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Impact on Hydrogenation Catalytic Cycle of the R Groups' Cyclic Feature in "R-SMS-Phos"

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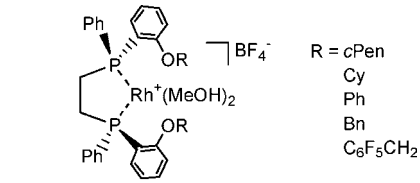
ABSTRACT

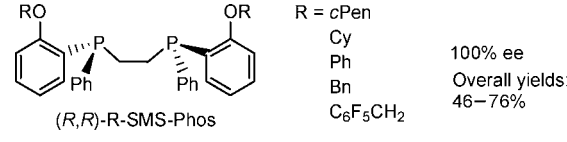


[Rh((*R*,*R*)-R-SMS-Phos)(MeOH)$_2$]BF$_4$

A series of R-SMS-Phos ligands was evaluated in the Rh(I)-catalyzed hydrogenation of a set of olefins showing a marked influence of the cyclic nature and structure of the R groups. Overall, *c*Pen- and Cy-SMS-Phos performed efficiently, while Ph- and Bn-SMS-Phos exhibited slower kinetics and furnished lower ee's also compared with $C_6F_5CH_2$-SMS-Phos. The Rh(I)-(Cy-SMS-Phos) catalyst was screened under mild conditions displaying excellent enantioselectivities and high TOFs. Cases of catalysis under catalyst or substrate control were identified.

Undoubtedly, promoted by chiral Rh, Ru, or Ir complexes of phosphorus-based ligands, asymmetric hydrogenation of prostereogenic olefins offers a viable cost-effective alternative for the production of enantiopure bioactive ingredients or their components.[1] Nevertheless, in the race to ally high enantioselectivity with high catalytic activity, catalysis proved to be critically sensitive to the ligand structure. In particular, *P*-stereogenic diphosphines have indelibly marked and advanced this technology on both the applied and fundamental levels.[1,2]

In our continuing research on Rh(I)-(*P*-stereogenic phosphine)-catalyzed hydrogenation of olefins,[3] we present herein our comparative study and application of a new 1,2-bis-[(*o*-RO-phenyl)(phenyl)phosphino]ethane (R-SMS-Phos) series wherein R = *c*Pen, Cy, Ph, Bn, and $C_6F_5CH_2$ with the various R groups sharing a common cyclic feature.



Readily prepared in 46−76% overall yields via the easy-to-perform Jugé−Stephan route[4] or from the crystalline

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(1) (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.

(2) Following publications and references cited therein: (a) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998–2007. (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069. (c) Grabulosa, A.; Granell, J.; Muller, G. *Coord. Chem. Rev.* **2007**, *251*, 25–90. (d) *Phosphorus Ligands in Asymmetric Catalysis*; Börner, A., Ed.; Wiley-VCH: Weinheim, 2008; Vols. 1−3.

(3) (a) Stephan, M.; Mohar, B. FR2887253, 2005; WO2006136695, 2006. (b) Zupančič, B.; Mohar, B.; Stephan, M. *Adv. Synth. Catal.* **2008**, *350*, 2024–2032. (c) Stephan, M.; Šterk, D.; Mohar, B. *Adv. Synth. Catal.* **2009**, *351*, 2779−2786. (d) Zupančič, B.; Mohar, B.; Stephan, M. *Tetrahedron Lett.* **2009**, *50*, 7382–7384. (e) Zupančič, B.; Mohar, B.; Stephan, M. *Org. Lett.* **2010**, *12*, 1296–1299.

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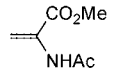
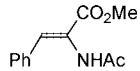
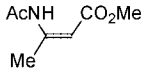
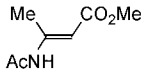
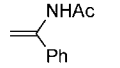
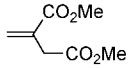
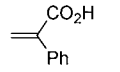
Table 1. [Rh((*R*,*R*)-R-SMS-Phos)(MeOH)$_2$]BF$_4$-Catalyzed Hydrogenation of **S1**−**S7**[a]

olefin		R = *c*Pen		R = Cy		R = Ph		R = Bn		R = $C_6F_5CH_2$	
		time, min	ee, %	time, min	ee, %	time, min	ee, %	time, min	ee, %	time, min	ee, %
	**S1** (MAA)	6	99.9	5	99.8	6	96.5	12	99.2	6	99.7
	**S2** (MAC)	3	99.9	3	99.9	9	97.1	5	99.6	3	99.8
	**S3** (*Z*-MAB)	10	84.8	15	88.2	90	66.6	4 h	63.9	15	81.5
	**S4** (*E*-MAB)	20	97.6	45	97.8	16 h[b]	78.1	21 h[c]	88.0	90	95.8
	**S5** (AS)	3	99.9	3	99.9	7	87.7	5	95.4	4	99.4
	**S6** (DMI)	3	99.3	3	99.3	7	91.7	15	96.9	3	98.7
	**S7** (AA)[d]	2 h	96.4	2 h	97.1	3.3 h[e]	61.1	3.3 h	76.8	3 h	94.8

[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 of MeOH) with a substrate/catalyst ratio (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 the hydrogenation product of **S7** was esterified with TMSCHN$_2$). With (*R*,*R*)-R-SMS-Phos, *S*-configured products were obtained except with **S6**. [b] 92% conversion. [c] 77% conversion. [d] In the presence of Et_3N (1.1 equiv). [e] 53% conversion.

1,2-bis[(*o*-hydroxyphenyl)(phenyl)phosphino-*P*-borane]-ethane,[3a] the R-SMS-Phos series was assessed under mild conditions in the asymmetric hydrogenation of an indicative set of olefinic substrates **S1**−**S7** (Table 1). The Rh(I)-(R-SMS-Phos)-catalyzed hydrogenation proved to be affected by the cyclic nature and structure of the R groups. The *c*Pen- and Cy-SMS-Phos ligands emerged as being superior, whereas Ph-SMS-Phos presented the lowest ee values followed by Bn-SMS-Phos. Interestingly, the latter's perfluorinated-ring analogue $C_6F_5CH_2$-SMS-Phos behaved in comparison to it noticeably better. Consequently, in the case of the Bn-SMS-Phos ligand, a deleterious interference of a Bn group with the Rh center appears to be attributable.

Thus, operating with a S/C 100 in MeOH at rt under 1 bar of H_2, the classical test substrates methyl α-acetamidoacrylate (**S1**: MAA) and cinnamate (**S2**: MAC) were hydrogenated invariably with >99% ee's within minutes, except for Ph-SMS-Phos which afforded ee's up to 97.1%. The Cy-SMS-Phos performed the best in the hydrogenation of methyl (*Z*)-3-acetamidobut-2-enoate (**S3**: (*Z*)-MAB) and its (*E*)-isomer (**S4**: (*E*)-MAB) attaining 88.2% and 97.8% ee, respectively. α-Acetamidostyrene (**S5**: AS) and dimethyl itaconate (**S6**: DMI) were hydrogenated within minutes with >99% ee using *c*Pen- or Cy-SMS-Phos, and the performance of $C_6F_5CH_2$-SMS-Phos was quite close. Notably, the hydrogenation of atropic acid (**S7**: AA) using *c*Pen- and Cy-SMS-Phos proceeded within 2 h leading to 96.4% and 97.1% ee, respectively. The latter result represents the highest enantioselectivity attained in such catalysis for the corresponding benchmark substrate.[3]

Investigating further the scope of the Rh(I)-(Cy-SMS-Phos) catalyst in hydrogenation, this was screened under mild conditions against a selection of a broad diversity of challenging and new olefins **S7**−**S24** (Table 2). Bn-substituted olefins (**S9**, **S19**, and **S24**) were considered as well. Overall, high reaction rates coupled with good to excellent ee's were obtained ranking among the top values reported in the literature for the hydrogenation of the corresponding substrates.[5]

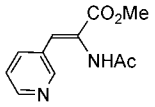
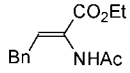
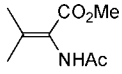
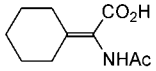
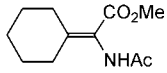
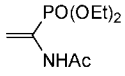
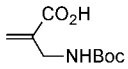
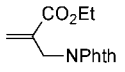
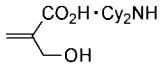
Under the adopted standard reaction conditions, the Rh(I)-(Cy-SMS-Phos) complex was effective in catalyzing the hydrogenation of a series of β-substituted and β,β-disubstituted dehydro-(*N*-acetyl)alaninates **S8**−**S12** with >99% ee and good reaction rates. In particular, methyl (*Z*)-2-acetamido-3-(3-pyridyl)propenoate (**S8**) in the form of its HBF_4 salt was hydrogenated with 99.6% ee within 24 h using a S/C 30 000. With comparable efficiency, ethyl α-acetamidovinylphosphonate (**S13**) led to 99.9% ee within a few hours

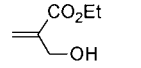
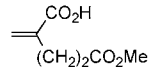
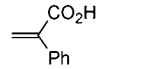
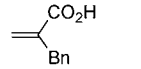
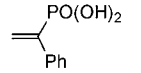
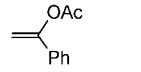
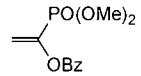
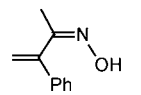
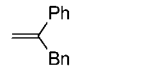
(4) Jugé, S.; Stephan, M.; Laffitte, J. A.; Genêt, J.-P. *Tetrahedron Lett.* **1990**, *31*, 6357–6360.

(5) For indicative literature data regarding metal-catalyzed hydrogenation of the known substrates or derivatives with representative phosphorus-based ligands, see the Supporting Information.

(6) (a) Talley, J. J. US5321153, 1994. (b) Breipohl, G.; Holla, W.; Jendralla, H.; Beck, G. WO55175, 2001. (c) Zeng, Q.; Liu, H.; Mi, A.; Jiang, Y.; Li, X.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron* **2002**, *58*, 8799–8803. (d) Blaser, H.-U.; Pugin, B.; Spindler, F. *J. Mol. Catal. A: Chem.* **2005**, *231*, 1–20.

Table 2. [Rh((*R*,*R*)-Cy-SMS-Phos)(MeOH)$_2$]BF$_4$-Catalyzed Hydrogenation of Miscellaneous Classes of Olefins[a]

olefin		S/C	time	ee, % (config.)
	**S8** [b]	100 1000 10000 30000	5 min 45 min 8 h 24 h	99.6 (*S*) 99.6 99.7 99.6
	**S9**	100 1000	2 min 17 min	99.6 (*S*) 99.6
	**S10**	1000	2 h	99.4 (*S*)
	**S11**	100 1000	20 min 4 h	99.1 (*S*) 99.1
	**S12**	1000	2 h	99.5 (*S*)
	**S13**	1000 10000 50000	5 min 1 h 4 h	99.9 (*R*) 99.9 99.9
	**S14**	100 1000	4 min 40 min	99.3 (*R*) 99.1
	**S15**	100	40 min	94.0 (*R*)
	**S16**	100 1000 [c]	16 h 16 h	93.2 (*S*) 93.1

olefin		S/C	time	ee, % (config.)
	**S17**	100 1000	7 min 1 h	97.8 (*R*) 97.5
	**S18**	100 [d]	4 h	81.2 (*S*)
	**S7**	100 [e] 100 [f]	2 h 2 h	97.1 (*S*) 97.4
	**S19**	100 [f] 100 [g] 100 [c,g]	16 h 16 h 3 h	66.6 (*S*) 74.7 74.9
	**S20**	100 [f]	3 h	84.8 (*S*)
	**S21**	100	15 min	97.1 (*S*)
	**S22**	1000 10000	20 min 3 h	99.8 (*R*) 99.8
	**S23**	100	4 h	93.0 (*Z*, +)
	**S24**	100 100 [c] 100 [j]	20 h 20 h 5 h	9 [h] (*R*) 12 [i] (*R*) 23 [i] (*S*)

[a] The catalyst was prepared in situ from [Rh(nbd)$_2$]BF$_4$ and (*R*,*R*)-Cy-SMS-Phos. Runs were carried out under 1 bar of H$_2$ (3 bar for **S10**, **S12**, **S19** and 10 bar for **S7**, **S16**, **S18**, **S20**, **S23**) at rt in MeOH (0.5 mmol of substrate in 7.5 mL of MeOH with a S/C = 100 or 1000; 10 mmol of substrate in 7.5 mL of MeOH with a S/C = 10 000; 30 mmol of substrate in 20 mL of MeOH with a S/C = 30 000; 50 mmol of substrate in 40 mL of MeOH with a S/C = 50 000) for the time indicated (100% conversion). Typical isolated yields were >90%. Ee's were determined by: chiral GC for **S7**−**S14**, **S16**−**S19**, **S21** (prior to analysis, the carboxylic groups of hydrogenation products of **S7**, **S11**, **S14**, **S16**, **S18**, and **S19** were esterified with TMSCHN$_2$); chiral HPLC for **S15**, **S22**−**S24**; ^{31}P NMR in the presence of (+)-ephedrine for hydrogenation product of **S20**. [b] In the presence of HBF$_4$·Et$_2$O (1.1 equiv); in the absence of HBF$_4$ (S/C = 100), a 40% conversion and 93.8% ee (*S*) were attained in 18 h. [c] 10 bar of H$_2$. [d] In the presence of *t*-BuNH$_2$ (1.1 equiv). [e] In the presence of Et$_3$N (0.05 equiv). [f] In the presence of Cy$_2$NH (0.05 equiv). [g] In the presence of Cy$_2$NH (1.1 equiv). [h] ^{1}H NMR analysis revealed that the 1,2-diphenylpropane (84%) was accompanied with α-methylstilbene (13% *trans*, 3% *cis*). [i] ^{1}H NMR analysis revealed that the 1,2-diphenylpropane (96%) was accompanied with α-methylstilbene (3% *trans*, <1% *cis*). [j] 50 bar of H$_2$.

using a S/C 50 000. Such unusual amino acids and simple reaction conditions are of industrial relevance.[6]

Moreover, two pairs of α-amidomethyl- (**S14**, **S15**) and α-hydroxymethyl-acrylic acid derivatives (**S16**, **S17**) underwent hydrogenation with particularly high ee's. Whereas the Ru-mediated catalysis largely dominated the hydrogenation of α-amidomethylacrylates with limited efficiency,[7] the hydrogenation of **S14** under our practical protocol afforded >99% ee within minutes. Analysis of the hydrogenation outcome of substrates **S8**−**S15** indicated an identical sense of hydrogenation in accordance with the quadrant rule[8] and taking into account the switch in the groups' priorities. However, while the ethyl ester **S17** was converted into the *R*-configured product equivalent of Roche ester with the highest reported hydrogenation ee (97.8% ee),[5] a reverse of stereoselectivity but still with high induction (93.2% ee) was observed with the dicyclohexylammonium salt derivative **S16**.[9] Projected mechanistic studies may elucidate the binding mode of these olefins to the Rh core and the underlying catalysis picture.

Conversely to the typical low enantioselectivity (<10% ee) encountered in the hydrogenation of the notorious α-methylideneglutaric acid derivatives in alcohols,[10] the monoester **S18** afforded as high as 81.2% ee.

Furthermore, while the hydrogenation (10 bar of H$_2$, 2 h) of atropic acid (**S7**: AA) proceeded equally well in the

(7) (a) Takagi, M.; Yamamoto, K. *Tetrahedron* **1991**, *47*, 8869–8882. (b) Dellis, P.; Gueirrero, P.; Genêt, J.-P. FR2801886, 2001. (c) Takagi, M.; Yamamoto, K. *Tetrahedron: Asymmetry* **2001**, *12*, 657–667. (d) Saylik, D.; Campi, E. M.; Donohue, A. C.; Jackson, W. R.; Robinson, A. J. *Tetrahedron* **2002**, *58*, 8799–8803. (e) Huang, H.; Liu, X.; Deng, J.; Qiu, M.; Zheng, Z. *Org. Lett.* **2006**, *8*, 3359–3362.

(8) Valid for amino acids, the empirical quadrant rule suggests that (*S*)-α-amino acids are obtained using (*R*,*R*)-DiPAMP-type ligands and vice versa. For this, see: ref 2a. .

(9) Krawczyk, H. *Synth. Commun.* **1995**, *25*, 641–650.

presence of 5 mol % of Cy_2NH furnishing 97.4% ee, its higher homologue α-benzylacrylic acid (**S19**) necessitated the addition of 1.1 equiv of Cy_2NH to achieve up to 74.9% ee (10 bar of H_2, 3 h). Interestingly, AA's phosphonic analogue **S20** was hydrogenated under similar conditions within 3 h albeit with 84.8% ee. Still, the latter result is the highest value reported for the corresponding substrate.[5]

Proceeding with our screening, the simplest α-arylvinyl acetate **S21** and methyl α-benzoyloxy-vinylphosphonate (**S22**) were hydrogenated once again[3e] reasonably fast and with high ee's. In the case of the latter substrate, a 99.8% ee was maintained with full conversion within 3 h using a S/C 10 000. Also, up to 93.0% ee was reached in the hydrogenation of methyl α-styryl ketoxime (**S23**).

Finally, we explored the hydrogenation of α-benzylstyrene (**S24**)[11] with disappointing results. Poor ee's in the range of 9−23% were obtained with a concurrent competing Rh-catalyzed isomerization−hydrogenation sequence. Nonetheless, it seems that a different catalytic cycle is active at higher pressures as an inversion of stereodirection occurred shifting from 1−10 to 50 bar of H_2.

(10) (a) Christopfel, W. C.; Vineyard, B. D. *J. Am. Chem. Soc.* **1979**, *101*, 4406–4407. (b) Duan, Z.-C.; Hu, X.-P.; Deng, J.; Yu, S.-B.; Wang, D.-Y.; Zheng, Z. *Tetrahedron: Asymmetry* **2009**, *20*, 588–592.

(11) For an early basic study with **S24**, see: Horner, L.; Siegel, H. *Phosphorus* **1972**, *1*, 209–216.

In conclusion, this exploratory investigation highlighted the prospects of the R-SMS-Phos family and demonstrated that the hydrogenation using the [Rh(R-SMS-Phos)$(MeOH)_2$] catalysts is markedly affected by the cyclic nature and structure of the R groups. The noncoordinating and inherent bulky Cy group bestowed interesting attributes on the [Rh(Cy-SMS-Phos)$(MeOH)_2$] catalyst displaying excellent ee's and high TOFs in the hydrogenation under mild conditions of a host of olefins. The degree and sense of enantioselection continue to be intrinsically dependent on the bulkiness and electronic properties of the various coordinating groups present in the medium as well as on the reaction conditions.

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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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