Kinetic Resolution of *rac*-4,12-Dibromo[2.2]paracyclophane in a Palladium [2.2]PHANEPHOS Catalyzed Amination

Kai Rossen,* Philip J. Pye,* Ashok Maliakal, and R. P. Volante

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

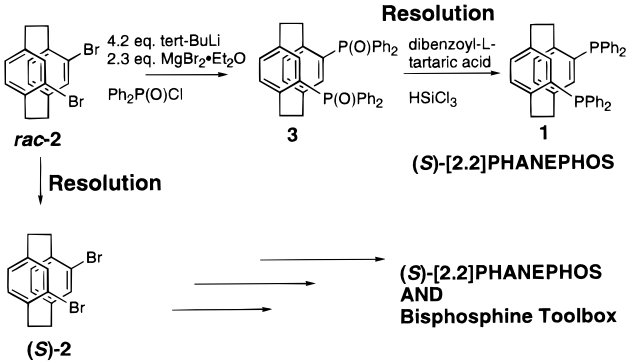
Received July 16, 1997

Although it was recognized as early as 1942 that the arrangement of planar aromatic fragments in space could lead to a chiral molecule,[1] only recently has planar chirality been exploited in the preparation of chiral catalysts.[2] We recently reported on the preparation of [2.2]PHANEPHOS **1** (4,12-bis(diphenylphosphino)[2.2]-paracyclophane)[3] and the use of this ligand in the formation of highly active and enantioselective catalysts for both Rh catalyzed hydrogenations of dehydro amino acids[3] and Ru-catalyzed hydrogenations of β-keto esters.[4] The success of [2.2]PHANEPHOS led us to consider further applications of this novel ligand for asymmetric catalysis.

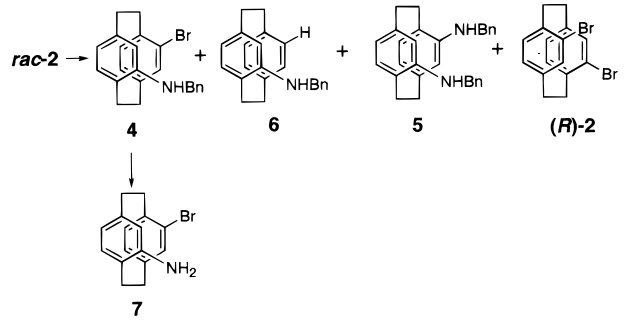
The preparation of [2.2]PHANEPHOS commenced with *rac*-4,12-dibromo[2.2]paracyclophane (**2**), which after metalation with *tert*-butyllithium and transmetalation with $MgBr_2$ was reacted with diphenylphosphoryl chloride to give racemic bisphosphine oxide **3** (Scheme 1). Resolution with dibenzoyltartaric acid and subsequent reduction of the phosphine oxides led to the enantiomerically pure ligand [2.2]PHANEPHOS. Although this route is efficient, optically pure **2** would be an excellent starting material for the preparation of [2.2]PHANEPHOS and, more importantly, of a toolbox of differently substituted bisphosphine ligands.

Recently, the groups of Buchwald and Hartwig have expanded the methodology available to the synthetic chemist by introducing efficient technology for the displacement of aromatic halides with amines, catalyzed by palladium bisphosphine complexes.[5] These groups explored the wide synthetic utility of these reactions and have developed a good understanding for the mechanism of this novel transition metal catalyzed transformation. In these reactions, both the aryl halide and amine starting material as well as the alkylaniline products are achiral, but nevertheless a number of the most successful catalysts are chiral. It occurred to us that the application of this amination reaction on the racemic mixture of the chiral dibromide **2** using an enantiomerically pure catalyst could reveal the enantiodifferentiating ability of these chiral bisphosphine Pd catalysts and thus afford a kinetic resolution of *rac*-**2**.

Scheme 1



Scheme 2



To this end *rac*-**2** was reacted with 2 equiv of benzylamine in toluene in the presence of 3 equiv of sodium *tert*-butoxide in toluene at 50 °C in the presence of either (*R*)-BINAP/Pd_2dba_3 or (*S*)-[2.2]PHANEPHOS/Pd_2dba_3 (tris-(dibenzylideneacetone)dipalladium(0)). As *rac*-**2** was consumed, a complex reaction mixture resulted, from which the monoaddition product **4** and small amounts of the bis(benzylamine) **5**, as well as the dehalogenated compound **6**, could be isolated. Additionally, the benzylamine **4** was readily oxidized in air to the imine,[6] so that variable amounts of the free amine **7** were obtained during SiO_2 chromatography (Scheme 2). The conversion of *rac*-**2** was measured by HPLC using 1-methylnaphthalene as an internal standard while the ee of the unreacted **2** was determined using a Chiralcel OD-H column on an SFC system (Table 1).[7] The data show that the Pd/[2.2]PHANEPHOS catalyst possesses considerably enhanced activity compared to the Pd/BINAP system: Pd/[2.2]PHANEPHOS appears to give an approximately 7 times faster reaction rate (rows a and b). Remarkably, Pd/[2.2]PHANEPHOS also led to a useful kinetic resolution,[8] with the (*S*) enantiomer of **2** reacting 3 to 4 times faster than (*R*)-**2** at 50 °C. A smaller, 2 fold rate difference between the enantiomers was observed for the Pd/BINAP catalyst.

In an exploration of reaction parameters, the amount of NaO*t*Bu and $BnNH_2$ was varied, but only a small

* Authors to whom correspondence should be addressed at the following: Fax: + 908 594 1499 or e-mail: kai_rossen@merck.com or philip_pye@merck.com.

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S0022-3263(97)01300-5 CCC: $14.00

Table 1. Fraction of Unreacted 2 (ee of unreacted 2, *s*: calculated enantiomeric discrimination)[a]

	reaction conditions	2 h	4 h	6 h	8 h
a	Pd BINAP	0.95	0.91	0.86	0.82 (5% ee, *s*=2)
b	Pd PHANEPHOS	0.62 (34% ee, *s* = 4)	0.39 (51%ee, *s* = 3)	0.29 (70%ee, *s* = 3)	0.23 (74% ee, *s* = 3)
c	Pd PHANEPHOS 10 equiv of $BnNH_2$	0.64 (36%ee, *s* = 6)	0.56 (42% ee, *s* = 5)	0.25 (45% ee, *s* = 2)	0.17 (47% ee, *s* = 2)
d	Pd PHANEPHOS 2 equiv of Br^-	0.58 (42% ee, *s* = 6)	0.39 (65% ee, *s* = 4)	0.27 (76% ee, *s* = 3)	0.19 (84% ee, *s* = 3)
e	Pd PHANEPHOS 10 equiv of NaO*t*Bu	0.48 (41% ee, *s* = 3)	0.32 (64% ee, *s* = 3)	0.23 (74% ee, *s* = 3)	0.12 (83% ee, *s* = 3)
f	Pd PHANEPHOS 2 equiv of Tl PF_6	0.84 (18% ee, *s* = 42)	0.70 (32% ee, *s* = 10)	0.66 (41% ee, *s* = 13)	0.63 (45% ee, *s* = 12)

[a] All reactions were run in a Schlenk tube under N_2 with catalyst prepared from 1 mol % of $Pd_2dba_3{\cdot}CHCl_3$ and 3 mol % of bisphosphine in thoroughly degassed toluene at 50 °C at 0.2 M concentration. All reactions used 2 equiv of $BnNH_2$ (except c) and 3 equiv of NaO*t*Bu (except e). Additionally, 2 equiv of $CH_3(CH2)_{17}NMe_3Br$ was added to d, and 2 equiv of Tl PF_6 was added to f. The reactions were quantified using HPLC intergration of the reaction mixture containing 1-methylnaphthalene as internal standard. The enantiomeric discrimination s was calculated from the conversion and the ee of the remaining **2** according to $s = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$. This number is expected to be constant over the course of the reaction, so that the decrease of *s* may indicate a change in catalytically active species.

influence on rate or selectivity was observed (Table 1). Addition of halide in the form of $CH_3(CH_2)_{17}NMe_3$ Br had little effect on the reaction. In contrast, addition of the halide scavenger Tl PF_6 greatly reduced the reaction rate, and at the same time *the enantiomeric discrimination increased to 10 −13:1* (Table 1). The influence of halide on the enantioselectivity is thus opposite from that observed by Overman in the chiral Heck reaction with Pd/BINAP.[9] The high enantiomeric discrimination of the (*S*)-[2.2]PHANEPHOS/Pd/Tl PF_6 system allows the practical preparation of enantiomerically pure **2** from its racemate. As described by Sharpless,[10] products of extremely high ee can be obtained when the reaction is driven to a high conversion; after 90% conversion the remaining 10% **2** is enantiomerically pure at >99.9% ee (*R* configuration). The practicality of this procedure was demonstrated in a preparative run where the conversion was driven to 79%: the remaining **2** had 93% ee (*R*),[11] corresponding to a 42% resolution yield.

Interestingly, enantiomerically pure (*S*)-**2** is the starting material for the preparation of the catalyst ligand (*S*)-[2.2]PHANEPHOS, and as the (*S*)-[2.2]PHANEPHOS/Pd-catalyzed reaction leaves behind (*R*)-**2**, the chiral catalyst is thus helping to breed its own chirality from racemic starting material, albeit in its enantiomeric form.[12]

In summary the Pd/[2.2]PHANEPHOS catalyst is highly active in the Buchwald/Hartwig amination of *rac*-4,12-dibromo[2.2]paracyclophane and gives practical enantiomeric discrimination when halide is removed from the reaction mixture. Based on the outstanding properties of the Pd/[2.2]PHANEPHOS catalyst in the amination of **2**, future work will be focused on the preparation of chiral amines and the application of the Pd/[2.2]PHANEPHOS combination in classical Pd-catalyzed reactions, such as the Heck reaction or allylic alkylation.

Supporting Information Available: ^1H and ^{13}C spectra and SFC traces (13 pages).

JO971300A

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(11) Experimental: To a solution of 1.014 g (2.77 mmol) of *rac*-**2** in 12 mL of thoroughly degassed toluene under N_2 in a Schlenk tube were added 1.06 g (11 mmol) of NaO*t*Bu followed by 1.39 g (4 mmol) of Tl (PF_6), 48 mg (0.083 mmol) of (*S*)-[2.2]PHANEPHOS, and 29 mg (0.028 mmol) of $Pd_2dba_3{\cdot}CHCl_3$. The mixture was warmed to 50 °C for 10 min, when 0.61 mL (5.5 mmol) of $BnNH_2$ was added. The reaction mixture was stirred at 50 °C for 10 h and quenched by addition of 5 mL of MeOH and 50 mL of EtOAc. The crude reaction mixture was filtered through a bed of SiO_2 to remove the Tl salts (HIGHLY TOXIC). The filtrate was worked up in a standard way, and the remaining **2** was isolated by SiO_2 chromatography as a white powder (0.214 g, 42% yield). The ee is determined to be 93% of (*R*)-**2** using a Hewlett Packard Supercritical Fluid Chromatography system with a Chiralcel OD-H column. Separation conditions: 300 bar CO_2 with MeOH modifier gradient: 4 min at 4% and then ramping up to 36% within 32 min, flow 1 mL/min. Retention times (*R*)-**2**: 22.6 min, (*S*)-**2**: 25.5 min.

(12) (a) The absolute configuration of (*R*)-**2** and (*S*)-**2** are known by correlation with the bisphosphine oxide of [2.2]PHANEPHOS, whose absolute configuration was determined by X-ray crystallography as a complex with dibenzoyl-D-tartaric acid. See also ref 3. (b) M. D. Fryzuk, B. Bosnich *J. Am. Chem. Soc.* **1978**, *100*, 5491.