Tetrahedron Letters 54 (2013) 1857–1861

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Hydrophilic pyrazine-based phosphane ligands: synthesis and application in asymmetric hydride transfer and H_2-hydrogenation of acetophenone

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ARTICLE INFO

Article history:
Received 29 November 2012
Revised 14 January 2013
Accepted 24 January 2013
Available online 1 February 2013

Keywords:
Asymmetric catalysis
Hydrogenation
Phosphanes
Pyrazine
Reduction

ABSTRACT

Pyrazine-based hydrophilic phosphanes are useful ligands for the ruthenium- and rhodium-catalyzed hydrogenations of acetophenone under hydride transfer and dihydrogen conditions. The effect of alcohol additives on the catalytic, enantioselective aqueous hydrogenation of acetophenone is examined with the newly developed (*R*,*R*)-DAMPYPHOS as the ligand and Rh_2(norbornadiene)$_2Cl_2$ as the catalyst precursor, giving rise to higher conversions (up to quantitative) and improved enantiomeric excesses (up to 95%) of the formed 1-phenylethanol.

The most frequently used methods for ketone reduction are transfer hydrogenation,[1] from a hydrogen donor molecule, usually isopropanol, and direct H_2-hydrogenation.[2] Common catalysts, employed in the former method involve a variety of Ru, Rh, and Ir complexes with polydentate phosphanes and amines.[3]

H_2-hydrogenation was one of the first transition metal catalyzed processes studied in aqueous medium and continues to attract interest.[4] Sulfonated triarylphosphanes were reported for alkene hydrogenation in aqueous biphasic systems,[5] however, typically revealing modest or low activities. In general, water-soluble phosphanes, containing ionic substituents, have several disadvantages, among which are their high pH sensitivity[6] and the high charge accumulation in the coordination sphere of the metal complex that leads to a significant Coulombic interligand repulsion and to lower stability of the catalyst.[7]

On the other hand, one of the major challenges in aqueous-biphasic catalysis[8] is to promote interactions of the water-soluble catalyst and other reagents with the hydrophobic substrate. For polar molecules, being slightly soluble in water, the reaction can occur in the aqueous bulk, however, as the substrate becomes less soluble in water, the rate of the reaction decreases due to the lower concentration of the substrate in the aqueous phase. This problem can be solved by the use of either water-miscible organic cosolvents[9] or phase-transfer agents,[10] but often phase separation problems are encountered. Therefore, the design of ligands resulting in a catalyst which is able to operate in both phases, and that needs no cosolvent or surfactant, is very important. Remarkable examples were reported of quantitative asymmetric hydrogenations of various acrylic acid derivatives in aqueous medium using highly air-sensitive carbohydrate-backboned phosphanes with ees >99%.[11] Conversely, achieving such high enantioselectivities in ketone hydrogenation is much more difficult due to the poor donor ability of the carbonyl group and the lack of additional anchoring sites.[12]

An electron-attracting pyrazine backbone affects the electronic properties of a phosphane-containing ligand, enhancing its π-acceptor properties,[13] as well as impacting on the catalytic activity.[14] The operational convenience, due to the air stability of such ligands, is another property potentially of use for various asymmetric catalyzes.[15] This has motivated us to design and prepare neutral, hydrophilic pyrazine-containing ligands. Here we present a simple and versatile synthesis of three novel, hydrophilic, and non-ionic phosphane ligands with a pyrazine backbone, named AMPYPHOS, AMPYMORPH, and DAMPYPHOS.[16] The successful application of these ligands in the hydride-transfer and aqueous biphasic H_2-hydrogenation of acetophenone, as a model substrate, is reported.

Ligand synthesis

We previously reported a facile and high-yielding method for the introduction of phosphorus-containing functional groups onto pyrazine scaffolds.[17,18] In particular, it was found that phosphanopyrazines were readily accessible in excellent yields via a palladium-catalyzed P-C cross-coupling reaction of various chloropyrazines

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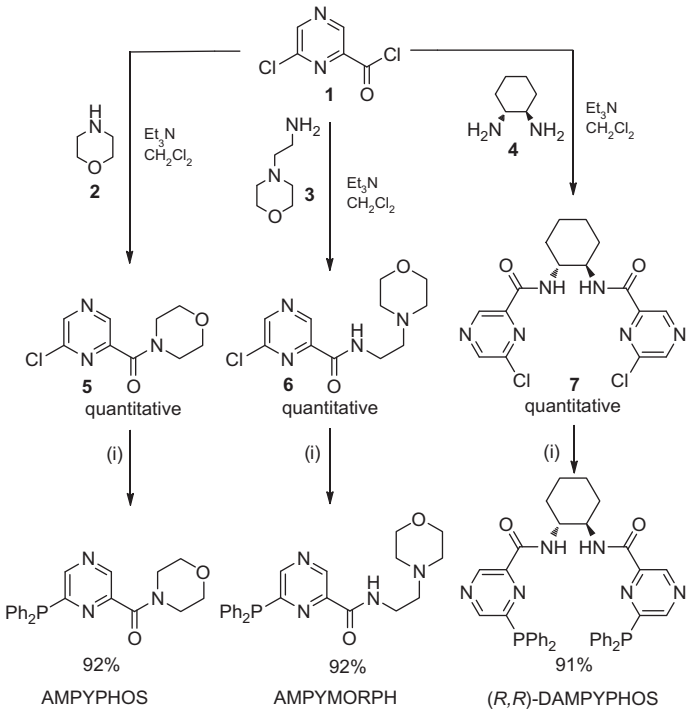
http://dx.doi.org/10.1016/j.tetlet.2013.01.108



Scheme 1. Synthesis of the pyrazine-based phosphanes: AMPYPHOS, AMPYMORPH, and (*R*,*R*)-DAMPYPHOS; (i) $HPPh_2$, DBU, $Pd(OAc)_2$, MeCN, reflux.

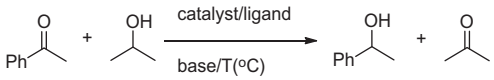
with secondary phosphanes. The novel phosphanopyrazines, AMPYPHOS, AMPYMORPH, and (*R*,*R*)-DAMPYPHOS, were prepared in two steps starting from simple amines, employing this methodology. Starting amines **2**–**4** were acylated quantitatively with a stoichiometric amount of 6-chloropyrazine-2-carbonyl chloride (**1**) in the presence of 2 equiv of triethylamine in dichloromethane to give amides **5**–**7**, respectively, each bearing a 6-chloropyrazine moiety. Subsequent palladium-catalyzed P-C cross-coupling with diphenylphosphane using 1 mol % of $Pd(OAc)_2$ as the catalyst in the presence of DBU in refluxing acetonitrile afforded AMPYPHOS, AMPYMORPH, and (*R*,*R*)-DAMPYPHOS, respectively, as oily or waxy air-stable materials, in over 90% yields (Scheme 1). (For further details see the Supplementary data).

In the ^{1}H NMR spectra the signal for the pyrazine proton adjacent to the chlorine at 8.66 ppm in **5** was shifted to 8.43 ppm in AMPYPHOS. The formation of AMPYMORPH and (*R*,*R*)-DAMPYPHOS was also confirmed by the shift of the characteristic pyrazine proton singlets from 9.22 and 8.69 ppm in **6** and 9.18 and 8.70 ppm in **7** to 9.15 and 8.38 ppm in AMPYMORPH and 8.92 and 8.39 ppm in (*R*,*R*)-DAMPYPHOS, respectively. All the above phosphanes revealed distinct signals in the ^{31}P NMR spectra, being −7.42, −8.06, and −8.02 ppm for AMPYPHOS, AMPYMORPH, and DAMPYPHOS. In addition to the NMR spectra, all the compounds exhibited the requisite molecular ion peaks in electrospray mass spectra.

Catalytic activity

To evaluate the most active catalytic system with $Ru(PPh_3)_3Cl_2$ and Rh_2(norbornadiene)$_2Cl_2$ ($Rh_2nbd_2Cl_2$) as catalyst precursors, and using acetophenone as the model substrate, an initial study was performed under transfer hydrogenation conditions in isopropanol in the presence, as well as absence, of a base with the nonchiral ligands AMPYPHOS and AMPYMORPH (Scheme 2). The results are summarized in Table 1.

In the absence of a base none of the catalytic systems revealed any significant activity (Table 1, entries 1–4). On the other hand, the addition of 10 mol % of a base promoted efficiently the catalysis



Scheme 2. Transfer hydrogenation of acetophenone.

showing an increase of conversion upon increasing the base strength. Adding Cs_2CO_3 to the reaction mixture resulted in ~20% conversion (Table 1, entry 5). The effect of the base was even more pronounced for DBU giving 70% conversion (Table 1, entry 7), reaching a maximum for *i*-PrONa with 85% and 100% conversions with the Ru and Rh catalysts, respectively (Table 1, entries 9 and 11). Thus the best system for ketone transfer hydrogenation was found to be $Rh_2nbd_2Cl_2$/AMPYPHOS in the presence of *i*-PrONa. These conditions were used for the asymmetric transfer hydrogenation of acetophenone with $Rh_2nbd_2Cl_2$ in the presence of chiral (*R*,*R*)-DAMPYPHOS (Table 1, entries 13 and 16). Despite excellent catalytic activity at 83 °C (reflux temperature of isopropanol), the enantiomeric excess was only 70% (Table 1, entry 13). A decrease of the reaction temperature to 50 °C only slightly improved the optical yield providing an ee of 75%. A further decrease of the reaction temperature resulted into considerably lower conversions.

Subsequently, the activity of rhodium catalysts with the newly prepared ligands was investigated for the hydrogenation of acetophenone, under 10 bar of H_2 at room temperature, in a biphasic system consisting of aqueous NaOH (1 M) and the substrate (0.1 M) (Table 2). Experiments without any additive or cosolvent only showed moderate conversions of acetophenone into 1-phenylethanol (Table 2, entries 1 and 2). Grzybek[19] observed a significant effect of methanol used as a cosolvent in the aqueous biphasic hydrogenation of olefins. Therefore it was of interest to study the effect of various alcohols on the conversion, as well as on the enantioselectivity, in the case of our catalytic system. A preliminary experiment with benzyl alcohol as an additive revealed not only an enhancement of the reaction rate, but also an increase in the optical yield of the product, 1-phenylethanol (Table 2, entry 5). The addition of EtOH, $PhCH_2OH$, *i*-PrOH, and *t*-BuOH gave rise to

Table 1
Transfer hydrogenation of acetophenone in isopropanol in the presence of 1 mol % of $Ru(PPh_3)_3Cl_2$ or 0.5 mol % of $Rh_2nbd_2Cl_2$ as the catalyst precursor and 2% or 1% of the monodentate or bidentate ligand, respectively, for 15 h

Entry	Catalyst precursor	Ligand	Base	T (°C)	Conversion (%), (ee, %)
1	$Ru(PPh_3)_3Cl_2$	AMPYPHOS	None	83	<2
2	$Ru(PPh_3)_3Cl_2$	AMPYMORPH	None	83	<2
3	$Rh_2nbd_2Cl_2$	AMPYPHOS	None	83	5
4	$Rh_2nbd_2Cl_2$	AMPYMORPH	None	83	<2
5	$Ru(PPh_3)_3Cl_2$	AMPYPHOS	Cs_2CO_3 (10%)	83	20
6	$Ru(PPh_3)_3Cl_2$	AMPYMORPH	Cs_2CO_3 (10%)	83	15
7	$Ru(PPh_3)_3Cl_2$	AMPYPHOS	DBU (10%)	83	70
8	$Ru(PPh_3)_3Cl_2$	AMPYMORPH	DBU (10%)	83	57
9	$Ru(PPh_3)_3Cl_2$	AMPYPHOS	*i*-PrONa (10%)	83	85
10	$Ru(PPh_3)_3Cl_2$	AMPYMORPH	*i*-PrONa (10%)	83	0
11	$Rh_2nbd_2Cl_2$	AMPYPHOS	*i*-PrONa (10%)	83	100
12	$Rh_2nbd_2Cl_2$	AMPYMORPH	*i*-PrONa (10%)	83	75
13	$Rh_2nbd_2Cl_2$	(*R*,*R*)-DAMPYPHOS	*i*-PrONa (10%)	83	100 (70) (*R*)
14	$Rh_2nbd_2Cl_2$	AMPYPHOS	*i*-PrONa (10%)	50	97
15	$Rh_2nbd_2Cl_2$	AMPYMORPH	*i*-PrONa (10%)	50	70
16	$Rh_2nbd_2Cl_2$	(*R*,*R*)-DAMPYPHOS	*i*-PrONa (10%)	50	97 (75) (*R*)

Table 2
Hydrogenation of acetophenone under 10 bar of H_2 at room temperature in an aqueous NaOH (1 M) biphasic system in the presence of $Rh_2nbd_2Cl_2$/AMPYPHOS or (*R*,*R*)-DAMPYPHOS for 15 h

Entry	$Rh_2nbd_2Cl_2$ (%)	Ligand	Additive (equiv)	Conversion (%), (ee, %)
1	1	AMPYPHOS	None	47
2	1	(*R*,*R*)-DAMPYPHOS	None	73 (75) (*R*)
3	1	(*R*,*R*)-DAMPYPHOS	EtOH (1 equiv)	100 (79) (*R*)
4	1	AMPYPHOS	$PhCH_2OH$ (1 equiv)	40
5	1	(*R*,*R*)-DAMPYPHOS	$PhCH_2OH$ (1 equiv)	100 (93) (*R*)
6	0.5	(*R*,*R*)-DAMPYPHOS	$PhCH_2OH$ (1 equiv)	40 (92) (*R*)
7	0.5	(*R*,*R*)-DAMPYPHOS	$PhCH_2OH$ (2 equiv)	80 (93) (*R*)
8	0.5	(*R*,*R*)-DAMPYPHOS	$PhCH_2OH$ (3 equiv)	100 (93) (*R*)
9	0.5	(*R*,*R*)-DAMPYPHOS	*i*-PrOH (1 equiv)	100 (95) (*R*)
10	0.25	(*R*,*R*)-DAMPYPHOS	*i*-PrOH (2 equiv)	33 (93) (*R*)
11	0.05	(*R*,*R*)-DAMPYPHOS	*i*-PrOH (2 equiv)	10 (90) (*R*)
12	0.5	(*R*,*R*)-DAMPYPHOS	*t*-BuOH (1 equiv)	61 (83) (*R*)
13	0.25	(*R*,*R*)-DAMPYPHOS	*t*-BuOH (2 equiv)	23 (80) (*R*)
14	0.05	(*R*,*R*)-DAMPYPHOS	*t*-BuOH (2 equiv)	8 (80) (*R*)

considerably higher conversions of 100%,[20] 40%, 100%, and 61%, respectively (Table 2, entries 3, 6, 9, and 12). Furthermore, the enantiomeric excess of the product was different, depending on the alcohol used, being maximal for *i*-PrOH (Table 2, entry 9). Subsequently, the effect of a reduced catalyst load was studied (Table 2, entries 6–14). Halving the amount of $Rh_2nbd_2Cl_2$ required the presence of 3 equiv. of $PhCH_2OH$ to accomplish full conversion (Table 2, entries 5 and 8).

Kinetic study

To study the hydrogenation in more detail, the reaction was followed over time, using the $Rh_2nbd_2Cl_2$/(*R*,*R*)-DAMPYPHOS catalytic system and water as the solvent, with *i*-PrOH as an additive under a constant hydrogen pressure of 10 bar. Figure 1 shows a sigmoidal conversion of acetophenone over time, and a drastic reaction rate acceleration after an induction period of about 6 h. However, when the catalyst was activated in advance under 10 bar of hydrogen for 6 h, a linear relationship was observed for the formation of 1-phenylethanol; the reaction in this case was complete in 8 h, compared to 15 h without prior activation. The catalyst activation can be visualized as shown in Scheme 3. Rapid hydrogenation of the diene ligand occurs upon exposure of the catalyst precursor solution to a hydrogen atmosphere.

The resulting tetracoordinated rhodium species reveals almost no further hydrogen uptake due to the *trans*-effect of the bidentate phosphane ligand, which makes the formation of a dihydride

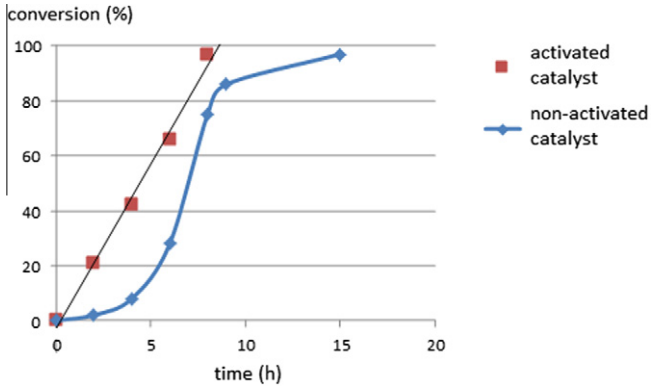
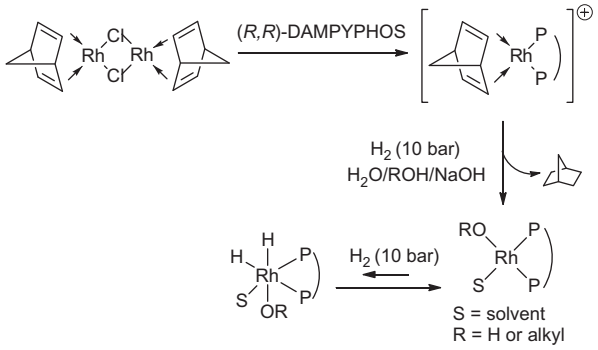


Figure 1. Conversion of acetophenone into 1-phenylethanol over time under catalytic hydrogenation conditions: acetophenone (0.1 M) in aqueous NaOH (1 M) with *i*-PrOH (0.1 M) at 20 °C in the presence of 0.5% of $Rh_2nbd_2Cl_2$/(*R*,*R*)-DAMPYPHOS under 10 bar of H_2, with and without catalyst activation.

Rh(III) complex unfavorable. This effect is also responsible for the oxidative addition of dihydrogen being, most likely, the rate-limiting step.

Reaction mechanism and origin of the increase in enantioselectivity in the presence of an alcohol

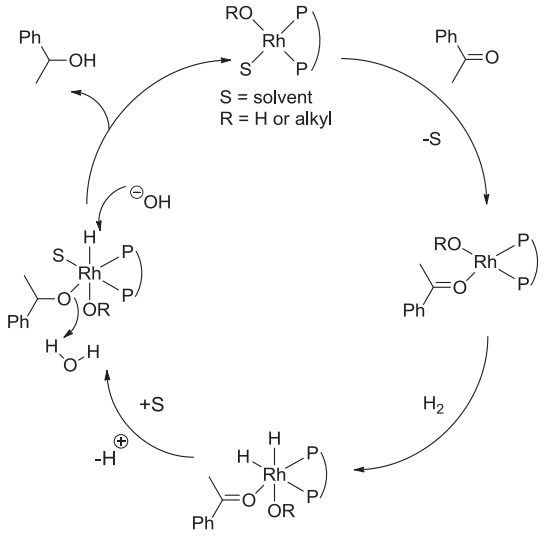
When acetophenone was hydrogenated in D_2O/d_1-EtOD/NaOD with H_2 employing $Rh_2nbd_2Cl_2$/(*R*,*R*)-DAMPYPHOS as the catalyst,



Scheme 3. Proposed catalyst activation sequence.

the reaction product was characterized by ^{1}H NMR spectroscopy to be a mixture of isotopomers with a high degree of deuteration of the methyl group of 1-phenylethanol, which mostly results from enolization of the parent acetophenone under basic conditions in the deuterated aqueous medium. However, deuteration at the carbon adjacent to the hydroxyl group was almost negligible. These results prove the absence of proton/deuteron exchange between the catalytically active rhodium hydride species and the deuterated (protic) reaction medium, excluding the possibility of the heterolytic cleavage of dihydrogen, which is typical for rhodium-amido[21] and iridium-amidophosphane ambifunctional catalysts.[22] Furthermore, it supports the oxidative addition of dihydrogen to the rhodium metal center as the key step in the catalytic cycle. Consistent with this, under comparable conditions, using 10 bar of Ar instead of H_2 gas, no conversion of acetophenone was observed after 15 h. This result rules out the possibility of transfer hydrogenation by the alcohol introduced into the reaction mixture.

Based on these data, a mechanism as summarized in Scheme 4, is proposed. The reaction follows the classical Schrock–Osborn dihydride mechanism[23] involving substrate coordination and the oxidative addition of dihydrogen with the formation of an Rh(III) dihydride complex. Subsequent migratory insertion of a hydride ligand into the C=O bond results in the formation of an Rh(III) monohydride complex with the product alkoxide ligand. This monohydride complex ultimately needs the simultaneous assistance of a base, to abstract the remaining proton from the metal center, and a proton donor to protonate the product alkoxide, in order to eliminate the product alcohol and to form the initial tetracoordinated Rh(I) complex, thereby completing the catalytic cycle.



Scheme 4. Proposed mechanism of acetophenone hydrogenation by H_2 catalyzed by $Rh_2nbd_2Cl_2$/(*R*,*R*)-DAMPYPHOS in water.

The amplification of enantioselectivity upon the addition of different alcohols to the reaction mixture can be explained by replacement of the hydroxide ligand by the corresponding alkoxide making the resulting complex more sterically demanding.[24] From several possible coordination modes of acetophenone to the catalytically active tetracoordinate rhodium species, only those that provide the lowest steric interactions of the acetophenone phenyl group with the bulky alkoxide ligand, undergo dihydrogen oxidative addition followed by the preferable formation of the (*R*)-enantiomer of 1-phenylethanol. This is clearly reflected in the enantiomeric excesses of 79%, 93%, and 95%, obtained for EtOH, $PhCH_2OH$, and *i*-PrOH, (Table 2, entries 3, 5 and 9), respectively, having increasing bulkiness in this series of alcohols. The ligand steric bulk finally shields the active site of the catalyst, preventing it from substrate coordination when switching to *tert*-butanol, resulting in lower conversions and an enantiomeric excess close to the values obtained without any additive (Table 2, entries 12–14).

In conclusion, excellent ees, up to 95%, have been obtained in the rhodium-catalyzed aqueous hydrogenation of acetophenone using a simple and easy-to-make chiral bidentate pyrazinophosphane ligand. The enantioselectivity of the reaction, as well as the catalyst activity were found to be significantly improved by adding a small amount of an alcohol, indicating the enhancement of the enantiocontrol of the reaction via binding of an alcohol molecule by the catalyst. The found enantiomeric excesses are as high as those reported recently for chiral ruthenabicyclic complexes,[25,26] these being presently to our knowledge, the best catalysts for acetophenone reduction. However, in our case, full conversion is achieved at five times lower hydrogen pressure and requires no decreased temperatures. The easy preparation, stability toward air oxidation, and amphiphilic nature, that enables application of the described ligands in aqueous organometallic catalysis, should reduce strongly the environmental impact of large scale catalytic processes.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.108.

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