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(-)-(4S,5R)-4-(2-Pyridyl)-5-(diphenylphosphino)methyl-2,2-dimethyl-1,3-dioxolane a new chiral ligand for enantioselective catalysis

Giorgio Chelucci,[a]* M. Antonietta Cabras,[a] Carlo Botteghi[b] and Mauro Marchetti.[c]

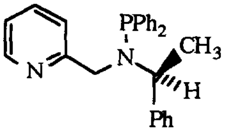
[a]Dipartimento di Chimica, Università di Sassari, via Vienna 2, I-07100 Sassari, Italy;

[b]Dipartimento di Chimica, Università di Venezia, Calle Larga, S. Marta 2137, Venezia, Italy;

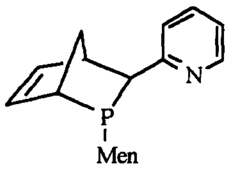
[c]Istituto A.T.C.A.P.A., C.N.R., via Vienna 2, I-07100 Sassari, Italy.

Abstract: The title compound (PYDIPHOS) has been prepared by a ten reaction sequence from dimethyl L-(+)-tartrate and checked in the palladium-catalyzed asymmetric hydroesterification of styrene and in the nickel catalyzed asymmetric cross-coupling reaction of 1-phenylethyl magnesium bromide with vinylbromide.

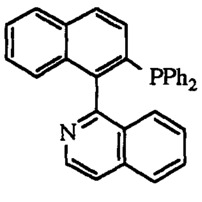
The synthesis of new chiral ligands for transition metals is an essential tool for the development of novel catalytic systems exhibiting high reactivity and enantioselectivity.[1] In this context, the complex forming properties of pyridylphosphine ligands attract increasing attention and the study of their catalytic activity has been recently undertaken.[2] Some chiral pyridylphosphines bearing the chiral group bound to the phosphorus atom by a N-P linkage (**A**) have been described.[3] Instead, only two literature reports are available on the synthesis of optically active pyridylphosphines without N-P bonds, namely the menthylphosphine **B**[4] and the (-)-(S)-1-(2-diphenylphosphino)-1-naphtyl)isoquinoline **C**.[5]



A

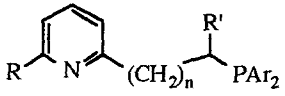


B



C

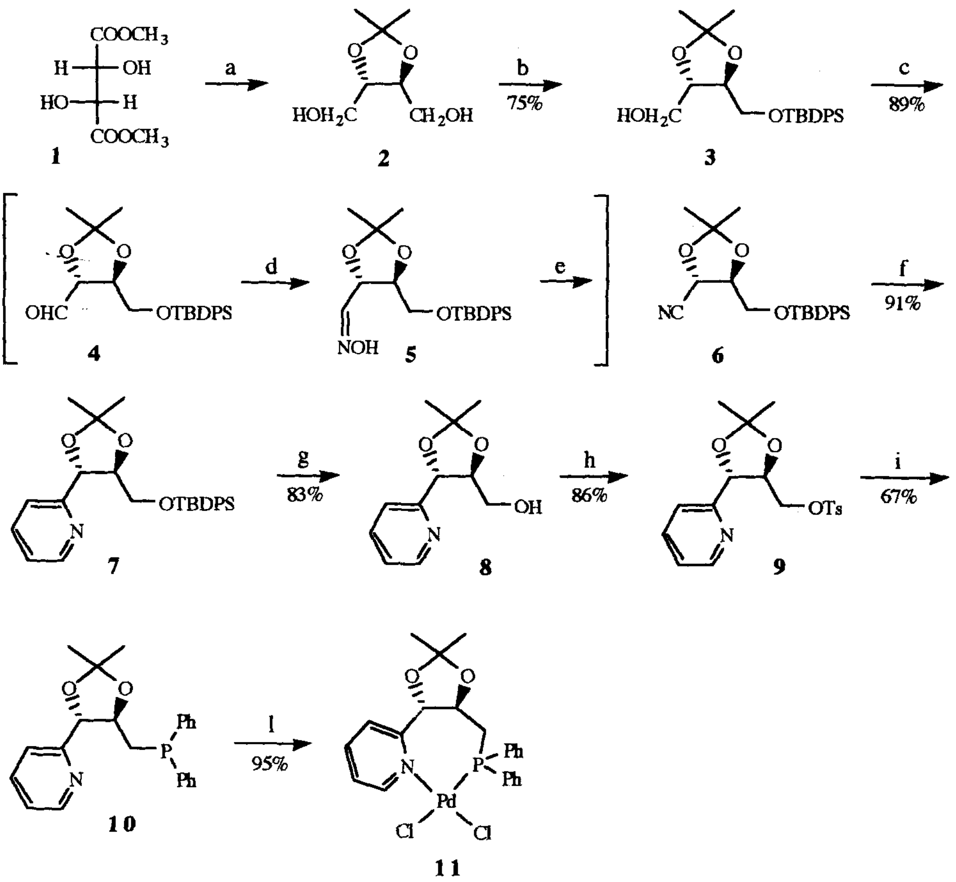
As a part of our work aimed at the synthesis of chiral pyridine ligands,[6] we undertook a study on general methods to obtain chiral pyridylphosphines (**D**) from cheap naturally occurring chiral compounds. Now, we report the preparation of PYDIPHOS (**10**) as the first representative member of enantiomerically pure pyridylphosphines using L-(+)-tartaric acid as the starting material.



D

Synthesis of **10** starts from the diol **2**, which was prepared by literature procedures[7] from diethyl

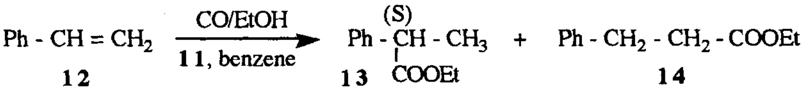
Scheme



a: Literature; b: NaH (1 equiv), t-$BuPh_2SiCl$ (TBDPSCl); c: $(COCl)_2$, DMSO, Et_3N, -78 °C; d: $NH_2OH{\cdot}HCl$, 10% K_2CO_3; e: N,N'-carbonyldiimidazole; f: CpCo(COD), acetylene, toluene, 120 °C, 14 atm; g: Bu_4NF, THF; h: TsCl, Et_3N, DMPA, CH_2Cl_2; i: Ph_3P, Na/K, dioxane; l: $(PhCN)_2PdCl_2$, CH_2Cl_2, 25 °C

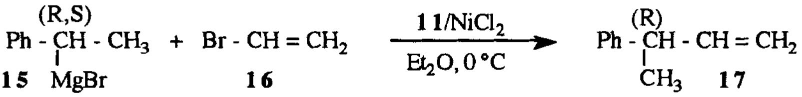
L-(+)-tartrate (Scheme). Selective protection of **2** (75%) and Swern's oxidation gave the aldehyde **4**. The crude aaldehyde was converted into the nitrile **6** (89% based on **3**) *via* formation of the corresponding oxime followed by dehydration with N,N'-carbonyldiimidazole. Cobalt catalyzed co-cyclotrimerization of nitrile **6** with acetylene afforded the key pyridine intermediate **7** (91%).[7] The hydroxyl group was then deprotected and converted into the tosylate **9** (86%). Finally, nucleophilic displacement of tosyl group with a Na/K diphenylphosphide mixture gave PYDIPHOS in 29% overall yield based on **2**.[9]

The enantioselective ability of the new chiral ligand was checked in two classical reactions catalyzed by a transition metal complex. At first we examined the hydrocarbethoxylation of styrene[10] in the presence of the catalytic precursor (PYDIPHOS)$PdCl_2$ prepared by treating a solution (CH_2Cl_2) of **10** with $(PhCN)_2PdCl_2$. The complex is crystalline and exhibits a fairly good stability in the air. The branched ethyl ester **13** was obtained regiospecifically with a very high chemoselectivity (≥ 90%); the prevailing configuration of **13** was (S) and its enantiomeric purity about 20%.



$$\underset{\mathbf{12}}{\mathrm{Ph-CH=CH_2}} \xrightarrow[\mathbf{11},\ \text{benzene}]{\text{CO/EtOH}} \underset{\mathbf{13}}{\overset{(S)}{\mathrm{Ph-CH(COOEt)-CH_3}}} + \underset{\mathbf{14}}{\mathrm{Ph-CH_2-CH_2-COOEt}}$$

We then considered the cross-coupling reaction[11] of 1-phenylethylmagnesium bromide with vinylbromide catalyzed by the *in situ* formed complex from anhydrous Nickel(II)chloride and PYDIPHOS ($NiCl_2$ to **10** molar
ratio 1/1).[3]



$$\underset{\mathbf{15}}{\overset{(R,S)}{\mathrm{Ph-CH(MgBr)-CH_3}}} + \underset{\mathbf{16}}{\mathrm{Br-CH=CH_2}} \xrightarrow[\mathrm{Et_2O},\ 0\,^{\circ}\mathrm{C}]{\mathbf{11}/\mathrm{NiCl_2}} \underset{\mathbf{17}}{\overset{(R)}{\mathrm{Ph-CH(CH_3)-CH=CH_2}}}$$

Enantioselectivity (26%) was comparable to that of the above mentioned process but in this case the chemoselectivity was rather poor (50%) and the (-)-(R)-2-phenyl-1-butene was recovered in only 40% yield. The enantioselectivity of this catalytic process, although low, resulted to be however remarkably higher than that (1.4%) obtained for the cross-coupling reaction between 1-phenylethylmagnesium chloride and vinyl bromide catalyzed by $NiCl_2$ complex with a pyridylphosphine containing a N-P bond.[3]

Efforts to achieve a higher enantiodifferentiation degree by structural modifications of PYDIPHOS are in progress in our laboratories.

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8. The cobalt(I)-catalyzed co-cyclotrimerization reaction of alkynes with nitriles is one of the most useful methods for the preparation of pyridines and their derivatives.[12] We used this reaction to obtain chiral alkylpyridines,[13] 1-(2-pyridyl)alkylamines[14] and alkyl-2,2'-bipyridines.[15]
9. The structure assigned to each compound was in agreement with its spectral (^{1}H and ^{13}C NMR, IR, and mass) characteristics, the optical rotation of PYDIPHOS obtained in two different preparations was $[\alpha]^{25}_D$ - 48.0 (*c* 7, $CHCl_3$). Yield cited are for compounds proved to be >95% pure.
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