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Tetrahedron Letters 45 (2004) 8153–8156
Tetrahedron Letters

Chiral 1,2,5-triphenylphospholanium tetrafluoroborate as ligand precursor in Rh-catalyzed asymmetric hydrogenation of methyl (*Z*)-2-acetamidocinnamate

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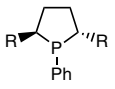
Received 23 July 2004; revised 3 September 2004; accepted 6 September 2004
Available online 21 September 2004

Abstract—(*S*,*S*)-1,2,5-Triphenylphospholanium tetrafluoroborate salt **2** was conveniently used as chiral ligand precursor in rhodium-catalyzed asymmetric hydrogenation of methyl (*Z*)-2-acetamidocinnamate. ^{31}P NMR showed the existence of a solvent-dependent equilibrium between the salt and the free phosphine.

1. Introduction

Following the report on the preparation of the enantiomerically pure *trans*-2,5-disubstituted-1-phenylphospholanes **1a**–**c** by Burk et al.,[1] we described the synthesis of the *trans*-2,5-diphenyl-1-phenylphospholane **1d** by a different route,[2] and reported the use of this phosphine in rhodium-catalyzed asymmetric hydrogenation of methyl (*Z*)-2-acetamidocinnamate.[3]



1 a R = Me ; b R = Et; c R = *i*-Pr; d R = Ph

Although being a dialkylarylphosphine, **1d** undergoes easy oxidation when handled in air. It was then desirable to find out a convenient way of protection, storage and deprotection of this phosphine.

Ways for protection of phosphines from oxidation are well documented, involving the formation of their oxide, sulfide or borane. The deprotection requires either a reduction step for the two former, or the displacement of the borane group.

Recently, a convenient protection of air-sensitive tertiary alkylphosphines (tributyl or tri-*tert*-butylphosphine) through formation of their conjugate acid has been reported by Netherton and Fu.[4] The phosphonium salts were used as catalysts precursors in the presence of a base to liberate the free phosphine, usually a tertiary amine.[4,5] Imamoto synthesized P-chirogenic diphosphonium salts of ethylene- or methylene-bridged P-chirogenic trialkyldiphosphines and showed that they were convenient precursors in the rhodium-catalyzed asymmetric hydrogenation of methyl (*Z*)-2-acetamidocinnamate.[6] Moreover, in some cases, no added base was needed to liberate the free base and generate the catalytic species.

During the course of our studies on the development of new monophosphine ligands, we have recently described the synthesis of new electron rich chiral and enantiopure 1-*r*,2-*c*,5-*t*-triphenylphospholane **1d** (noted as P* in the following).

We wish to describe the preparation of the chiral (*S*,*S*)-1,2,5-triphenylphospholanium tetrafluoroborate salt **2** and the first results on the use of this phosphonium as ligand precursor for Rh-catalyzed enantioselective hydrogenation.

Keywords: Asymmetric catalysis; P ligand; Ligand design; Hydrogenation; Enantioselectivity.
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doi:10.1016/j.tetlet.2004.09.031

2. Results and discussion

A convenient preparation of phosphonium salts through direct reaction with strong acids as trifluoromethanesulfonic acid or tetrafluoroboric acid was unsuccessful in our hands, probably due to the not sufficiently basic character of the free P-arylphospholane, compared to the tri-alkyl phosphines described in the literature. Although the reaction occurs (NMR monitoring) an analytically pure product could not be obtained. The only satisfactory method proved to be the reaction of the phosphine with the ethereal complex of tetrafluoroboric acid ($HBF_4{\cdot}OEt_2$). Under these conditions, the clean phospholanium salt precipitated as a white powder, and could be used as ligand precursor without purification. The same result was obtained from the phosphine-borane complex **3** at lower temperature (Scheme 1).

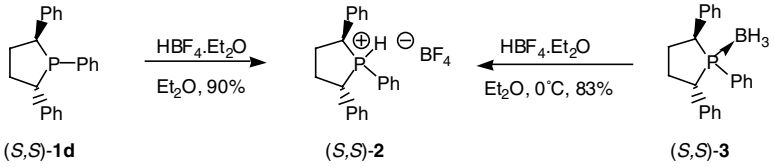
The isolated salt showed no decomposition after three months storage in air. The $^{31}P\{^1H\}$ NMR spectrum of **2** was realized in CD_2Cl_2 under an argon atmosphere to show one major signal at 34.6 ppm; the proton-coupled spectrum exhibited a doublet (34.6 ppm, $^1J_{P-H}$ = 519 Hz) characteristic of a P–H bond. The ^{31}P NMR spectrum of **2** in methanol-d_4 displays a singlet at 27.9 ppm (the free phosphine **1d**), both under proton-coupling or proton-decoupling conditions. It is noteworthy that the salt is hardly dissociated in chlorinated solvents (analogous spectra were recorded in $CHCl_3$), but almost totally dissociates in methanol liberating the free phosphine, which indeed reacts under an air atmosphere with oxygen to give the corresponding triphenylphospholane oxide **4**. This fact enhances the importance of solvent used in the hydrogenation experiments (see Scheme 2).

^{31}P NMR examination of the complex resulting from a mixture of $[Rh(COD)_2]BF_4$ and 2 equiv of phosphonium salt (*S*,*S*)-**2d** in methanol showed one clean sharp doublet (δ = 51.4 ppm, J = 151 Hz), revealing the formation of the C_2-symmetric $[Rh(COD)(P^*)_2]$ complex. In CD_2Cl_2, the cationic phosphine complex ($^{31}P\{^1H\}$ NMR, doublet, δ = 46.65 ppm, J = 151 Hz) was formed upon reaction of (*S*,*S*)-**2d** with 0.5 equiv of $[Rh(COD)_2]BF_4$ with entire consumption of the salt. This indicates that the rhodium complex is formed in spite of a low dissociation of the phosphonium salt.

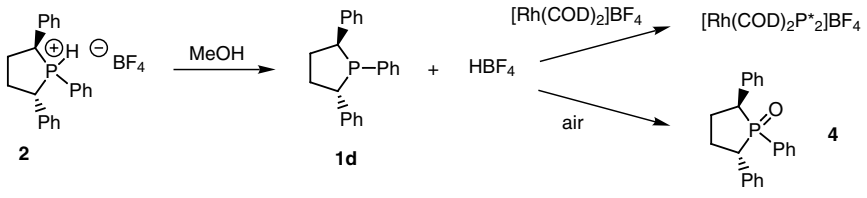
The newly prepared chiral phosphonium salt was used in the asymmetric hydrogenation of methyl (*Z*)-2-acetamidocinnamate. The catalyst was generated by mixing 1 mol% of rhodium precursor with 2.2 mol% of phosphonium salt (in some cases in the presence of a base). Since the 2,5-diarylphospholanes proved to form very active catalytic species,[3] most of the first tests were performed under an atmospheric pressure of dihydrogen and at room temperature.

With the cationic rhodium precursor $[Rh^I(COD)_2]BF_4$ (Table 1), the reaction was very fast in methanol and a half-reaction time of about 8 min was recorded (entry 1). A similar result has been obtained from the free phosphine **1d**.[3b] Although the enantioselectivities observed were slightly lower (85% vs 93%) than those previously recorded with the free ligand, very high reproducibilty was obtained. Addition of 1 equiv of base neither speeded up the reaction nor altered the selectivity (entry 2). However, the addition of 5 equiv of amine seriously slowed down the reaction rate (half-time of about 3 h), albeit the selectivity remained similar (entry 3). A slight increase of asymmetric induction was obtained at lower temperature without loss of reactivity (entry 4). There was only small effect of pressure upon enantioselectivity (entries 5, 6 and 7).

Using dichloromethane as the solvent had a retarding effect: the reaction was quite sluggish and less enantioselective (entry 8). We assumed that the active catalytic species needed more time to form. This interpretation is supported by the fact that an induction period of about 20 min was observed before any hydrogen consumption.

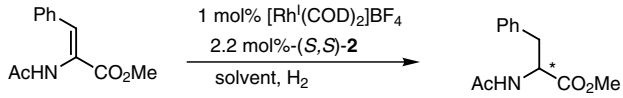


Scheme 1. Synthesis of (*S*,*S*)-1,2,5-triphenylphospholanium tetrafluoroborate salt **2**.



Scheme 2. Equilibrium between the (*S*,*S*)-1,2,5-triphenylphospholanium tetrafluoroborate salt and the free phosphine.

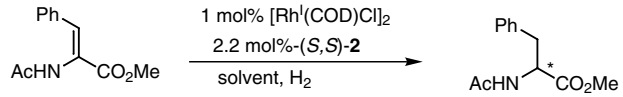
Table 1. Rh-catalyzed enantioselective hydrogenation of methyl (*Z*)-2-acetamidocinnamate using (*S*,*S*)-phospholanium salt **2d**[a] and $[Rh(COD)_2]BF_4$ as rhodium source



Entry	Solvent	Additive	Pressure (atm)	$t_{1/2}$ (min)/reaction time (h)	Conv.[c]/(%) ee[d] (config.)
1	MeOH	None	1	8/0.3	100/85.6 (*R*)
2	MeOH	*i*-Pr_2NEt (1 equiv)	1	10/0.5	100/85.3 (*R*)
3	MeOH	*i*-Pr_2NEt (5 equiv)	1	200/12	100/83.8 (*R*)
4[b]	MeOH	None	1	—/1	100/89.5 (*R*)
5	MeOH	None	5	—/16	100/85.5 (*R*)
6	MeOH	None	40	—/16	100/86.6 (*R*)
7	MeOH	None	80	—/16	100/87.3 (*R*)
8	CH_2Cl_2	None	1	27/1	100/68 (*R*)

[a] All reactions were carried out under one hydrogen atmosphere at room temperature unless otherwise noted.
[b] The reaction was carried out at 0 °C.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC analysis on a Chiralcel OD-H column, with hexane/isopropanol 9/1 as eluent.

Table 2. Rh-catalyzed enantioselective hydrogenation of methyl (*Z*)-2-acetamidocinnamate using (*S*,*S*)-phospholanium salt **2d**[a] and $[Rh(COD)Cl]_2$ as neutral complex



Entry	Solvent	Additive	Pressure (atm)	$t_{1/2}$ (min)/reaction time (h)	Conv.[b]/(%) ee[c] (config.)
1	MeOH	None	1	—/12	100/87 (*R*)
2	MeOH	None	50	—/16	100/78 (*R*)
3	CH_2Cl_2	None	1	—/24	0/—
4	CH_2Cl_2	*i*-Pr_2NEt (1 equiv)	1	—/24	0/—
5	CH_2Cl_2	HBF_4 (2–3 equiv)	1	—/12	100/66 (*R*)
6	MeOH	HBF_4 (2–3 equiv)	1	12/0.5	100/79 (*R*)

[a] All reactions were carried out under hydrogen atmosphere at room temperature unless otherwise noted.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC analysis on a Chiralcel OD-H column, with hexane/isopropanol 9/1 as eluent.

As a matter of comparison, the same reactions were carried out using $[Rh(COD)Cl]_2$ as a neutral precursor catalyst (Table 2).

The change of the Rh-precursor for a neutral one resulted in a lower reaction rate. Twelve hours were needed for total conversion of the substrate with $[Rh^I(COD)Cl]_2$ compared with only 0.5 h for $[Rh^I(COD)_2]BF_4$ (Table 1, entry 1; Table 2, entry 1). Under the same conditions of reaction, an increase of hydrogen pressure was detrimental to the enantioselectivities: 87% ee under 1 atm of dihydrogen, 78% ee under 50 atm (entries 1 and 2).

No reaction occurred in dichloromethane, and the addition of base did not change this result (entries 3 and 4), suggesting that no active catalytic species could be formed in the reaction. However, addition of 2 or 3 equiv of tetrafluoroboric acid allowed the recovery of a total conversion in 12 h with only a slight decrease of enantioselectivity (entry 5). It is noteworthy, although not understood that the presence of HBF_4 in methanol accelerated the reaction, which was then completed in 30 min (12 h without acid) (entries 6 and 1).

The presence of a polar protic solvent such as methanol or of an acid like HBF_4 appears to be necessary to form an active catalyst. Tetrafluoroboric acid is probably generated from dissociation of the phospholanium salt, more easily in methanol than in dichloromethane.

3. Conclusion

As a conclusion, the chiral 1,2,3-triphenylphospholanium tetrafluoroborate salt **2d** has been prepared from Brønsted acid (HBF_4) as a stable chiral salt of a dialkylarylphosphine. The free phosphine is the major species present (NMR) in a methanol solution, whereas the phosphonium salt is dominant in dichloromethane. This air stable salt was conveniently used in rhodium-catalyzed enantioselective hydrogenation of methyl (*Z*)-2-acetamidocinnamate to provide methyl *N*-acetyl phenylalaninate in excellent yield and good enantioselectivity.

4. Experimental section

4.1. General remarks

Proton NMR spectra were recorded on a 250 MHz Bruker spectrometer. Proton chemical shifts were reported in parts per million (δ) relative to internal tetramethylsilane (TMS, $\delta = 0.0$). Carbon NMR spectra were recorded on a 400 MHz (75.45 MHz) or 250 MHz (62.9 MHz) Bruker spectrometer with complete proton decoupling. Phosphorus NMR spectra were recorded at 101.2 MHz spectrometer with complete proton decoupling, and the corresponding chemical shifts are reported in parts per million (δ) relative to external phosphoric acid (H_3PO_4, $\delta = 0.0$).

Flash column chromatography was performed using silica gel Merck (0.04–0.063 μm). Optical rotations were recorded at the sodium D line with a Perkin Elmer 341 polarimeter. High-resolution mass spectra were obtained with a MAT95 Thermo-Finnigan spectrometer.

Enantiomeric excesses were determined by chiral analytical HPLC on Chiralcel OD-H column using hexane/isopropanol as eluent. Analytical HPLC was performed and monitored with a single wavelength UV detector (254 nm).

All reactions were carried out in Schlenk tubes under an argon atmosphere. Methanol was stored over molecular sieves 4 Å and CH_2Cl_2 was distilled over CaH_2 under argon. $HBF_4{\cdot}OEt_2$ (85%) was purchased from Aldrich).

4.2. (*S*,*S*)-1,2,5-Triphenylphospholanium tetrafluoroborate salt (2)

To a solution of (*S*,*S*)-1,2,5-triphenylphospholane (**1**, 316 mg, 1 mmol) in dry degassed diethyl ether (5 mL) were added 3 equiv of $HBF_4{\cdot}Et_2O$ complex (85%). After a few minutes the precipitate was collected by filtration, washed with diethyl ether (3×10 mL) and dried, to give the phospholanium salt as a white powder (90% yield). $[\alpha]_D^{20}$ +87.5 (*c* 0.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.10$–2.70 (2H, m), 2.90 (1H, m), 3.00 (1H, m), 4.40 (1H, m), 5.00 (1H, m), 7.15–7.40 (5H, m), 7.40–7.50 (9H, m), 7.60 (1H, m), 7.36 (1H, d, $J_{P-H} = 520$ Hz). ^{13}C NMR (62.9 MHz, CD_2Cl_2): $\delta = 32.70$ (d, $J = 6.5$ Hz), 33.30 (d, $J = 9.5$ Hz), 42.60 (d, $J = 41$ Hz), 43.35 (d, $J = 44$ Hz), 128.00 (d, $J = 6.5$ Hz), 128.30 (d, $J = 3$ Hz), 128.65 (d, $J = 5.5$ Hz), 129.00 (d, $J = 2$ Hz), 129.05 (d, $J = 3$ Hz), 129.75 (d, $J = 2$ Hz), 130.10 (d, $J = 12.5$ Hz), 131.45 (d, $J = 6.5$ Hz), 132.10 (d, $J = 5.5$ Hz), 1338.0 (d, $J = 9.5$ Hz), 135.40 (d, $J = 3$ Hz). ^{31}P NMR (101.2 MHz, $CDCl_3$): δ 34.4 (d, $J_{P-H} = 519$ Hz). HRMS (IE): $m/z = 317.1454$ found. Calculated for $C_{22}H_{22}P$: 317.1459.

4.3. Rhodium-catalyzed asymmetric hydrogenation: general method

A Schlenk tube was charged with (*S*,*S*)-(**2**) (7 mg, 0.022 mmol) and bis(cyclooctadiene)rhodium tetrafluoroborate (4 mg, 10 μmol). The tube was purged with argon and degassed, anhydrous methanol (5 mL) was added. The solution was stirred for 10 min, and the yellow solution obtained was cannulated into a Schlenk tube containing (*Z*)-methyl *N*-acetyl dehydrocinnamate (219 mg, 1 mmol) under a hydrogen atmosphere. The uptake of hydrogen began immediately upon stirring. After completion of the reaction (no further hydrogen uptake), the resulting solution was concentrated in vacuo, taken up in dichloromethane (10 mL) and stirred with activated carbon for 1.5 h. Filtration over Celite and removal of the solvent afforded the hydrogenated product. Enantiomeric excesses were determined by chiral HPLC on a Chiralcel OD-H column, with hexane/*i*-PrOH (9/1) as eluent.

Acknowledgements

We wish to thank the Agence Universitaire de la Francophonie and the Romanian Ministry of Education for financial support.

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