. Ding and A. Zhang, *Chem. Commun.*, 2010, **46**, 156–158 with Pd: (*s*) H.-Z. Ma, B. Wang and Q.-Z. Shi, *Synth. Commun.*, 2003, **33**, 175–182; (*t*) T. Sugimura, T. Uchida, J. Watanabe, T. Kubota, Y. Okamoto, T. Misaki and T. Okuyama, *J. Catal.*, 2009, **262**, 57–64.

13 For the preparation of the rest of the (R_P,R_P)-series and some (S_P,S_P)-enantiomers, see ref. 9 and the ESI†.