Simple Mixed Tricyclohexylphosphane–Triarylphosphite Complexes as Extremely High-Activity Catalysts for the Suzuki Coupling of Aryl Chlorides**

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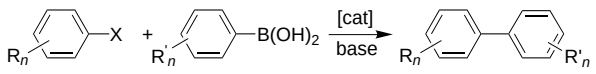
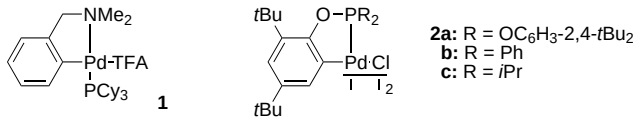
The coupling of aryl halides with aryl boronic acids, the Suzuki reaction (Scheme 1), is one of the most powerful and versatile methods for the synthesis of biaryls.[1] There has



Scheme 1. The Suzuki coupling of aryl halides.

recently been considerable interest in the development of new catalysts that can couple aryl chlorides because of the lower cost and greater availability of these substrates compared with their bromide or iodide counterparts.[2] Unfortunately the comparatively high C–Cl bond strength makes aryl chlorides difficult to activate. Consequently most catalysts that are able to catalyze aryl chloride coupling reactions still need to be used in relatively high loadings. Therefore the advantages associated with the use of aryl chlorides may be negated by the high cost of the catalyst systems.

We recently reported that complex **1**, based on the comparatively inexpensive ligands *N*,*N*-dimethylbenzylamine and tricyclohexylphosphane, shows very high activities in Suzuki coupling reactions of aryl chlorides at low catalyst loadings.[2c] Previously we had shown that the orthopalladated



complex **2a**, which is easily prepared from the very inexpensive ligand tris(2,4-di-*tert*-butylphenyl)phosphite (**3**)[3] shows good activity in the Suzuki coupling of aryl bromide substrates.[4] This latter complex shows no propensity to couple even electronically activated aryl chlorides such as 4-chloroacetophenone. Therefore we were highly surprised to find that mixed PCy_3–$P(OAr)_3$ complexes either formed in situ or preformed show, to the best of our knowledge, the highest activity reported to date in aryl chloride coupling reactions. Preliminary findings of this study are reported below.

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The initial coupling studied was that of the deactivated substrate 4-chloroanisole with phenylboronic acid using the catalyst formed in situ from PCy_3 and the dimeric complex **2a**. As can be seen from the results summarized in Table 1, good to excellent conversions are obtained at 0.01 mol% Pd loadings with K_3PO_4, K_2CO_3, KF, or a mixture of K_3PO_4/KF acting as base (Table 1, entries 2–5, respectively). When cesium carbonate is used then even higher activity results. Under these conditions astonishingly high turnover numbers (TONs) of up to 34000 are seen (Table 1, entries 7 and 8). By comparison, the previous highest reported TONs observed in this reaction were 8000, which was obtained under the same conditions using complex **1** as catalyst, and 12800 when the highly sterically encumbered ligand $PBu(Ad)_2$ (Ad = adamantyl) was employed.[2c,e] Increasing the PCy_3:Pd ratio from 1:1 to 2:1 led to a decrease in catalyst performance. When the orthopalladated phosphite precursor **2a** was replaced by the analogous phosphinite-containing complexes **2b** and then **c**[5] a slight decrease in activity was observed with decreasing π-acidity of the orthopalladated ligand (Table 1, entries 11 and 12).

These results clearly demonstrate that complexes of the simple, inexpensive, easily handled PCy_3 ligand can show excellent activity, providing that the correct choice of palladium precursor is made.[2c,f] "Classical" palladium precursors such as palladium acetate or palladium dibenzylideneacetone are generally very poor in this regard.[2f] Indeed we find that when the coupling is performed with an equimolar mixture of palladium acetate, ligand **3,** and PCy_3, substantially lower activity results (Table 1, entry 13). The use of the preformed complex **4**, which is readily synthesized by reaction of **2a** with an excess of PCy_3 (Scheme 2),[6] gave no advantage over the catalyst formed in situ.

The catalyst formed from **2a** and PCy_3 shows an order of magnitude higher activity than catalysts formed in situ from palladium acetate and either PCy_2(*o*-biphenyl) or $PtBu_3$ (Table 1, entries 15 and 16), both of which have previously been shown to be excellent catalysts for the Suzuki coupling of aryl chlorides.[2h,d] In addition catalysts formed in situ from **2a** and these phosphanes were not as active as that formed from PCy_3 although they were substantially better than those formed in situ from palladium acetate.

It may be anticipated that a catalyst formed in situ from complex **1** and one equivalent of ligand **3** would show essentially identical activity to that formed from **2a** and PCy_3. Indeed an increase in conversion at 17 h is observed compared to that of **1**, but it is not as high as that observed when the phosphite complex **2a** is used as the palladium precursor. Interestingly, it seems as if the added phosphite ligand *decreases* the rate of conversion, as exemplified by the results after two hours compared with those with **1**, but increases the catalyst longevity (Table 1, entries 19–22)—catalyst **1** shows essentially no further activity after 2 h.

Next we investigated the couplings of electronically nonactivated and activated aryl chlorides (Table 1, entries 23–29) and found that extremely high TONs of up to 1000000 were observed. By contrast, to the best of our knowledge, the highest TONs reported for any Suzuki, or indeed any coupling reaction with an aryl chloride substrate is 100000, obtained with complex **1**.[2c]

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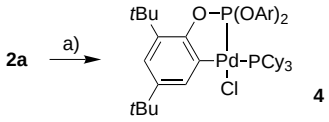
Table 1. Suzuki coupling of aryl chloride substrates.[a]

Entry	ArCl	$ArB(OH)_2$	Catalyst (mol %)	Base	Conv. [%][b]	TON mol product per mol Pd
1	C_6H_4-4-OMe	Ph	**2a** (0.5) + PCy_3 (1.0)	K_3PO_4	100	100
2	C_6H_4-4-OMe	Ph	**2a** (0.005) + PCy_3 (0.01)	K_3PO_4	91	9100
3	C_6H_4-4-OMe	Ph	**2a** (0.005) + PCy_3 (0.01)	K_2CO_3	82	8200
4	C_6H_4–4-OMe	Ph	**2a** (0.005) + PCy_3 (0.01)	KF	51	5100
5	C_6H_4-4-OMe	Ph	**2a** (0.005) + PCy_3 (0.01)	K_3PO_4/KF (1:1)	72	7200
6	C_6H_4-4-OMe	Ph	**2a** (0.005) + PCy_3 (0.01)	Cs_2CO_3	100	10000
7	C_6H_4-4-OMe	Ph	**2a** (0.0005) + PCy_3 (0.001)	Cs_2CO_3	34	34000
8	C_6H_4-4-OMe	Ph	**2a** (0.001) + PCy_3 (0.002)	Cs_2CO_3	68	34000
9	C_6H_4-4-OMe	Ph	**2a** (0.0015) + PCy_3 (0.003)	Cs_2CO_3	99	33000
10	C_6H_4-4-OMe	Ph	**2a** (0.001) + PCy_3 (0.004)	Cs_2CO_3	37	18500
11	C_6H_4-4-OMe	Ph	**2b** (0.0005) + PCy_3 (0.001)	Cs_2CO_3	29	29000
12	C_6H_4-4-OMe	Ph	**2c** (0.0005) + PCy_3 (0.001)	Cs_2CO_3	26	26000
13	C_6H_4-4-OMe	Ph	$Pd(OAc)_2$ (0.1) + **3** (0.1) + PCy_3 (0.1)	Cs_2CO_3	12	120
14	C_6H_4-4-OMe	Ph	**4** (0.001)	Cs_2CO_3	28	28000
15	C_6H_4-4-OMe	Ph	$Pd(OAc)_2$ (0.001) + PCy_2(*o*-biphenyl) (0.002)	Cs_2CO_3	4	4000
16	C_6H_4-4-OMe	Ph	$Pd(OAc)_2$ (0.001) + P*t*Bu_3 (0.002)	Cs_2CO_3	3	3000
17	C_6H_4-4-OMe	Ph	**2a** (0.0005) + PCy_2(*o*-biphenyl) (0.001)	Cs_2CO_3	8	8000
18	C_6H_4-4-OMe	Ph	**2a** (0.0005) + P*t*Bu_3 (0.001)	Cs_2CO_3	11.5	11500
19	C_6H_4-4-OMe	Ph	**1** (0.001)	Cs_2CO_3	6[c]	6000
20	C_6H_4-4-OMe	Ph	**1** (0.001)	Cs_2CO_3	6	6000
21	C_6H_4-4-OMe	Ph	**1** (0.001) + **3** (0.001)	Cs_2CO_3	3[c]	3000
22	C_6H_4-4-OMe	Ph	**1** (0.001) + **3** (0.001)	Cs_2CO_3	20	20000
23	C_6H_4-2-Me	Ph	**2a** (0.00005) + PCy_3 (0.0001)	Cs_2CO_3	10	100000
24	C_6H_4-2-Me	Ph	**2a** (0.0005) + PCy_3 (0.001)	Cs_2CO_3	82	82000
25	C_6H_4-4-Me	Ph	**2a** (0.00005) + PCy_3 (0.0001)	Cs_2CO_3	48	480000
26	C_6H_4-4-COMe	Ph	**2a** (0.00005) + PCy_3 (0.0001)	Cs_2CO_3	88	880000
27	C_6H_4-4-NO_2	Ph	**2a** (0.00005) + PCy_3 (0.0001)	Cs_2CO_3	92	920000
28	C_6H_4-4-COMe	C_6H_4-4-Me	**2a** (0.00005) + PCy_3 (0.0001)	Cs_2CO_3	100	1000000
29	C_6H_4-4-NO_2	C_6H_4-4-Me	**2a** (0.00005) + PCy_3 (0.0001)	Cs_2CO_3	100	1000000

[a] Reaction conditions: ArCl (10 mmol), $ArB(OH)_2$ (15 mmol), base (20 mmol), 1,4-dioxane (30 mL), 100 °C, N_2, 17 h. [b] Conversion to Suzuki product, based on aryl chloride determined by GC (hexadecane standard). [c] Reaction time = 2 h.



Scheme 2. a) PCy_3, 2 equiv per Pd, CH_2Cl_2, reflux 18 h.

Regardless of conditions, the mixed PCy_3–$P(OAr)_3$ systems show higher activity than complex **1**. Given that the rate-determining step in the Suzuki coupling of aryl chloride substrates is generally accepted to be oxidative addition, it is not surprising that catalysts that usually show good activity tend to have strongly electron-donating ligands that maximize electron density on the palladium center.[7] Thus it seems counter-intuitive that the inclusion of a π-*acidic* triarylphosphite ligand, which shows little or no tendency to facilitate the coupling of even activated aryl chlorides,[8] should enhance activity. Plots of conversion against time in the coupling of 4-chloroanisole with phenylboronic acid catalyzed by **1** and the catalyst formed in situ from **2a** and PCy_3 are shown in Figure 1. It is immediately apparent that the inclusion of the triarylphosphite ligand does not increase the rate, it may even lead to a slight decrease, instead it leads to greatly increased catalyst longevity compared with complex **1**. What is the basis of this increased longevity? If it is assumed that the rate-determining step is oxidative addition, then the catalyst spends most of its time "resting" in a zerovalent state.[9] This "resting" state will be stabilized both thermodynamically and kinetically by the reversible coordination of the π-acidic triarylphosphite ligand. Decoordination of the phosphite ligand would give a low-coordinate, electron-rich complex readily able to oxidatively add the aryl chloride substrate and thus enter the catalytic manifold.

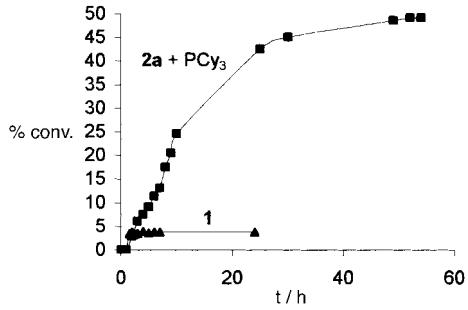


Figure 1. Plots of conversion [%] versus time (*t*) in the coupling of 4-chloroanisole (10 mmol) with phenylboronic acid (15 mmol) catalyzed by **1** (▲) and 0.5 **2a** + PCy_3 (■) (both at 0.001 mol % Pd). Reaction conditions: Cs_2CO_3 (20 mmol), 1,4-dioxane (27 mL), hexadecane internal standard (3.0 mL, 0.034 M in 1,4-dioxane), 100 °C, N_2. Conversions determined by GC.

In summary, catalysts formed from mixtures of the readily available, easily handled and inexpensive ligands **3** and PCy_3 show by far the highest activity yet reported in the Suzuki coupling of aryl chlorides.

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[1] For recent reviews see: a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457 – 2483; b) S. P. Stanforth, *Tetrahedron* **1998**, *54*, 263 – 303; c) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147 – 168.

[2] Recent examples of Suzuki coupling reactions with aryl chlorides: a) L. Botella, C. Nájera, *Angew. Chem.* **2002**, *114*, 187 – 189; *Angew. Chem. Int. Ed.* **2002**, *41*, 179 – 181; b) S.-Y. Liu, M. J. Choi, G. C. Fu, *Chem. Commun.* **2001**, 2408 – 2409; c) R. B. Bedford, C. S. J. Cazin, *Chem. Commun.* **2001**, 1540 – 1541; d) M. R. Netherton, G. C. Fu, *Org. Lett.* **2001**, *3*, 4295 – 4298; e) A. Zapf, A. Ehrentraut, M. Beller, *Angew. Chem.* **2000**, *112*, 4315 – 4317; *Angew. Chem. Int. Ed.* **2000**, *39*, 4153 – 4155; f) M. G. Andreu, A. Zapf, M. Beller, *Chem. Commun.* **2000**, 2475 – 2476; g) D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 9722 – 9723; h) J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9550 – 9561; i) X. Bei, H. W. Turner, W. H. Weinberg, A. S. Guram, *J. Org. Chem.* **1999**, *64*, 6797 – 6803; j) C. Zhang, J. Huang, M. L. Trudell, S. P. Nolan, *J. Org. Chem.* **1999**, *64*, 3804 – 3805; k) A. F. Littke, G. C. Fu, *Angew. Chem.* **1998**, *110*, 3586 – 3587; *Angew. Chem. Int. Ed.* **1998**, *37*, 3387 – 3388.

[3] Ligand **3** is cheaper than triphenylphosphane (source: Aldrich Chemicals catalogue).

[4] D. A. Albisson, R. B. Bedford, S. E. Lawrence, P. N. Scully, *Chem. Commun.* **1998**, 2095 – 2096.

[5] R. B. Bedford, S. L. Welch, *Chem. Commun.* **2001**, 129 – 130.

[6] Complex **4** could not be isolated pure, but rather contained small amounts of dimer **2a**, even when a large excess of PCy_3 was used in the synthesis. ^{31}P NMR spectroscopy the confirmed *cis* disposition of P donors ($^2J_{PP} = 40$ Hz).

[7] Fu and co-workers have recently reported that highly sterically hindered tri*aryl*phosphanes can catalyze couplings of electronically deactivated aryl chlorides (see ref. [2b]), indicating that more subtle effects than brute donor-strength can play an important role.

[8] Beller and Zapf have shown that non-orthometalated complexes of triarylphosphites can couple activated aryl chlorides: A. Zapf, M. Beller, *Chem. Eur. J.* **2000**, *6*, 1830 – 1833.

[9] We are assuming that the catalytic cycle proceeds by a Pd^0/Pd^{II} pathway. This assumption is made on the basis of studies into the activation of palladacyclic precatalysts in Suzuki coupling reactions. See reference [2c] for leading references.

Synthesis of *cis,cis,cis,cis*-[5.5.5.5]-1-Azafenestrane**

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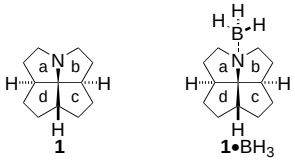
The structural theory of organic chemistry is one of the most highly evolved constructs in natural science. The ability to explain and correctly predict the detailed molecular structure of millions of compounds naturally inspires research to test the limits of the theory. One important subset of this field of investigation probes the extent to which a tetracoordinate carbon atom (bearing all carbon substituents) can deviate from the van't Hoff/Le Bel tetrahedral geometry. The interesting family of compounds called fenestranes[1] comprises molecules with planarizing distortion of the central carbon atom. The magnitude of the distortion is dependent on the size and configuration of the fused rings. Because the parent, unsubstituted fenestranes are low molecular weight hydrocarbons, they are not amenable to X-ray crystallographic analysis. The few X-ray structures on record are of substituted and functionalized derivatives.[2]

We were intrigued by the possibility of replacing one of the ring-fusion carbon atoms with a nitrogen atom to facilitate salt formation and provide an opportunity for X-ray analysis of an unsubstituted fenestrane. In addition to establishing the full molecular structure and the extent of the central carbon planarization, the pyramidal distortion of the nitrogen atom would also be of interest; to our knowledge, no monoazafenestranes have been prepared. An unusual tetraamino [5.5.5.5]fenestrane is known and it exists as an equilibrium mixture of (degenerate) open and closed forms when protonated.[3] We describe herein the first synthesis of an unsubstituted 1-azafenestrane **1** along with the synthesis and X-ray crystallographic analysis of the borane adduct **1**·BH_3.



Analysis of the tetracyclic ring structure of **1** reveals that it contains an embedded pyrrolizidine unit fused to a bicyclo[3.3.0]octane system. In recent years, a large number of pyrrolizidine-based alkaloid natural products in the necine, alexine and australine families have been synthesized in these laboratories.[4] The key strategic operation in all of these syntheses is the tandem [4+2]/[3+2] cycloaddition of nitroalkenes.[5] This process allows for the facile and stereocontrolled construction of highly functionalized nitroso acetals that serve as precursors for pyrrolizidines upon catalytic hydrogenolysis.

The application of the tandem cycloaddition strategy to the synthesis of **1** is outlined in Scheme 1. Constructing the core of **1** requires the creation of one of the four rings in the tandem [4+2]/[3+2] process by cycloaddition of a C_2 dienophile (butyl vinyl ether (**3**)) with a cyclopentenyl nitro diene **2** (ring C) bearing the suitable dipolarophilic tether. The tetracyclic nitroso acetal **4** is then poised for hydrogenolytic unmasking to a tricyclic pyrrolizidine (third ring, c) which should undergo spontaneous lactam formation (→**5**; fourth ring, d) from the appended carboxylic ester. Thus, three of the four rings of [5.5.5.5]-1-azafenestrane can be assembled in two chemical manipulations. Two-stage reduction of the α-hydroxy lactam **5** leads to the target azafenestrane **1**. This approach allows for a modular synthesis of fenestranes containing rings of different size at various positions. With regard to the configuration at the ring fusions, only one relationship was expected to be variable. In the [4+2] process, the approach of the dienophile can take place on the two diastereotopic faces of the nitroalkene to create *cis* and *trans* isomers. The [3+2] process is formally in the spiro mode family[6] and thus is expected to

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