Zirconium-Mediated Synthesis of a New Class of 1,4-Bis(diphenylphosphino)-1,3-butadiene-Bridged Diphosphine, NUPHOS: Highly Efficient Catalysts for Palladium-Mediated Cross Couplings

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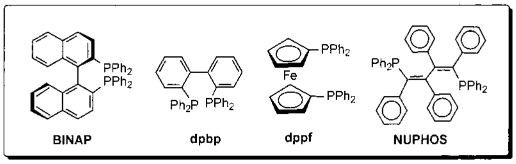
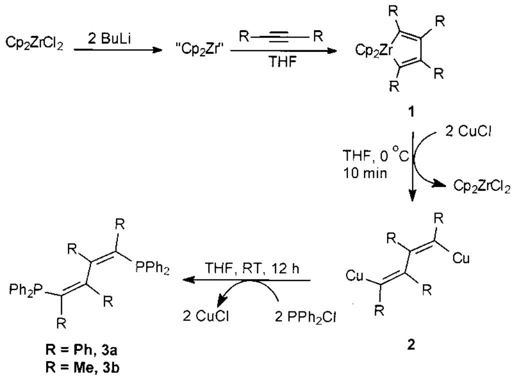
Over the past two decades 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) has proven to be an extremely versatile bidentate phosphine which, in combination with an appropriate transition metal, forms catalysts that are highly active and selective for a range of reactions.[1] For reactions that do not involve an asymmetric transformation it would be more practical to find an alternative less expensive but structurally similar diphosphine. One such diphosphine is 2,2′-bis(diphenylphosphino)-1,1′-biphenyl (dpbp).[2] This ligand has several features in common with BINAP in that it is a bidentate triaryl phosphine with two diphenylphosphino groups bridged by a four-carbon tether, composed of sp^2-hybridized atoms, and forms a skewed seven-membered ring when coordinated to a metal center.



Hayashi and co-workers have recently reported the first results of catalyst testing using dpbp.[2] They showed that the selectivity of palladium-based catalysts in the cross coupling of *sec*-BuMgCl with vinyl halides was higher than that obtained with more common diphosphines such as dppe and comparable to 1,1′-bis(diphenylphosphino)ferrocene (dppf)-based catalysts.[3] This ligand has also been shown to form highly efficient palladium catalysts for the amination of aryl bromides and the rhodium-catalyzed conjugate addition of boronic acid to enones. Given the effectiveness of catalysts based on dpbp and their obvious potential in a range of platinum group-catalyzed reactions there is likely to be considerable interest in the preparation and applications of related diphosphines, especially if their synthesis is straightforward and versatile.

Several years ago Fagan and co-workers demonstrated that 1-phenylphospholes could be liberated directly from the corresponding zirconacycle using dichlorophenylphosphine.[4] We have been investigating the synthesis of bidentate diphosphines by this route and have found that (i) reaction of zirconacycle **1** with chlorodiphenylphosphine does not give the corresponding diphosphine and (ii) diphosphines can be prepared by transmetalation of the zirconacycle to copper before quenching with chlorodiphenylphosphine. While examples of transmetalation from zirconium to copper are commonplace,[5] the application of this procedure to the synthesis of bidentate phosphines has not yet been reported. Herein, we report details of the synthesis of a new class[6] of 1,4-bis(diphenylphosphino)-1,3-butadiene-bridged diphosphine (NUPHOS) from the corresponding zirconacyclopentadiene. Results of preliminary catalyst testing have demonstrated that palladium complexes of 1,4-bis(diphenylphosphino)-1,2,3,4-tetraphenyl-1,3-butadiene (1,2,3,4-Ph$_4$-NUPHOS) are an order of magnitude more active for cross couplings than any catalyst system previously reported. One of the most attractive features of the chemistry described herein is the scope for structural modification, since the basic building block is an alkyne or diyne.

Scheme 1



On the basis of Fagan's synthesis of heterocycles via the reductive coupling of alkynes and diynes, we reasoned that treatment of zirconacycle **1** with diphenylchlorophosphine would liberate the corresponding diphosphine, **3,** directly. Unfortunately, we have been unable to isolate any phosphorus-containing species from this reaction. Remarkably though, transmetalation of zirconacyclopentadiene **1** with copper(I) chloride prior to the addition of diphenylchlorophosphine gave 1,4-bis(diphenylphosphino)-1,2,3,4-tetraphenyl-1,3-butadiene copper complex, which can be liberated by repeated extraction of a dichloromethane solution with aqueous ammonia (Scheme 1). Crystallization from toluene−hexane gave 1,4-bis(diphenylphosphino)-1,2,3,4-tetraphenyl-1,3-butadiene (1,2,3,4-Ph$_4$-NUPHOS, **3a**) as colorless prisms.[7] Similarly, when but-2-yne is used in the reductive coupling step, the product 1,4-bis(diphenylphosphino)-1,2,3,4-tetramethyl-1,3-butadiene (1,2,3,4-Me$_4$-NUPHOS, **3b**) is isolated in 53% yield. Alternatively, **3a** can be prepared by transmetalation of 1,4-dilithiotetraphenylbutadiene[8] with copper(I) chloride followed by quenching with diphenylchlorophosphine. The use of zirconacyclopentadienes to prepare C$_4$-bridged diphosphines offers several attractive features including: (i) a one-pot straightforward synthesis, (ii) variability since a wide range of alkynes and diynes are known to undergo reductive coupling by Negishi's reagent, and (iii) access to a range of chiral diphosphines.

The reaction of **3a**−**b** with [(COD)PdCl$_2$] in dichloromethane affords [(NUPHOS)PdCl$_2$] (**4a**−**b**). An X-ray analysis[9] of **4a** (Figure 1) clearly shows that the palladium atom is distorted away from square planar, as indicated by the dihedral angle of 12.1° between the planes containing Pd(1), P(1), P(2) and Pd(1), Cl(1),

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(6) There has been a single report of a related four-carbon-bridged diphosphine, 2,2′-bis(diphenylphosphino)-3,3,4,4,3′,3′,4′,4′-octafluoro-bicyclobutyl-1,1′-diene, isolated from the reaction between diphenylphosphine and 2,2′-dichlorooctafluoro(bi-1-cyclobuten-1-yl). For details see: Cullen, W. R.; Williams, M. *J. Fluorine Chem.* **1979**, *14*, 85.

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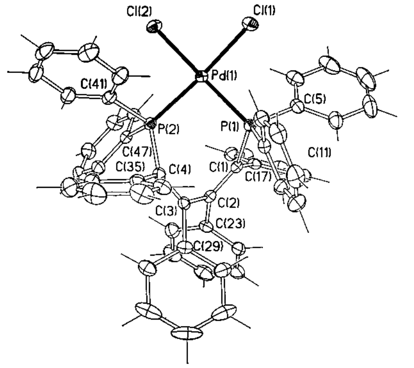

Figure 1. Molecular structure of [(1,2,3,4-Ph_4-NUPHOS)$PdCl_2$] (**4a**).

Table 1. Cross-Coupling Reactions with *sec*-Butyl Magnesium Chloride[a]

$$\text{R-Br} + sec\text{-BuMgCl} \xrightarrow{L_2PdCl_2} sec\text{-BuR} \qquad (1)$$

entry	substrate (R−Br)	diphosphine	catalyst (mol %)	TOF[b]	GC yield %[c]
1	bromobenzene	**3a**	0.1	6900	100 (3h)
2	bromobenzene	**3b**	0.1	270	78 (17 h)
3	bromobenzene	**dppf**	0.1	145	100 (22 h)
4	bromobenzene	**BINAP**	0.1	260	64 (22 h)
5	2-bromopropene	**3a**	0.1	2200	99 (2 h)[d]
6	2-bromopropene	**3b**	0.1	620	65 (2 h)[e]
7	2-bromopropene	**dppf**	0.1	2200	100 (1 h)
8	2-bromopropene	**BINAP**	0.1	220	61 (4 h)[f]

[a] Reaction conditions, 1.0 equiv of RBr, 2 equiv of *sec*-butylmagnesium chloride (2.0 mol dm^{-3}), 0.1 mol % palladium, 0.5 equiv *n*-decane internal standard, diethyl ether 1 mL/5 mmol bromide. [b] Initial turn over frequency, determined by GC analysis. [c] Determined by GC analysis of the reaction mixture, based on product. The reaction time is given in parentheses. [d] 1% *n*-BuCMe═CH_2 detected. [e] 7% *n*-BuCMe═CH_2 detected. [f] 6% *n*-BuCMe═CH_2 detected.

Cl(2), presumably enforced by the torsional twist about C(2)−C(3). Similar distortions have been reported for [(BINAP)$PdCl_2$][10] and [(dpbp)$PdCl_2$],[2] which are based on structurally related four-carbon atom tethers. The natural bite angle of 92.066(15)° is comparable to that reported for [(BINAP)$PdCl_2$] (92.69(8)°) and [(dpbp)$PdCl_2$] (92.24(4)°) and is characteristic of diphosphines bridged by a four-carbon atom sp^2-hybridized tether. In contrast, the natural bite angle of diphosphines with four-carbon atom sp^3 tethers is generally much larger and close to 100°.

Preliminary results have revealed that catalysts formed from [(NUPHOS)$PdCl_2$] are highly active and selective for the cross-coupling of *sec*-butylmagnesium chloride with aryl and alkenyl bromides, with TOF superior to those obtained with catalysts based on BINAP and dppf (Table 1). For example, the reaction of *sec*-butylmagnesium chloride with bromobenzene, carried out in the presence of 0.1 mol % of [(1,2,3,4-Ph_4-NUPHOS)$PdCl_2$] (**4a**) in Et_2O, begins to reflux within 5 min, and reaction is complete within 30 min (entry 1). Under the same conditions, catalysts based on BINAP and dppf are significantly less active, the reaction requiring 5 and 7 h, respectively, to reach completion. The initial TOF of 6900 (mol product) (mol palladium)$^{-1}$ h^{-1} for catalysts based on **3a** is an order of magnitude greater than the initial TOF of 145 and 260 (mol product) (mol palladium)$^{-1}$ h^{-1} for catalysts based on dppf and BINAP, respectively. For comparison, Hayashi reported that coupling of bromobenzene and *sec*-butylmagnesium chloride, catalyzed by 1 mol % of [(dpbp)$PdCl_2$], requires 6 h to reach 93% completion.

Interestingly, the activity of catalysts formed from NUPHOS-type diphosphines depends markedly on the substitution pattern of the C_4-tether. Specifically, substitution of the phenyl groups with methyl groups results in a dramatic decrease in catalyst activity to 270 (mol product) (mol palladium)$^{-1}$ h^{-1}, although it should be noted that the activity of catalysts formed from **3b** is comparable to values reported for most common bidentate phosphines. A major problem associated with cross-coupling reactions involving secondary Grignard reagents is isomerization of the alkyl group: in the case of *sec*-butylmagnesium chloride to give *n*-butyl derivatives via a β-hydride elimination pathway. One of the most effective catalyst systems capable of achieving high *iso*/*n* selectivity is [(dppf)$PdCl_2$] reported by Hayashi. The high selectivity was attributed to the large natural bite angle of dppf and its concomitantly small Cl−Pd−Cl angle that accelerates reductive elimination of the diorganopalladium intermediate. In this regard, palladium catalysts based on **3a**−**b** are also particularly effective, the cross coupling of *sec*-butylmagnesium chloride with bromobenzene giving exclusively *sec*-butylated products, with none of the *n*-butyl product detected by GC. Notably though, the natural bite angle formed by NUPHOS-based diphosphines (∼ 92°) is significantly smaller than that of dppf.

In a comparative study, catalysts formed from **3a** and **3b** also show disparate activities toward 2-bromopropene, with initial TOF of 2200 and 620 (mol product) (mol palladium)$^{-1}$ h^{-1}, respectively (entries 5 and 6). The activity of 2200 (mol product) (mol palladium)$^{-1}$ h^{-1} for catalysts based on [(dppf)$PdCl_2$] is similar to that of **3a** and somewhat unexpected, considering the poor activity of the same system in the reaction between bromobenzene and *sec*-butylmagnesium chloride (entry 3). Such high activities have not previously been reported for dppf-based catalysts, presumably because bromobenzene is the most common substrate for screening new catalysts for cross-couplings.

Kamer has clearly demonstrated a relationship between the natural bite angle of Xanthphos-type diphosphines and their activity and selectivity in palladium-catalyzed cross-couplings. Both the rate and selectivity of the cross-coupling were found to increase with increasing bite angle, reaching a maximum value with DPEphos (102.7°).[12] In contrast, NUPHOS-type diphosphines, which have much smaller natural bite angles, typically close to 92°, form catalysts that are considerably more active. It is clearly difficult to reconcile the differences between the activity of catalysts formed from **3a**, biaryl, and Xanthphos diphosphines with bite angle effects alone, and a more credible explanation is likely to involve a combination of factors.

In summary, we have shown that a new range of potentially versatile C_4-bridged diphosphines can be prepared directly from zirconacycles. Results of preliminary catalyst testing are extremely encouraging, and it is clear that this new class of diphosphine may be effective in a host of platinum group-catalyzed reactions. Further studies are underway to understand the origin of the high catalyst activity achieved with NUPHOS-type diphosphines, to establish the scope of this synthetic protocol, and to exploit the application of these ligands in catalysis, in particular, the development of chiral versions and their application in asymmetric transformations.

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Supporting Information Available: Synthetic procedures and characterization data for compounds **3a,b** and **4a,b** and tables of crystal data, structure solution and refinement, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for **3a** and **4a** and catalyst testing procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org. Observed and calculated structure factor tables are available from the authors upon request.

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(9) *Crystal data for **4a***: $C_{53}H_{42}Cl_4P_2Pd$, $M = 989.01$, monoclinic space group $P2_1/n$, $a = 12.7804(4)$ Å, $b = 22.2135(6)$ Å, $c = 16.3605(5)$ Å, $\beta = 101.657(2)°$, $V = 4548.9(2)$ Å^3, $Z = 4$, $D_c = 1.444$ g cm^{-3}, μ(Mo Kα) = 0.750 mm^{-1}, $F(000) = 2016$, $T = 160(2)$ K, 10900 independent reflections; $R_1 = 0.0252$, $wR_2 = 0.0651$.

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