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MaxPHOS Ligand: PH/NH Tautomerism and Rhodium-Catalyzed Asymmetric Hydrogenations

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Abstract: MaxPHOS is an active and robust P-stereogenic ligand for asymmetric catalysis. The presence of an −NH− bridge between the two phosphine moieties allows the NH/PH tautomerism to take place. The neutral ligand, in which the NH form predominates, is an air-sensitive compound. However, protonation of MaxPHOS leads to the stable PH form of the ligand, in which the overall positive charge is distributed on both P centers. This protonation turns the MaxPHOS·HBF_4 salt **3** into an air-stable compound both in the solid state and in solution. The salt **3** is also a convenient precursor for the preparation of rhodium(I) complexes by direct ligand exchange with the complex [Rh(acac)(cod)]. Finally, the corresponding rhodium(I)-MaxPHOS complex was tested in the asymmetric hydrogenation of a wide range of substrates. The complex proved to be a highly selective and robust system in these reactions.

Keywords: asymmetric catalysis; hydrogenation; P ligands; rhodium; tautomerism

Introduction

Chiral phosphines make a critical contribution to the achievement of high activity and selectivity in asymmetric catalysis.[1] Consequently, much research effort has been devoted to developing a wide array of efficient phosphine ligands for a range of catalytic processes. Among these, P-stereogenic electron-rich alkylphosphines are highly proficient in asymmetric hydrogenation and other industrially relevant processes.[2] A critical disadvantage of this class of compounds is that some of them are prone to oxidation when exposed to air and therefore have to be handled under a strictly inert atmosphere.[3] P-stereogenic secondary phosphine oxides (SPOs) and P-stereogenic secondary iminophosphoranes (SIPs) do not have this limitation as there is tautomeric equilibrium between the pentavalent iminophosphorane and the corresponding aminophosphane (Figure 1).[4] This equilibrium is usually shifted towards the P(V) form, which makes SPOs and SIPs stable to oxidation. However, in the presence of a metal source, coordination to the metal efficiently shifts the equilibrium towards the P(III) form. We and others have shown that SIPs are configurationally stable through the PH/NH tauto-

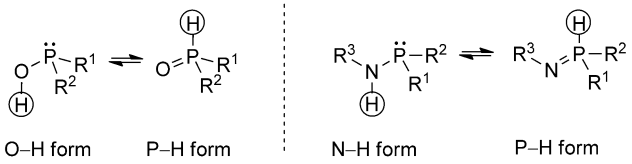
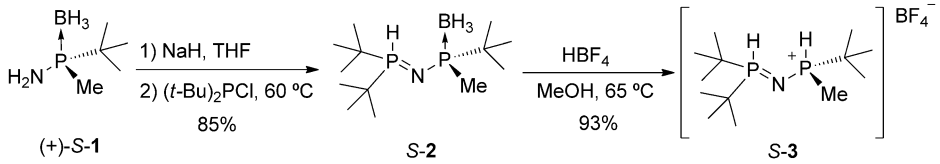


Figure 1. Phosphinous acid/SPO tautomerism (*left*) and aminophosphine/SIP tautomerism (*right*).



Scheme 1. Synthesis of MaxPHOS·HBF_4 salt *S*-**3**.

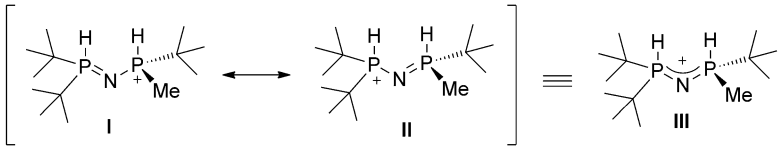


Figure 2. Resonance descriptors for MaxPHOS·HBF_4, *S*-**3**.

meric equilibrium, thus proving that P-stereogenic SIPs are valuable pre-ligands for asymmetric catalysis.[5,6]

We recently described the synthesis of the P-stereogenic aminophosphine building block *S*-**1** and its applicability in the synthesis of HBF_4 salt of MaxPHOS *S*-**3** (Scheme 1).[7,8] *S*-**1** is a convenient P-stereogenic building block. Both enantiomers can be prepared in an optically pure form on a multigram scale using either enantiomer of *cis*-1-amino-2-indanol as chiral auxiliary.[9] Deprotonation of *S*-**1** with sodium hydride and reaction with $(t\text{-Bu})_2PCl$ provides the intermediate iminophosphorane *S*-**2**, in which the tautomeric equilibrium is completely shifted towards P(V). Removal of the borane group is achieved by heating *S*-**2** with HBF_4 in MeOH to afford the phosphonium salt *S*-**3** in 79% yield (2 steps). The occurrence of the PH/NH equilibrium in *S*-**3** turns this compound into an air-stable phosphine pre-ligand.

The promising reactivity of MaxPHOS rhodium complexes and the interesting structure of the putative free ligand, which can have various resonance descriptors, led us to further address their structure and to explore the scope of the asymmetric hydrogenation reaction catalyzed by the Rh-MaxPHOS system. Here we report on the chemical properties of MaxPHOS. Convenient ligand exchange reactions for the preparation of its corresponding Rh(I) complexes along with a complete study of its use in asymmetric hydrogenation are also provided.

Results and Discussion

Chemical Properties of MaxPHOS·HBF_4 and MaxPHOS

The ^1H NMR spectrum of MaxPHOS·HBF_4 salt *S*-**3** in $CDCl_3$ is consistent with a single compound present in solution. Two distinct resonances for the non-equivalent PH groups were visible at 6.57 and 6.83 ppm with $J_{H,P}$ values of 458 and 477 Hz, respectively, suggesting that the tautomeric equilibrium is fully displaced towards the PH form. In this scenario, two electron distributions (**I** and **II)** are feasible for MaxPHOS·HBF_4 (Figure 2). To shed light on the electronic and structural features of *S*-**3**, we sought to elucidate the corresponding solid-state structure by X-ray diffraction analysis. Suitable crystals of *S*-**3** were obtained by crystallization from hot ethyl acetate. The solved crystal structure showed two independent and very similar salt pairs in the unit cell (Figure 3).[10] The almost identical P(1)–N(1) and P(2)–N(1) bond distances found in the X-ray structure suggest that the resonance-hybrid **III** is the most accurate descriptor for the $[MaxPHOS\cdot H]^+$ cation and that the positive charge is evenly distributed between the two P atoms. The angle (134.6/137.3°) of P(1)–N(1)–P(2) is notice-

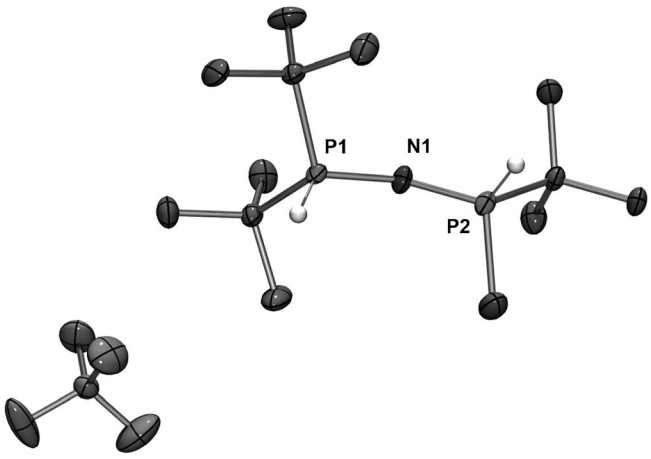
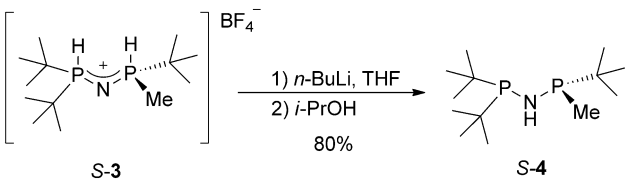


Figure 3. X-ray structure of (*S*)-MaxPHOS·HBF_4 salt *S*-**3**. Only one of the two independent salt pairs in the unit cell is shown. ORTEP drawing showing 50% probability ellipsoids. Selected bond distances (Å) and angles: P(1A)–N(1A) 1.594; P(2A)–N(1A) 1.585; P(1B)–N(1B) 1.585; P(2B)–N(1B) 1.585; P(1A)–N(1A)–P(2A) 134.6°; P(1B)–N(1B)–P(2B) 137.3°; H(1PA)–P(1A)–P(2 A)-H(2PA) 67.7°; and H(1PB)–P(1B)–P(2B)–H(2PB) 66.1°.

ably distant from the 118° found in the structurally related diphosphinoamine ligand $Ph_2P–NH–PPh_2$.[11] This observation is possibly attributable to the steric strain imposed by the three bulky *tert*-butyl groups. In the solid state, the [MaxPHOS·H]$^+$ adopts a distorted C_{2v} conformation, with the P–H bonds pointing in the same direction. The torsion angle between H(1P)–P(1)–P(2)–H(2P) shows a deviation of 67.7/66.1° from planarity. This deviation again can be attributed to the bulkiness of the groups attached to the phosphorus atoms.

Isolation of MaxPHOS in its salt form (*S*-**3**) has several advantages over unprotected electron-rich phosphines. *S*-**3** is a shelf-stable crystalline solid that can be stored indefinitely in air without noticeable decomposition or oxidation. This salt is soluble in high and medium polarity organic solvents (e.g., MeOH, CH_2Cl_2, EtOAc). In solution, *S*-**3** is also stable towards oxidation in non-deoxygenated solvents due to its low acidity. For example, no noticeable decomposition of this salt was observed when solved for a month in non-deoxygenated $CDCl_3$. In the presence of 2 equivalents of NEt_3, no more than 5% of *S*-**3** was deprotonated, as monitored by ^{1}H NMR ($CDCl_3$), thereby suggesting that the salt is less acid that the corresponding [$HNEt_3$]$^+$, which has a $pK_a = 9$ (in water).

Neutral MaxPHOS (*S*-**4**) was prepared by deprotonation of *S*-**3** with *n*-BuLi at −78 °C and treatment of the resulting mixture with deoxygenated *i*-PrOH to ensure the neutrality of the resulting aminophosphine product (Scheme 2). This approach allowed us to isolate *S*-**4** as an air-sensitive oil with ^{31}P NMR resonances at 79.5 and 52.8 ppm (C_6D_6). The ^{1}H NMR of *S*-**4** in C_6D_6 did not show the characteristic H–P resonances, thus indicating that the only species in solution for the neutral ligand is the NH tautomer (Figure 4). This observation contrasts with the related (*t*-Bu)$_2$PNHP(*t*-Bu)$_2$ ligand, which is present as a 70:30 mixture of NH/PH tautomers in toluene solution.[12] The preference of one tautomer over the other can be explained in terms of the relative basicity of the lone pair on phosphorus.[13] Electron-releasing groups on P enhance its basicity, thus favoring the corresponding PH tautomer. In this respect, the experimental results indicate that switching a single *tert*-butyl group to a methyl is enough to drive the tautomeric equilibrium towards the NH form.



Scheme 2. Preparation of the neutral MaxPHOS ligand.

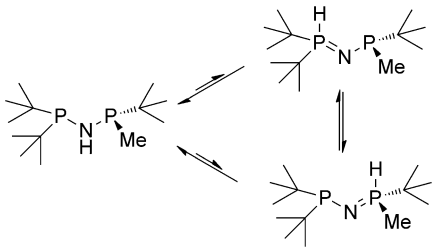
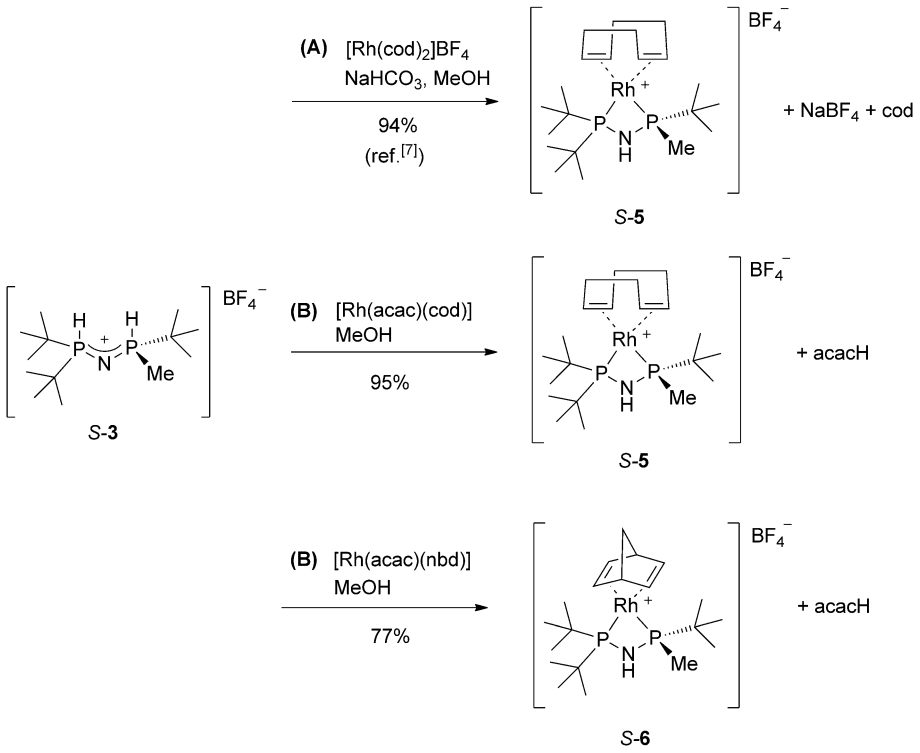


Figure 4. Neutral MaxPHOS and its three tautomeric forms.

Synthesis of MaxPHOS-Derived Rh(I) Complexes

The stability of the MaxPHOS·HBF_4 salt made this compound an ideal precursor for the reliable preparation of Rh(I) complexes. Our initial procedure used [$Rh(cod)_2$]BF_4 as source of metal (Scheme 3, method A).[7] In these conditions, an equivalent of base ($NaHCO_3$) was required to neutralize the evolving acid, and the resulting $NaBF_4$ salts had to be selectively precipitated and filtered to isolate pure [Rh(*S*-MaxPHOS)(cod)]BF_4 (*S*-**5**) as an orange crystalline solid. The use of [Rh(acac)(cod)] resulted in an improved and more expedient synthesis of complex *S*-**5** (Scheme 3, method B). In this procedure the departing acetylacetonate ligand quenched the H^+, and no salt by-products were formed. This approach allowed the direct isolation of complex *S*-**5** by crystallization in a simple and high-yielding reaction. Using this same procedure, the analogous norbornadiene complex *S*-**6** was synthesized in 77% yield using [Rh(acac)(nbd)] as a metal source. Complex *S*-**6** is also an orange crystalline solid; however, switching the 1,5-cyclooctadiene (cod) moiety for the 2,5-norbonadiene (nbd) ligand decreased the stability of the resulting Rh complex. Complex *S*-**5** showed high stability both in solid state and in solution. After one week a solution of *S*-**5** in non-deoxygenated $CDCl_3$ did not show noticeable decomposition by ^{1}H and ^{31}P NMR.[14] In contrast, complex *S*-**6** showed poor bench stability, and when left in the open air for several hours it quickly decomposed.

Suitable crystals of *R*-**6** for X-ray analysis were obtained upon layering diethyl ether over a solution of Rh complex in CH_2Cl_2 (Figure 5).[10] The solid state structure of *R*-**6** is very similar to that previously reported for complex *S*-**5**.[7] The Rh-coordinated MaxPHOS ligand shows a bite angle of 70.1° and a P–N–P angle of 101.9°. In this respect, it is interesting to note the difference in P–N–P angles between the uncoordinated MaxPHOS·HBF_4 salt (137–134°) and the coordinated ligand (101.9°). When not coordinated, the P–N–P angle widens 32–35° to accommodate the steric bulk on the phosphorus atoms.



Scheme 3. Preparation of MaxPHOS-derived Rh(I) complexes.

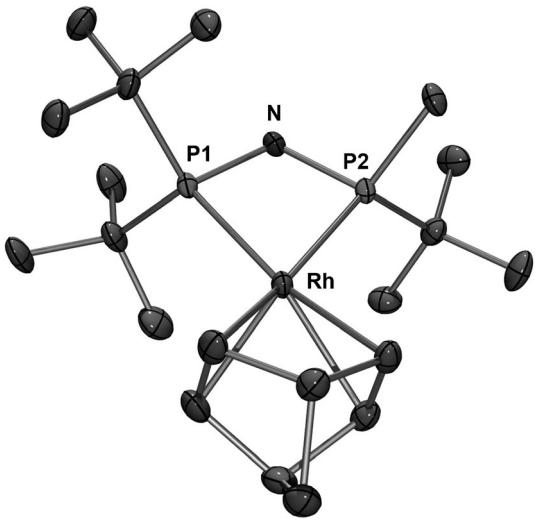


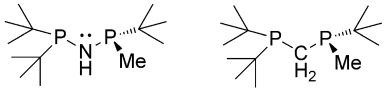
Figure 5. X-ray structure of [Rh(*R*-MaxPHOS)(nbd)]BF_4 complex *R*-**6**. ORTEP drawing showing 50% probability ellipsoids. Counter ion was omitted for clarity. Selected bond distances (Å) and angles: P(1)–N(1), 1.706; P(2)–N(1), 1.697; P(1)–Rh, 2.317; P(2)–Rh, 2.284; P(1)–N(1)–P(2), 101.9°; and P(1)–Rh–N(1), 70.1°.

Evaluation of the Electronic Properties of MaxPHOS

Assessment of the steric and electronic properties of a particular ligand contributes to understanding and building structure-activity relationships. Bulky electron-donating diphosphine ligands provide highly active and selective catalysts for Rh-catalyzed asymmetric hydrogenations.[15] In this regard, we compared the electronic nature of MaxPHOS ligand with the corresponding carbon-bridged analog trichickenfootphos (TCFP) ligand.[16] With this purpose, we prepared the corresponding square planar [Rh(MaxPHOS)$(CO)_2$]BF_4 and [Rh(TCFP)$(CO)_2$]BF_4 through carbonylation of the bis-olefin complexes under CO atmosphere and compared the resultant symmetric IR stretching frequency for the coordinated CO ligands (Table 1). This method has been used by Tolman and others to quantify the donor-acceptor capacity of phosphines.[17] We also prepared the corresponding diselenides of MaxPHOS and TCFP by direct treatment with elemental selenium (see the Supporting Information). Despite the presence of steric interference, $^{31}P,^{77}Se$ coupling constants on phosphine selenides have also been used to compare the σ-donor capacity of phosphorus ligands.[18] For example, PPh_3 shows a $^{31}P,^{77}Se$ coupling constant of 760.3 Hz, while the more electron-donating PCy_3 has a J ($^{31}P,^{77}Se$) of 712 Hz.

The data in Table 1 indicate that MaxPHOS ligand is overall less electron-rich that the all-carbon analog TCFP. The CO symmetric stretching for [Rh(MaxPHOS)$(CO)_2$]BF_4 and [Rh(TCFP)$(CO)_2$]BF_4 were found at 2091 and 2085 cm^{-1}, respectively, thus suggesting a more electron-rich metal in the case of the TCFP ligand. Also, the larger $^{31}P,^{77}Se$ coupling

Table 1. IR stretching frequencies and selenide $^{31}P,^{77}Se$ coupling constants for MaxPHOS and TCFP ligands.



Ligand	ν_{CO} symmetric (cm^{-1}) $[Rh(L)(CO)_2]BF_4$	J ($^{31}P,^{77}Se$) (Hz) Diselenide
MaxPHOS	2091	776, 740
TCFP	2085	723, 713

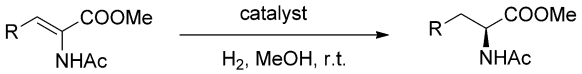
constants for the MaxPHOS diselenide indicate lower σ-donor capacity than the all-carbon analog. Thus, we conclude that the electron-withdrawing inductive effect of the nitrogen atom in MaxPHOS prevails over its mesomeric effect, and that the switch from a $-CH_2-$ to an $-NH-$ bridge produces a less electron-rich ligand.

MaxPHOS in Rh-Catalyzed Asymmetric Hydrogenation

To evaluate the performance of MaxPHOS, we first undertook the hydrogenation of the benchmark substrates methyl α-acetamidoacrylate (MAA) and (*Z*)-methyl α-acetamidocinnamate (Z-MAC) using [Rh(*S*-MaxPHOS)(cod)]BF_4 (*S*-**5**) as pre-catalyst and compared it to that of the carbon analog [Rh(*S*-TCFP)-(cod)]BF_4[16] (Table 2). Hydrogenation of MAA in MeOH at S/C = 100 took place with complete stereocontrol (99% *ee*) within 10 min for both catalysts, as monitored by H_2 uptake (Table 2, entries 1 and 2). The results at lower catalyst loading (S/C = 10,000) confirmed a similar reactivity for both catalytic systems in the reduction of MAA (Table 2, entries 3 and 4). The reaction of the trisubstituted Z-MAC substrate was somewhat slower for the *S*-**5** catalyst and took 30 min to reach full conversion while the TCFP catalyst reached full conversion in only 15 min (Table 2, entries 5 and 6). An interesting feature of the present ligand is that the catalyst system can be easily prepared *in situ* by mixing the air-stable MaxPHOS·HBF_4 salt (*S*-**3**) and [Rh(acac)(cod)] in MeOH. The *in situ* generation of catalyst provided similar results in terms of activity and selectivity to those achieved with the pre-formed catalyst (Table 2, entry 7). Finally, hydrogenation of Z-MAC with *S*-**5** catalyst was carried out at S/C = 10,000 and complete conversion and selectivity were achieved in 43 h (Table 2, entry 8).

To further confirm the capacity of *S*-**5** in the asymmetric hydrogenation, we addressed the reduction of a series of α-amino acid precursors (Table 3). Substrates with either alkyl or aryl side-chains were hydrogenated in high enantiomeric excess. The catalyst system is compatible with the use of Cbz and Boc groups as protective and chelating moieties on the amine function (Table 3, entries 1–3).[19] Aromatic side chains with electron-donating substituents produced the reduction products with near to perfect selectivities. Also, bulky substrates with *ortho*-substituted aromatic groups were reduced with high selectivity. Thus, catalyst *S*-**5** reduced the *ortho*-methoxy-substituted substrate in 98% *ee* (Table 3, entry 5) while the

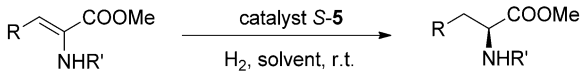
Table 2. Hydrogenation of MAA and Z-MAC using MaxPHOS and TCFP ligands.

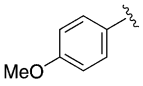
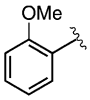
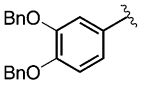
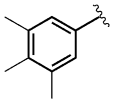
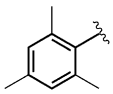
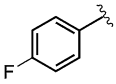
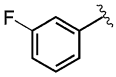
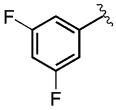
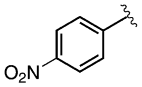
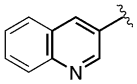


Entry	R	Cat.	S/C	H_2 [bar]	Time[a]	Conversion [%][b]	*ee* [%][c]
1	H	*S*-**5**	100[f]	3	10 min	>99	99
2	H	TCFP[d]	100[f]	3	10 min	>99	99
3	H	*S*-**5**	10,000[g]	5	16 h	>99	99
4	H	TCFP[d]	10,000[g]	5	16 h	>99	99
5	Ph	*S*-**5**	100[f]	3	30 min	>99	99
6	Ph	TCFP[d]	100[f]	3	15 min	>99	99
7	Ph	*in situ*[e]	100[f]	3	30 min	>99	99
8	Ph	*S*-**5**	10,000[h]	5	43 h	>99	99

[a] Reaction time monitored by means of hydrogen uptake.
[b] Conversion was determined by ^1H NMR of the crude reaction mixture.
[c] Enantiomeric excess determined by chiral GC or HPLC.
[d] Commercial [Rh(*S*-TCFP)(cod)]BF_4 provided by Strem® was used as a catalyst.
[e] Catalyst was generated *in situ* by mixing the ligand salt *S*-**3** and [Rh(acac)(cod)] in MeOH.
[f] Reactions carried out with 0.4 g of substrate and 5 mL of MeOH.
[g] Reaction carried out with 10 g of MAA and 10 mL of MeOH.
[h] Reaction carried out with 2 g of Z-MAC and 7 mL of MeOH.

Table 3. Asymmetric hydrogenation of α-amino acid precursors using *S*-**5** as catalyst.



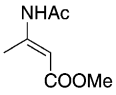
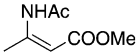
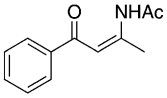
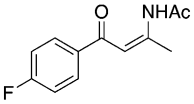
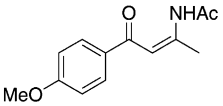
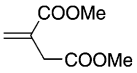
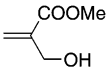
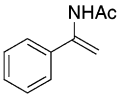
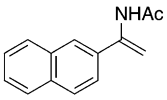
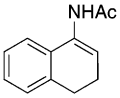
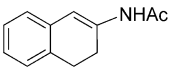
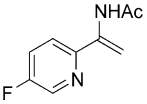
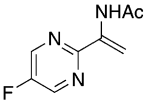
Entry	R	R′	H_2 [bar]	Cat. [mol%]	Solvent	Conv. [%][a]	*ee* [%][b]
1	H	Cbz	3	0.3	MeOH	>99	99
2	Me	Boc	3	0.3	MeOH	>99	97
3	Me	Cbz	3	0.3	MeOH	>99	99
4		Ac	3	0.3	MeOH	>99	99
5		Ac	1	1	MeOH	>99	98
6		Ac	16	3	MeOH	>99	99
7		Ac	2	1	MeOH	> 99	99
8		Ac	60	3	MeOH	>99[c]	97
		Ac	5	1	MeOH	99[d]	92
9		Ac	3	1	THF	> 99	99
		Ac	3	0.3	MeOH	>99	98
10		Ac	3	0.3	MeOH	>99	98
11		Boc	3	0.3	MeOH	>99	96
12		Ac	3	0.3	MeOH	>99	96
13[21]		Ac	15	3	MeOH	>99	99

[a] Reactions were left to react overnight at room temperature unless otherwise specified. Conversion was determined by ^{1}H NMR of the crude reaction mixture.
[b] Enantiomeric excess was determined by chiral HPLC or GC.
[c] Reaction time 48 h at room temperature.
[d] Reaction time 72 h at 75 °C.

mesityl-substituted acrylate was reduced in 97% *ee* (Table 3, entry 8). Substrates with electron-withdrawing groups on the aromatic ring provided somewhat lower enantiomeric excesses, ranging from 96% to 99% *ee* (Table 3, entries 9–12).[20] In some cases, for these substrates, switching the solvent from MeOH to THF enhanced reaction selectivity (Table 3, entry 9). Finally, hydrogenation of dehydroamino acid substrate containing a 3′-quinolyl side chain proceeded with complete selectivity (Table 3, entry 13).[21]

We also tested other types of substrate, the results of which are reported in Table 4. Both (*E*)- and (*Z*)-β-acetamido esters were reduced in synthetically useful high enantiomeric excess (Table 4, entries 1 and 2). While (*E*)-methyl 3-acetamido-2-butenoate was reduced in complete selectivity using MeOH, the reduction of the *Z* isomer was less selective in this solvent. Reduction of (*Z*)-methyl 3-acetamido-2-butenoate in MeOH afforded the product in 89% ee; however, switching the solvent to THF increased the enantiomeric excess to 96%.[22] β-Keto enamides were also reduced to the corresponding acetamido ketones with selectivities ranging from 92 to 97% *ee* (Table 4, entries 3–5). The reaction in this case had to be carefully monitored and stopped when the first enamide function was reduced. 1,3-Acetamido alcohols were

Table 4. Asymmetric hydrogenation of miscellaneous substrates using complex *S*-**5** as catalyst.[a]

Entry	Substrate	H_2 [bar]	Cat. [mol%]	Solvent	Conv. [%][b]	*ee* [%][c]
1[7]		3	0.3	MeOH	>99	99 (*S*)
2		3	1	MeOH	>99	89 (*S*)
		3	1	THF	>99	96 (*S*)
3		3	1	MeOH	>99[d]	92 (*S*)
4		1.5	1	MeOH	>99[d]	96 (*S*)
5		1.5	1	MeOH	>99[d]	97 (*S*)
6		3	0.3	MeOH	>99	95 (*R*)
7		3	1	MeOH	>99[e]	87 (*R*)
8		3	0.3	MeOH	>99	97 (*S*)
9		3	0.3	MeOH	>99	97 (*S*)
10		2	1	MeOH	>99	75 (*S*)
11		14	1	MeOH	>99	33 (*S*)
12		12	3	MeOH	>99	99 (*S*)
13		12	1	MeOH	>99	99 (*S*)

[a] Hydrogenation reactions were carried out at room temperature unless otherwise specified.
[b] Reactions were left to react overnight unless specified. Conversion was determined by ^{1}H NMR of the crude reaction mixture.
[c] Enantiomeric excess was determined by chiral HPLC or GC. Absolute configuration of the products is shown in brackets.
[d] Reaction time between 0.8 and 1.5 h. Longer reaction times provided conversion to the 1,3-acetamido alcohols.
[e] Reaction was carried out at 0 °C.

produced when the hydrogenation was left to proceed.[23] Dimethyl itaconate and the precursor of the Roche ester were reduced in 95 and 87% *ee*, respectively (Table 4, entries 6 and 7). Simple vinyl acetamides were also tested, producing mixed results. Open-chain phenyl and 2-naphthyl vinylamides were reduced in 97% *ee* (Table 4, entries 8 and 9). However, cyclic enamides provided poorer selectivity; 1-acetamido-3,4-dihydronaphthalene was hydrogenated in 75% *ee* and the corresponding 2-acetamido derivative was hydrogenated at 14 bar with 33% *ee* (Table 4, entries 10 and 11).[24,25] Finally, vinyl acetamides containing fluoropyridinyl and fluoropyrimidinyl substituents were hydrogenated in 99% *ee* using the Rh-MaxPHOS system (Table 4, entries 12 and 13). These substrates are precursors for a variety of highly active

kinase inhibitors currently under clinical development for cancer therapy.[26]

Conclusions

In summary, we have shown that the P-stereogenic aminodiphosphine MaxPHOS is a novel ligand system with interesting properties. The presence of a nitrogen linkage between the two phosphine moieties makes MaxPHOS a less electron-rich ligand than the all-carbon analog TCFP. The presence of the −NH− bridge between the two P-centers allows the NH/PH tautomerism to take place. For the neutral ligand, the NH form predominates; however, protonation of MaxPHOS leads to a particular stable form of the ligand in which the two phosphorus atoms are linked to a hydrogen atom and the overall positive charge is distributed on both P centers through resonance. Thus, NH/PH tautomerism makes the corresponding MaxPHOS·HBF_4 salt **3** completely air-stable since both phosphorus atoms are protected from oxidation. Also, we have shown that the MaxPHOS·HBF_4 salt **3** is a convenient precursor for the preparation of Rh(I) complexes by direct ligand exchange with [Rh(acac)(cod)]. Finally, we have demonstrated that MaxPHOS is a selective and robust ligand system for the asymmetric Rh(I)-catalyzed hydrogenation of a wide range of substrates.

Experimental Section

Neutral (*S*)-MaxPHOS (*S*-4)

(*S*)-MaxPHOS·HBF_4[7] (176 mg, 0.5 mmol) was dissolved in 10 mL of anhydrous, deoxygenated THF and cooled to −78 °C in a CO_2/acetone bath. *n*-BuLi (0.32 mL of a 1.6 M solution, 0.5 mmol) was carefully added using a syringe, and the mixture was left stirring for 30 min. After this period, the cooling bath was removed and 1 mL of deoxygenated *i*-PrOH was added. The solvents were removed under vacuum, and the residue was extracted with thoroughly deoxygenated CH_2Cl_2/water. The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under vacuum to give the title product as a colorless air-sensitive oil. Yield: 105 mg (80%). ^{1}H NMR (400.1 MHz, C_6D_6): $\delta = 1.09$ (d, $J = 10.8$ Hz, 9H), 1.05 (d, $J = 10.8$ Hz, 9H), 1.00 (d, $J = 6.0$ Hz, 3H), 0.98 (d, $J = 11.6$ Hz, 9H); ^{31}P NMR (121 MHz, C_6D_6): $\delta = +79.5$ (d, $J = 179.1$ Hz, 1P), +52.8 (d, $J = 179.1$ Hz, 1P).

[Rh(*S*-MaxPHOS)(cod)]BF_4 (*S*-5)

[Rh(acac)(cod) (34.54 g, 111.36 mmol), (*S*)-MaxPHOS·HBF_4 *S*-**3** (39.49 g, 112.47 mmol) and anhydrous MeOH (800 mL) were stirred in a round-bottomed flask under N_2 atmosphere overnight. The MeOH was removed under vacuum and solved again with CH_2Cl_2 (140 mL). The solution was filtered through a cannula to another flask, and crystallization was then induced by adding anhydrous Et_2O (500 mL) to afford *S*-**5** as an orange crystalline solid; yield: 59.3 g (95%). IR (film): $\nu_{max} = 3277$, 2946, 1475, 1056 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.21$ (d, $J = 16$ Hz, 9H), 1.38 (d, $J = 15$ Hz, 9H), 1.40 (d, $J = 14$ Hz, 9H), 1.77 (dd, $J = 8$ and 1 Hz, 3H), 2.10–2.30 (m, 4H), 2.36–2.57 (m, 4H), 5.11 (br, 2H), 5.39 (br, 1H), 5.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.6$ (d, $J_{P,C} = 20$ Hz, CH_3), 26.4 (d, $J_{P,C} = 5$ Hz, $3CH_3$), 28.8 (CH_2), 28.9 (CH_2), 29.0 (d, $J_{P,C} = 6$ Hz, $3CH_3$), 29.1 (d, $J_{P,C} = 6$ Hz, $3CH_3$), 31.3 (CH_2), 31.9 (CH_2), 35.8 (d, $J_{P,C} = 26$ Hz, C), 38.8 (d, $J_{P,C} = 12$ Hz, 2 C), 91.1 (dd, $J_{P,C} = 10$ and 7 Hz, CH), 91.7 (t, $J_{P,C} = 8$ Hz, CH), 95.5 (dd, $J_{P,C} = 9$ and 6 Hz, CH), 98.1 (dd, $J_{P,C} = 9$ and 7 Hz, CH); ^{31}P NMR (121 MHz, $CDCl_3$): $\delta = 47.8$ (dd, $J = 128$ and 48 Hz), 70.1 (dd, $J = 128$ and 49 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -151.3$; HR-MS-ESI: $m/z = 474.1919$, calcd. for $C_{21}H_{43}NP_2Rh$ [M−BF_4]$^+$: 474.1920.

[Rh(*S*-MaxPHOS)(nbd)]BF_4 (*S*-6)

[Rh(acac)(nbd)] (0.227 g, 0.941 mmol) and (*S*)-MaxPHOS·HBF_4 *S*-**3** (0.350 g, 0.996 mmol) were stirred in a flame-dried Schlenk tube under N_2 in MeOH (6 mL) for 2 h. The solvent was removed under vacuum. The residue obtained was dissolved in the minimum amount of CH_2Cl_2 (1.6 mL) in a Schlenk tube before being frozen in liquid N_2. An excess of Et_2O was added, and the tube was placed in the fridge overnight to allow the solid to slowly melt and to permit slow diffusion of the two solvent layers to form crystals. The next day the product was isolated as orange crystals; yield: 0.330 g (77%). IR (KBr): $\nu_{max} = 3273$, 2950, 2868, 2348, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.80$ (br s, 1H), 5.59 (br s, 1H), 5.46 (br s, 1H), 5.39 (br s, 2H), 4.22 (d, $J = 10.6$ Hz, 2H), 1.72 (s, 2H), 1.67 (dd, $J = 1.4$, 7.6 Hz, 3H), 1.37 (d, $J = 16.3$ Hz, 9H), 1.33 (d, $J = 15.0$ Hz, 9H), 1.14 (d, $J = 15.0$ Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 89.8$ (dd, $J_{P,C} = 9.7$, 6.3 Hz, CH), 86.6 (dd, $J_{P,C} = 11.0$, 6.1 Hz, CH), 82.6 (dd, $J_{P,C} = 9.7$, 7.5 Hz, CH), 82.4 (dd, $J_{P,C} = 8.9$, 7.2 Hz, CH), 71.2 (CH_2), 56.3 (CH), 55.9 (CH), 38.8 (d, $J_{P,C} = 12.4$ Hz, C), 38.5 (d, $J_{P,C} = 14.4$ Hz, C), 35.7 (d, $J_{P,C} = 26.9$ Hz, C), 29.0 (d, $J_{P,C} = 6.8$ Hz, $3CH_3$), 28.9 (d, $J_{P,C} = 6.7$ Hz, $3CH_3$), 26.4 (d, $J_{P,C} = 6.3$ Hz, $3CH_3$), 13.0 (dd, $J_{P,C} = 19.0$, 2.1 Hz, CH_3); ^{31}P NMR (121 MHz, $CDCl_3$): $\delta = 76.3$ (dd, $J = 136.0$, 54.6 Hz), 52.52 (dd, $J = 138.2$, 54.6 Hz); HR-MS-ESI: $m/z = 458.1604$, calcd. for [M−BF_4]$^+$ ($C_{22}H_{45}NP_2Rh$): 458.1607.

Representative Rh-Catalyzed Asymmetric Hydrogenations

(*S*)-Methyl 2-acetamido-3-(3,4,5-trimethylphenyl)propanoate: (*Z*)-Methyl 2-acetamido-3-(3,4,5-trimethylphenyl)acrylate (470 mg, 1.8 mmol), and catalyst *S*-**5** (10.1 mg, 0.018 mmol) were weighed and placed in an Ace® glass pressure tube equipped with a pressure gauge and valve. The vessel was introduced into the glove box, and anhydrous deoxygenated MeOH (5 mL) was added to the reaction mixture. The pressure tube was removed from the glove box and connected to a hydrogen manifold. With stirring, the vessel was then purged with the aid of vacuum and hydrogen, and finally charged at 2 bar of hydrogen gas. The vessel was then removed from the hydrogen manifold, and the mixture was left under stirring to react overnight at room

temperature in a fume hood. The tube was then depressurized and the reaction mixture was filtered through a short pad of SiO_2 and subsequently eluted with EtOAc. The resulting solution was concentrated under vacuum to afford the desired compound as a white solid; yield: 464 mg (98%). Conversion was determined by ^{1}H NMR (>99%) and enantiomeric excess by HPLC. $[\alpha]_D$: +103.7 (*c* 0.5, $CDCl_3$); mp 88–91 °C. IR (KBr): ν_{max} = 3267(br), 2936, 1759, 1637 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.72 (s, 2H, 2 CH Ar), 5.88 (d, *J* = 7 Hz, NH), 4.82 (dt, *J* = 8.0, 6.0 Hz, CHa), 3.74 (s, 3H, OCH_3), 3.01 (qd, *J* = 14.0, 6.0 Hz, 2H, CH_2b), 2.24 (s, 6H, 2 CH_3), 2.13 (s, 3H, CH_3), 1.98 [s, 3H, C(O)CH_3]; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6 (C, NHCO), 170.0 (C, CO), 136.8 (2C, Ar), 134.0 (C, Ar), 132.7 (C, Ar), 128.6 (2CH, Ar), 53.5 (CH), 52.4 (OCH_3), 37.5 (CH_2), 23.3 [C(O)-CH_3], 20.8 (2Ar-CH_3), 15.3 (Ar-CH_3); HR-MS: *m/z* = 264.1601, calcd. for $C_{15}H_{21}NO_3+H^+$ $[M+H]^+$: 264.1600; HPLC [Chiralpak® IA, 95:5 heptane/2-propanol, 1 mL min^{-1}, 254 nm]: $t_R(S)$ = 10 min (major peak), $t_R(R)$ = 12 min.

(*S*)-Methyl 2-acetamidopropanoate:[27] Methyl 2-acetamidoacrylate (10.0 g, 69.8 mmol) and *S*-**5** catalyst (3.9 mg, 0.0069 mmol) were weighed and placed in a Büchi® 250 Miniclave. At this point the vessel was introduced in the glove box, and anhydrous deoxygenated MeOH (10 mL) was added to the reaction mixture. The vessel was removed from the glove box, and the pressure vessel was connected to a hydrogen manifold. With stirring, the vessel was then purged with the aid of vacuum and hydrogen, and finally charged at 5 bar of hydrogen gas. The vessel was then removed from the hydrogen manifold, and the mixture was left under stirring to react at room temperature for 16 h in a fume hood. The autoclave was then depressurized. The reaction mixture was filtered through a short pad of SiO_2 and subsequently eluted with EtOAc. The resulting solution was concentrated under vacuum to afford the desired compound as a colorless oil; yield: 9.8 g (97%). Conversion was determined by ^{1}H NMR (>99%) and enantiomeric excess by chiral GC. $[\alpha]_D$: −91.2 (*c* 1.0, H_2O), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.31 (d, *J* = 7.3 Hz, 3H), 1.94 (s, 3H), 3.67 (s, 3H), 4.6 (p, 7.2 Hz, 1H), 6.06 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2 (CH_3), 22.9 (CH_3), 58.0 (CH), 52.3 (CH_3), 169.9 (C=O), 173.6 (C=O); GC [Supelco Beta DEX™ 120 (30 m × 0.25 mm × 0.25 μm), isothermal 90 °C, 15 psi He]: $t_R(S)$ = 59.5 min (major peak), $t_R(R)$ = 60.5 min.

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