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Heavyweight "R-SMS-Phos" Ligands in the Olefins' Hydrogenation Arena

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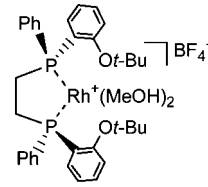
ABSTRACT

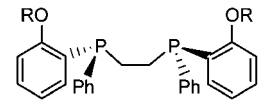


[Rh((*R*,*R*)-*t*-Bu-sms-phos)(MeOH)$_2$]BF$_4$

A series of enantiopure *P*-stereogenic 1,2-bis[(*o*-RO-phenyl)(phenyl)phosphino]ethane (R-SMS-Phos) ligands wherein R= *i*-Pr, *i*-Bu, *t*-Bu, 3-Pen, and CH_2TMS was assessed in the Rh(I)-catalyzed hydrogenation of an indicative set of olefins. The best performing *t*-Bu-SMS-Phos ligand was screened against a wide range of representative classes of standard and new olefinic substrates such as dehydroamido esters, dehydro-α-amido-phosphonates, enamides, itaconates, acrylates, enol acetates, α-phosphonovinyl benzoates, α-(2-pyridyl *N*-oxide)styrenes, and α-(1-hydroxyliminoethyl)styrenes. Excellent enantioselectivities and high TOFs were attained under mild conditions.

Since the conception of the Rh(I)-DiPAMP (DiPAMP= 1,2-bis[(*o*-anisyl)(phenyl)phosphino]ethane) catalyst for the asymmetric hydrogenation of olefins more than four decades ago,[1] stiff competition to attain higher catalyst performances is ever-increasing.[2] In particular, *P*-stereogenic diphosphines have further advanced this field and are making a comeback. Innovation through optimization of chiral ligand designs with a proven track record is enticing for improved or even new industrial applications. A comprehensive survey of the literature reveals a number of study cases whereby diversification of a given diphosphine by judicious alterations was undertaken.[2,3]

In our ongoing research focus on *P*-stereogenic ligands,[3n,o] we present herein our exploratory optimization results of our recently introduced 1,2-bis[(*o*-isopropoxyphenyl)(phenyl)phosphino]ethane (*i*-Pr-SMS-Phos) ligand[3o] for the Rh(I)-mediated hydrogenation of olefins. Higher homologues at the level of the branched alkoxy groups were prepared.



(*R*,*R*)-R-SMS-Phos (100% ee)
(*R*,*R*)-DiPAMP: R= Me

R= *i*-Pr
i-Bu
t-Bu
3-Pen
CH_2TMS

Overall yields:
50 - 55%

Isolated in 50−55% overall yields following the Jugé-Stephan route[4] or following a straightforward functionalization−decomplexation sequence from the crystalline 1,2-bis[(*o*-hydroxyphenyl)(phenyl)phosphino-*P*-borane]ethane,[5] the R-SMS-Phos (1,2-bis[(*o*-RO-phenyl)(phenyl)phosphino]-ethane) series (R= *i*-Pr, *i*-Bu, *t*-Bu, 3-Pen, and CH_2TMS) was screened under mild conditions in the asymmetric

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(1) (a) Knowles, W. S.; Christopfel, W. C.; Koenig, K. E.; Hobbs, C. F. *Advances in Chemistry Series*; American Chemical Society: Washington D.C., 1982; Vol. 196, pp 325−336. (b) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998–2007.

(2) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vols. 1−3. (b) *Asymmetric Catalysis on Industrial Scale*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, 2004. (c) *Handbook of Homogeneous Hydrogenation*; de Vries J. G., Elsevier C. J., Eds.; Wiley-VCH: Weinheim, 2006; Vols. 1−3.

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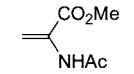
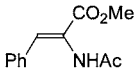
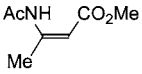
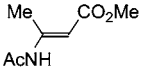
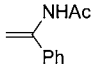
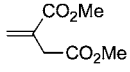
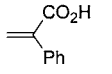
Table 1. [Rh((*R*,*R*)-R-sms-phos)(MeOH)$_2$]BF$_4$-Catalyzed Hydrogenation of **S1**−**S7**[a]

olefin		R= *i*-Pr		R= *i*-Bu		R= *t*-Bu		R= 3-Pen		R= CH_2TMS	
		t, min	ee, %	t, min	ee, %	t, min	ee, %	t, min	ee, %	t, min	ee, %
	**S1** (MAA)	6	99.4	6	99.4	4	99.9	5	99.8	6	99.7
	**S2** (MAC)	4	99.7	4	99.7	2	99.8	4	99.4	4	99.7
	**S3** (*Z*-MAB)	20	82.1	30	70.2	7	80.1	15	84.4	30	71.4
	**S4** (*E*-MAB)	90	93.0	90	93.4	60	97.3	90	94.9	120	95.1
	**S5** (AS)	3	97.8	5	96.9	2	99.3	4	98.5	8	98.1
	**S6** (DMI)	5	98.1	5	98.5	2	99.8	4	98.6	7	99.1
	**S7** (AA)[b]	120	88.0	120[c]	86.0	120	94.7	120	92.9	120[d]	86.8

[a] The catalyst was prepared in situ from [Rh(nbd)$_2$]BF$_4$. Runs were carried out under 1 bar of H_2 (10 bar for **S7**) at rt 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 (prior to analysis the carboxylic group of hydrogenation product of **S7** was esterified with $TMSCHN_2$). 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] 78% conversion. [d] 59% conversion.

hydrogenation of an indicative set of olefinic reference substrates **S1**−**S7** (Table 1). Within the adopted systematic bulkiness modification of the R groups, valuable changes in reactivity and enantioselectivity of the Rh(I)-(R-SMS-Phos) catalysts were noticeable. Operating with a S/C 100 in methanol at rt under 1 bar of H_2, methyl α-acetamidoacrylate (**S1**: MAA) and cinnamate (**S2**: MAC) were hydrogenated invariably with >99% ee's within minutes. However, the best hydrogenation results of methyl (*Z*)-3-acetamidobut-2-enoate (**S3**: (*Z*)-MAB) and its (*E*)-isomer (**S4**: (*E*)-MAB) were achieved with 3-Pen-SMS-Phos and *t*-Bu-SMS-Phos furnishing 84.4% and 97.3% ee, respectively. Further on, the hydrogenation of α-acetamidostyrene (**S5**: AS) and dimethyl itaconate (**S6**: DMI) also proceeded smoothly within minutes with an incremental increase in the ee, reaching, respectively, the maxima of 99.3% and 99.8% with *t*-Bu-SMS-Phos. Interestingly enough, the bulkiest 3-Pen-SMS-Phos and *t*-Bu-SMS-Phos designs afforded hydratropic acid from atropic acid (**S7**: AA) with reasonably good ee's, with up to 94.7% ee being attained with *t*-Bu-SMS-Phos. Hydratropic acid constitutes the basic model of nonsteroidal antiarthritics.[6] Thus, among the screened ligand set, the *t*-Bu-SMS-Phos ligand emerged as being superior. Hence, the Rh(I)-(*t*-Bu-SMS-Phos) catalyst was screened under mild hydrogenation conditions against a selection of a broad diversity of conventional, more challenging benchmark and new classes of olefins **S8**−**S19** (Table 2).

High reaction rates coupled with excellent ee's were reached in the hydrogenation of virtually all of the considered various olefin groups.[7] In particular, the representative standard test substrate MAC (**S2**) was hydrogenated (100% conversion) in 99.8% ee within 5.5 h using a S/C 30000. β,β-Disubstituted dehydro-(*N*-acetyl)-alaninates (**S8** and **S9**) were hydrogenated equally well under 3 bar of H_2 in >99% ee within 2 h using a S/C

(3) (a) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988–2989. (b) Gridnev, I. D.; Yamanoi, Y.; Higashi, N.; Tsurata, H.; Yasutake, M.; Imamoto, T. *Adv. Synth. Catal.* **2001**, *343*, 118–136. (c) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612–1614. (d) Tang, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4159–4161. (e) Tang, W.; Zhang, X. *Org. Lett.* **2003**, *5*, 205–207. (f) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 3509–3511. (g) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069. (h) Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc.* **2004**, *126*, 5966–5967. (i) Liu, D.; Zhang, X. *Eur. J. Org. Chem.* **2005**, 646–649. (j) Grabulosa, A.; Granell, J.; Muller, G. *Coord. Chem. Rev.* **2007**, *251*, 25–90. (k) Chen, W.; McCormack, P. J.; Mohammed, K.; Mbafor, W.; Roberts, S. M.; Whittall, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4141–4144. (l) *Phosphorus Ligands in Asymmetric Catalysis*; Börner, A., Ed.; Wiley-VCH: Weinheim, 2008; Vols. 1−3. (m) Gridnev, I. D.; Imamoto, T.; Hoge, G.; Kouchi, M.; Takahashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 2560–2572. (n) Zupančič, B.; Mohar, B.; Stephan, M. *Adv. Synth. Catal.* **2008**, *350*, 2024–2032. (o) Stephan, M.; Šterk, D.; Mohar, B. *Adv. Synth. Catal.* **2009**, *351*, 2779–2786.

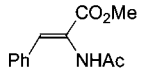
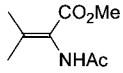
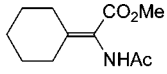
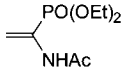
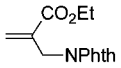
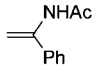
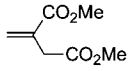
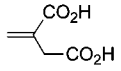
(4) Jugé, S.; Stephan, M.; Laffitte, J. A.; Genêt, J.-P. *Tetrahedron Lett.* **1990**, *31*, 6357–6360.

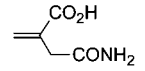
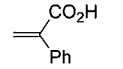
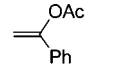
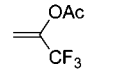
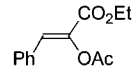
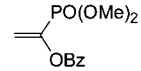
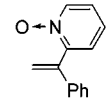
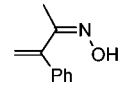
(5) Stephan, M.; Mohar, B. FR2887253, 2005; WO2006136695, 2006.

(6) Kar, A. *Medicinal Chemistry*; New Age International Ltd.: New Delhi, 2005; pp 450−470.

(7) For indicative literature data regarding Rh-catalyzed hydrogenation of these substrates with representative phosphines, see the Supporting Information.

Table 2. [Rh((*R*,*R*)-*t*-Bu-sms-phos)(MeOH)$_2$]BF$_4$-Catalyzed Hydrogenation of Miscellaneous Classes of Olefins[a]

olefin		S/C	t, min	ee, % (config.)
	**S2**	1000	13	99.8 (*S*)
		10000	3 h	99.8
		30000	5.5 h	99.8
	**S8**	1000	2 h	99.2 (*S*)
	**S9**	1000	2 h	99.6 (*S*)
	**S10**	1000	6	99.9 (*R*)
	**S11**	100	30	94.6 (*R*)
	**S5**	1000	20	99.4 (*S*)
		10000	4 h	99.3
	**S6**	1000	15	99.7 (*R*)
		10000	3 h	99.4
		30000	6 h	99.4
	**S12**	1000	6	99.7 (*R*)

olefin		S/C	t, min	ee, % (config.)
	**S13**	1000	5	99.9 (*R*)
	**S7**	100 [b]	2 h	94.7 (*S*)
		100 [c]	2 h	95.6
	**S14**	100	30	98.7 (*S*)
		1000	5 h	98.7
	**S15**	100	10	>99 (*S*)
		1000	90	>99
	**S16**	100	2 h	99.9 (*S*)
	**S17**	100	3	99.6 (*R*)
		1000	25	99.6
	**S18**	100	7	99.2 (*S*)
		1000	60	99.2
	**S19**	100	4 h	94.0 (*Z*, +)

[a] The catalyst was prepared in situ from [Rh(nbd)$_2$]BF$_4$ and (*R*,*R*)-*t*-Bu-SMS-Phos. Runs were carried out under 1 bar of H_2 (3 bar for **S8**, **S9** and 10 bar for **S7**, **S19**) at rt (50 °C for **S18**) in MeOH (0.5 mmol of substrate in 7.5 mL MeOH with a S/C = 100 or 1000; 10 mmol of substrate in 7.5 mL MeOH with a S/C = 10000; 30 mmol of substrate in 20 mL MeOH with a S/C = 30000) for the time indicated (100% conversion) and are unoptimized. Typical isolated yields were >90%. Ee's were determined by: chiral GC for **S2**, **S5**−**S10**, and **S12**−**S14** (prior to analysis the carboxylic groups of hydrogenation products of **S7**, **S12**, and **S13** were esterified with TMSCHN$_2$); chiral HPLC for **S11** and **S16**−**S19**; ^{1}H NMR (in the presence of (+)-Pr(hfc)$_3$) for hydrogenation product of **S15**. [b] In the presence of Et_3N (0.05 equiv). [c] In the presence of Cy_2NH (0.05 equiv).

1000, and α-acetamido-vinylphosphonate (**S10**) led to 99.9% ee within minutes. The latter result presents the highest ee ever reported for the hydrogenation of the corresponding substrate. Up to 94.6% ee was achieved in the hydrogenation of ethyl α-(phthalimidomethyl)acrylate (**S11**) which also constitutes the highest ee attained with this substrate under the given reaction conditions.[8] Moreover, AS (**S5**) underwent hydrogenation using a S/C 10000 affording 99.3% ee within 4 h.

While a series of itaconates (**S6**, **S12**, **S13**) was hydrogenated with >99.7% ee within minutes using a S/C 1000, >99% ee was maintained with full conversion within 6 h for DMI (**S6**) using a S/C 30000.

A preliminary investigation on the variation of the reaction parameters toward hydratropic acid revealed that an incremental increase in the ee was feasible. Thus, the use of the bulkier Cy_2NH amine (5 mol %) further upgraded the ee to 95.6%.

In a similar vein, a variety of enol acetates (**S14**−**S16**) and a α-benzoyloxy-vinylphosphonate (**S17**) were hydrogenated reasonably fast with exceptionally high ee's. Namely, α-acetoxystyrene (**S14**), which presents a somewhat difficult challenge, was hydrogenated in up to 98.7% ee within 5 h using a S/C 1000. Here again, these results obtained under the given mild condtions are to the best of our knowledge the highest reported ones with these substrates.[3e,m,o,9]

Finally, olefins **S18** and **S19**,[10] which possess a "C−N−O" motif at the α-position, were hydrogenated in 99.2% and 94.0% ee, respectively.

In conclusion, the hydrogenation under mild conditions with excellent ee's and high TOFs of a wide spectrum of representative classes of olefins catalyzed by [Rh(*t*-Bu-sms-phos)(MeOH)$_2$] catalyst represents the advantages of this novel catalytic system. The overall results obtained with this catalyst are among the best ever reported in Rh-phosphine catalyzed hydrogenation.

(8) (a) Huang, H.; Liu, X.; Deng, J.; Qui, M.; Zheng, Z. *Org. Lett.* **2006**, *8*, 3359–3362. (b) Deng, J.; Hu, X.-P.; Huang, J.-D.; Yu, S.-B.; Wang, D.-Y.; Duan, Z.-C.; Zheng, Z. *J. Org. Chem.* **2008**, *73*, 2015–2017.

(9) Wang, D.-Y.; Hu, X.-P.; Huang, J.-D.; Deng, J.; Yu, S.-B.; Duan, Z.-C.; Xu, X.-F.; Zheng, Z. *Angew. Chem., Int. Ed.* **2007**, *46*, 7810–7813.

(10) Our NOESY analysis (see the Supporting Information) of **S19** and its hydrogenated product revealed a *syn*-conformation for both oximes. In the literature, **S19** was presented with an *anti*-conformation. For this, see: (a) Tishkov, A. A.; Lesiv, A. V.; Khomutova, Y. A.; Strelenko, Y. A.; Nesterov, I. D.; Antipin, M. Yu.; Ioffe, S. L.; Denmark, S. E. *J. Org. Chem.* **2003**, *68*, 9477–9480.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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