Suzuki Cross-Couplings on Aryl (Heteroaryl) Bromides and Chlorides with Bulky Aliphatic Phosphines/Pd(0)-Triolefinic Macrocyclic Catalyst

Marcial Moreno-Mañas,*[1] Roser Pleixats,* Anna Serra-Muns

Department of Chemistry, Universitat Autònoma de Barcelona, Cerdanyola, 08193 Barcelona, Spain
Fax +34(9)35811265; E-mail: roser.pleixats@uab.es

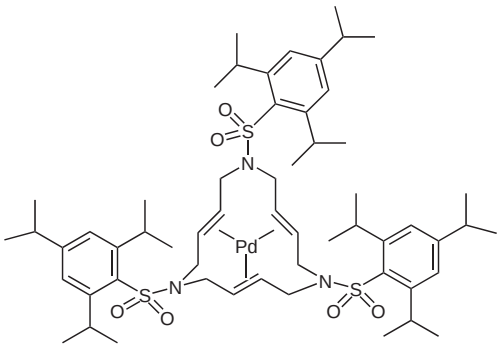
Received 23 March 2006

Dedicated to Prof. Richard Heck in recognition of his contribution to chemistry

Abstract: The combination of a bulky aliphatic phosphine, e.g. tricyclohexylphosphine or the tetrafluoroborate salt of tri-*tert*-butylphosphine, with the Pd(0) complex of a 15-membered triolefinic macrocycle is an excellent catalyst for the Suzuki cross-coupling of aryl and heteroaryl bromides and chlorides. The palladium can be recovered in the form of the initial complex.

Key words: macrocycle, olefin complex, catalysis by palladium, recovery

Suzuki cross-couplings have become a fundamental tool in synthetic methodology.[2] However, several problems are associated with the use of palladium(0)-catalyzed reactions. Thus, iodides are more active than bromides and chlorides. Recent progress has been made in the design and testing of catalysts that permit the use of the more economically friendly chlorides.[3] The use of sterically hindered and highly nucleophilic or basic aliphatic phosphines as ancillary ligands[4] has had a significant impact upon the performance of the catalysts, making the activation of aryl chlorides possible.



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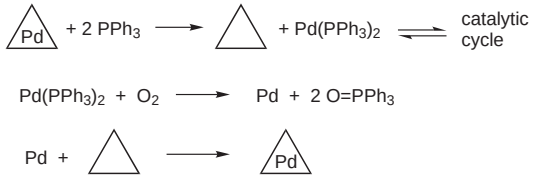


Scheme 1 Structure of complex **1** and role of the macrocycle and its complex in the telomerization of butadiene (ref. 8).

SYNLETT 2006, No. 18, pp 3001–3004
Advanced online publication: 04.08.2006
DOI: 10.1055/s-2006-948173; Art ID: S03806ST

It is assumed that this type of ligand promotes the in situ formation of coordinatively unsaturated PdL_n (n = 1, 2) species by sterically driven dissociation. In addition, due to their high donicity they are able to stabilize monoligated Pd(0) species, which function as the actual highly reactive catalytic species.[4]

We have reported the preparation and properties of macrocyclic complexes of type **1**. The free-of-metal macrocycles are easy to prepare and are excellent coordinating agents for Pd(0) and Pt(0) by the three olefins.[5] These macrocycles are catalysts or precatalysts in a number of Pd(0)-catalyzed organic reactions, and frequently they can be recovered. Thus, complex **1** is active in some selected Suzuki cross-couplings between activated partners.[6] No attempts were made to recover **1**. However, a polymeric version (polystyrene-grafted catalyst) was recovered and reused without apparent loss of activity.[6] Activated and non-activated aryl iodides gave good Suzuki couplings under catalysis by silica hybrids containing macrocyclic complexes covalently anchored.[7] Although these results were promising, they were limited in that only aromatic iodides showed activity in the cross-couplings, and preparation of the solid materials is painstaking.

The mechanisms by which these complexes act seem to be diverse. Thus, complex **1** is not active in telomerization of butadiene in the presence of alcohols. However, high activity is secured if two moles of triphenylphosphine per mol of palladium are added.[8] The subsequent mechanistic study revealed that the actual catalyst is $Pd(PPh_3)_2$, directly generated in high concentration by transfer of Pd(0) from the macrocyclic complex. Precipitation of Pd(0) as palladium black is prevented by formation of the complex. In summary, the macrocycle recovers the palladium.[8b]

In contrast, the macrocyclic complex is the direct catalyst in Mizoroki–Heck reactions with arenediazonium tetrafluoroborates as electrophilic partners, the complex being efficiently recovered.[9]

Other catalytic applications of complexes of type **1** are the hydroarylation of alkynes in ionic liquids,[10] and the application of macrocycle-based polypyrrole modified electrodes in the Suzuki cross-coupling.[11]

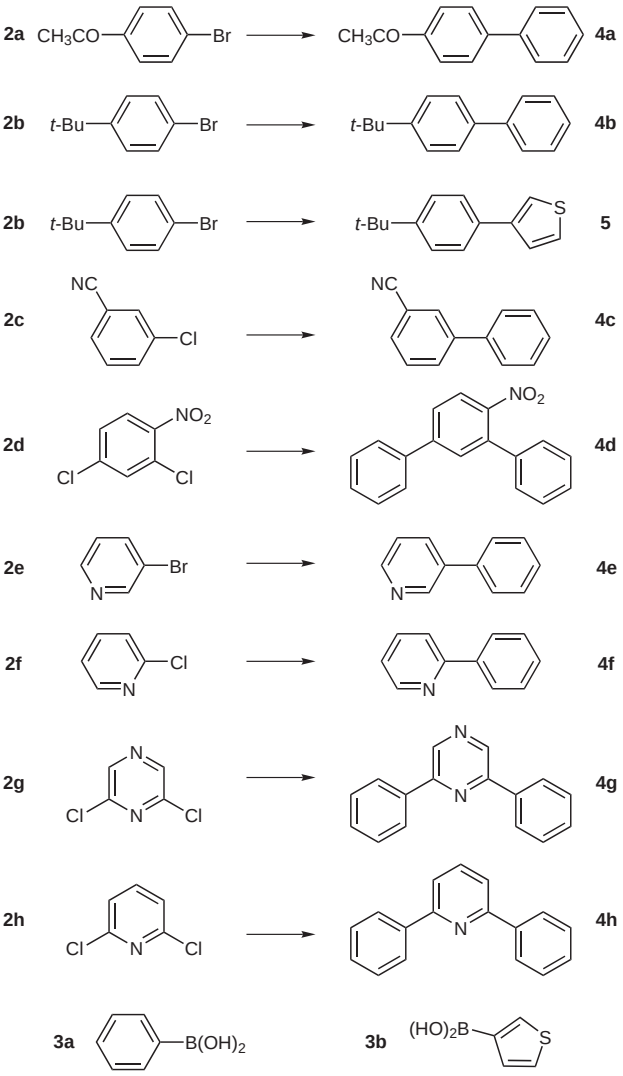
With these precedents in mind we considered the possibility of using the strategy devised in Scheme 1 to recover

palladium in Suzuki cross-couplings. Highly nucleophilic and sterically demanding phosphines have been recommended for Suzuki and other couplings.[3,4] Therefore, we decided to study the combination of macrocyclic complex **1** and phosphines such as $P(Cy)_3$ and $P(t\text{-}Bu)_3$ or, even better, its tetrafluoroborate.[3a,12,13] Spectral and analytical data of triolefinic complex **1** has been reported.[14] Although no crystals of **1** could be obtained, the X-ray structure and full analysis of very related azamacrocyclic triolefinic complexes was later published.[15]

First we studied the reaction of 4-bromoacetophenone (**2a**) with phenylboronic acid (**3a**) using the catalytic system **1**/PCy_3 (Scheme 2, Table 1). Toluene was superior to THF or dioxane and among the bases studied (K_3PO_4 + KF, Cs_2CO_3, and K_2CO_3), cesium carbonate gave the best results. An attempt was made to recover the catalyst by column chromatography. Thus, the reaction of entry 1 (Table 1) was repeated targeting the isolation of **1** at the end of the process. This was achieved with an 80% yield of recovery, eluting the complex with a mixture hexane–ethyl acetate 94:6. This recovered complex was used in a second run under the same conditions affording a 100% conversion of **2a** to **4a** after 22 hours. Then we found that tri(*tert*-butyl)phosphine was better than tricyclohexylphosphine, but due to the low quality of the commercially available tri(*tert*-butyl)phosphine,[16] we decided to use its salt with tetrafluoroboric acid. In summary, the chosen conditions for other organic halides were refluxing anhydrous and degassed toluene, cesium carbonate (2 equiv), macrocyclic complex **1**, and $P(t\text{-}Bu)_3{\cdot}HBF_4$.[12] Nevertheless, in several cases a higher boiling point solvent such as xylene was required in order to achieve higher conversions in reasonable times. The results are collected in Table 1 and in Scheme 2. Every reaction was performed twice. The first, on smaller scale to determine the optimal time at highest conversion of aryl halide **2** by means of GLC in the presence of an internal standard (hexadecane). Then the reaction was performed as indicated in the experimental section under the conditions of Table 1.

A variety of aryl bromides were active as well as chlorides **2c**,**d**. In the heterocyclic series, 3-bromopyridine (**2e**) performed well. However 3-chloropyridine was inert. More activated chlorides such as **2f**–**h** gave excellent results, even when a double substitution was required. Full conversions of the heteroaryl halides were achieved, lower yields of the isolated coupling products being due to the purification process.

The reaction between **2b** and **3a** described in entry 2 was followed by ^{31}P NMR. After one hour at reflux temperature two signals at $\delta = 65$ (attributed to the corresponding phosphine oxide) and 87 ppm were observed. This signal, which was assigned to a $Pd(P(t\text{-}Bu)_3)_2$ species by comparison with literature data,[12,17] disappeared from the crude mixture after four hours at reflux. In this case only the signal at $\delta = 65$ ppm was observed and the ^1H NMR spectrum showed the presence of complex **1**.



Scheme 2 Suzuki couplings catalyzed by complex **1**. For experimental conditions see Table 1.

Although some cases of room temperature Suzuki cross-couplings of aryl chlorides with palladium/bulky phosphines exist,[12,18] most of the reported works for aryl and heteroaryl chlorides[19] involve some heating of the reaction mixture. Beller[20] has shown that 1,6-diene palladium(0)–monophosphine complexes are also efficient catalysts for Suzuki coupling of aryl chlorides in THF at 100 °C. Our system based on macrocyclic complex **1** offers the possibility of recovery of the metal. Catalyst recovery by supporting the macrocycle in organic or inorganic polymers, an alternative that we have also undertaken,[6,7] requires the previous preparation of the heterogeneous version and would need also the addition of aliphatic bulky phosphines to accomplish the Suzuki coupling with aryl chlorides.

In summary, the use of macrocyclic complex **1** together with a sterically hindered σ-donor phosphine allows the efficient Suzuki cross-coupling with aryl bromides and chlorides. The macrocycle prevents the precipitation of palladium black and allows the recovery of the metal.

Table 1 Suzuki Cross-Couplings on Aryl (Heteroaryl) Bromides and Chlorides

Entry	Ar–X	**3**	**1** (mol%)	HP (*t*-Bu)$_3$BF$_4$ (mol%)[a]	Time (h)	**4** or **5** (%)[c]
1	**2a**	**3a**	0.5	0.8[b]	18	**4a** (85)
2	**2b**	**3a**	0.5	1.0	5	**4b** (82)
3	**2b**	**3b**	1.0	2.0	14	**5** (83)[d]
4	**2c**	**3a**	1.0	2.0	48	**4c** (68)
5	**2d**	**3a**	2.0	4.0	120	**4d** (76)[d,e]
6	**2e**	**3a**	0.5	1.0	5	**4e** (73)
7	**2f**	**3a**	1.0	2.0	48	**4f** (41)
8	**2g**	**3a**	2.0	4.0	60	**4g** (50)[d]
9	**2h**	**3a**	2.0	4.0	72	**4h** (98)[d]

[a] HP(*t*-Bu)$_3$BF$_4$ was used unless otherwise stated; Cs_2CO_3 (2 equiv) and refluxing toluene were the base, the solvent and the temperature; [**2a**–**h**] ca. 0.4×10^{-3} M.
[b] PCy_3 was used.
[c] Isolated yields.
[d] Refluxing xylene.
[e] After 3 d at reflux temperature one more equiv of **3a** was added and the mixture was refluxed for 2 d more.

Experimental Section

Preparation of 4b – General Procedure

Phenylboronic acid (1.05 g, 8.4 mmol), macrocycle **1** (36 mg, 0.032 mmol), tri(*tert*-butyl)phosphine tetrafluoroborate (19 mg, 0.063 mmol) and anhyd Cs_2CO_3 (4.22 g, 13 mmol) were added into a Schlenk flask. Three vacuum/argon cycles were made. *p*-Bromo-*tert*-butylbenzene (**2b**, 1.12 mL, 6.5 mmol) and degassed anhyd toluene (20 mL) were added. This solution was stirred for 5 h at reflux temperature under argon atmosphere and then it was maintained overnight at r.t. The solution was filtered and the organic phase was washed with a sat. NH_4Cl solution, with H_2O, and dried over Na_2SO_4. The solvent was evaporated to obtain a yellow solid which was purified by flash-chromatography (silica gel) with hexane to afford 1.2 g of **4b** (82% yield); mp 48–50 °C (lit.[21] 51–52 °C). IR (ATR): 3034, 2959, 1598, 1484, 1360 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 7.35–7.67 (m, 9 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 31.5, 34.7, 125.8, 126.9, 127.1, 127.2, 128.8, 138.5, 141.2, 150.4.

Physical Data of Products 4 and 5

Compound **4a**: mp 121 °C (lit.[22] 120.5 °C). IR (ATR): 2999, 1676, 1599, 1402, 1357, 1259 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.64 (s, 3 H), 7.37–7.51 (m, 3 H), 7.61–7.65 (m, 2 H), 7.69 (d, *J* = 8.7 Hz, 2 H), 8.04 (d, *J* = 8.7 Hz, 2 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 26.8, 127.3, 127.4, 128.4, 129.0, 129.1, 136.0, 140.0, 145.9, 197.9.

Compound **4c**: oil; (lit.[23] mp 49.1 °C). IR (ATR): 3032, 2229, 1580, 1476, 1451 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$):[24] δ = 7.42–7.65 (m, 7 H), 7.80–7.86 (m, 2 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 113.0, 118.9, 127.2, 128.5, 129.2, 129.6, 130.8, 131.6, 138.9, 142.5. MS (EI): *m/z* = 179.10 [M$^+$].

Compound **4d**:[25] oil. IR (ATR): 3061, 1519, 1350, 773 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.36–7.53 (m, 8 H), 7.62–7.71 (m, 4 H), 7.98 (d, *J* = 8.4 Hz, 1 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 125.1, 126.7, 127.5, 128.1, 128.4, 128.7, 128.8, 129.3, 130.8, 137.3, 137.8, 138.9, 145.6, 148.1. MS (EI): *m/z* = 275.05 [M$^+$].

Compound **4e**: oil. IR (ATR): 3030, 1581, 1472, 1047, 1006 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$):[26] δ = 7.34–7.61 (m, 6 H), 7.88 (ddd, *J* = 4.1, 2.3, 1.6 Hz, 1 H), 8.59 (dd, *J* = 4.8, 1.4 Hz, 1 H), 8.85 (d, *J* = 2.1 Hz, 1 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 123.6, 127.2, 128.2, 129.2, 134.4, 136.7, 137.9, 148.4, 148.6.

Compound **4f**:[27] oil. IR (ATR): 3059, 1579, 1563, 1467, 1449, 1424 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.19–7.25 (m, 1 H), 7.38–7.51 (m, 3 H), 7.71–7.74 (m, 2 H), 7.97–8.00 (m, 2 H), 8.68–8.71 (m, 1 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 120.7, 122.2, 127.0, 128.9, 129.0, 136.8, 139.5, 149.8, 157.6. MS (EI): *m/z* = 155.10 [M$^+$].

Compound **4g**: mp 84–86 °C (lit.[28] 91.0–92.5 °C). IR (ATR): 3034, 1518, 1416, 1277, 1014 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.47–7.59 (m, 6 H), 8.16 (dd, *J* = 8.2, 1.8 Hz, 4 H), 8.98 (s, 2 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 127.2, 129.1, 130.1, 136.7, 140.1, 151.7. MS (EI): *m/z* = 232.05 [M$^+$].

Compound **4h**: mp 79–80 °C (lit.[29] 80–81 °C). IR (ATR): 3057, 2961, 1561, 1452, 1268 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.40–7.54 (m, 6 H), 7.69–7.72 (m, 2 H), 7.83 (dd, *J* = 8.8, 6.8 Hz, 1 H), 8.15–8.18 (m, 4 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 118.8, 127.1, 128.8, 129.1, 137.6, 139.6, 156.9.

Compound **5**: mp 68–76 °C (lit.[30] 77.0–78.5 °C). IR (ATR): 2958, 2901, 1536, 1369, 1202 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 7.40–7.48 (m, 5 H), 7.58 (d, *J* = 8.6 Hz, 2 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 31.5, 34.7, 119.9, 125.8, 126.1, 126.3, 126.5, 133.2, 142.4, 150.2.

Acknowledgment

Financial support from MCyT of Spain (Project 2002BQU-04002), MEC of Spain (Project CTQ2005-04948/BQU and predoctoral scholarship to A.S.M.) and Generalitat de Catalunya (Projects 2001SGR00181 and 2005SGR00305) is gratefully acknowledged.

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