Tetrahedron 68 (2012) 2135–2140

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Few unexpected results from a Suzuki–Miyaura reaction

Elise Salanouve [a,b], Pascal Retailleau [c,*], Yves L. Janin [a,b,*]

[a] Institut Pasteur, 28 rue du Dr. Roux, F-75724 Paris cedex 15, France
[b] CNRS UMR 3523, 28 rue du Dr. Roux, F-75724 Paris cedex 15, France
[c] Service de Cristallochimie, Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, 1 avenue de la Terrasse, F-91198 Gif-sur-Yvette cedex, France

ARTICLE INFO

Article history:
Received 4 November 2011
Received in revised form 3 January 2012
Accepted 11 January 2012
Available online 16 January 2012

Keywords:
Palladacycle
Palladium(IV)
CH activation
C–C coupling
Cross-coupling

ABSTRACT

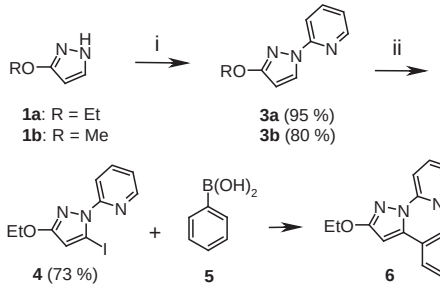
In the course of the synthesis of original anti-infectious compounds we focused on the palladium-catalyzed Suzuki–Miyaura aryl–aryl coupling reaction between 2-(3-ethoxy-5-iodo-1*H*-pyrazol-1-yl) pyridine and phenylboronic acid. A study of the reaction products obtained under different conditions (various ligands and solvents), not only provided us with insights to optimize this reaction but also with few side compounds, resulting from CH activation, along with the unexpected bis(3-ethoxy-1-(pyridin-2-yl)-1*H*-pyrazol-5-yl)palladium. Stochiometric experiments with this remarkably stable biscyclopalladated reagent and phenylhalides pointed out the occurrence of aryl–aryl coupling, possibly via palladium IV intermediates.

1. Introduction

Following our work on the preparation of libraries of new chemical entities in the pyrazole series,[1–6] screening campaigns resulted in the identification of few derivatives of potential biological interest. This led to renewed effort to design simple preparations of analogues of these compounds and, in the present instance, to focus on the model preparation of 2-(3-ethoxy-5-phenyl-1*H*-pyrazol-1-yl)pyridine (**6**). The synthesis of **6** was planned via a Suzuki–Miyaura aryl–aryl coupling[7–9] of the 5-iodinated pyrazole building block **4** and phenylboronic acid (**5**).

2. Results and discussion

As shown in Scheme 1, to avoid a low 11% overall yield we encountered in our previous preparation of compound **4**,[5] we undertook the pyridylation of 3-alkoxypyrazole **1a**,**b** with 2-fluoropyridine (**2**). Selective N-arylations of **1a**,**b** were achieved at 140 °C in 80–95 % yield using 2-fluoropyridine, caesium carbonate in acetonitrile. Treatment of the resulting 1-pyridyl-3-ethoxypyrazole **3a** with butyllithium followed by the addition of iodine then gave the 5-iodinated building block **4** in a much improved 60% overall yield.



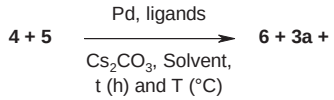
Scheme 1. i: 2-FC_5H_4N (**2**),Cs_2CO_3, MeCN, 140 °C ii: (a) BuLi, THF, −78 °C, (b) I_2, THF.

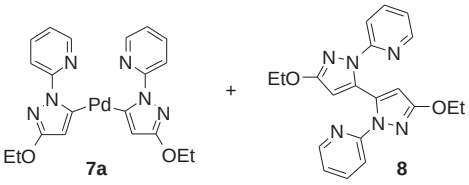
Table 1 summarizes up few Suzuki–Miyaura coupling trials between compound **4** and phenylboronic acid (**5**). Entry 1 describes our previously reported results for comparison purposes.[5] A change of solvent for a dioxane/water mixture with the same catalyst was not successful. The use of the combination of palladium acetate and XPhos depicted in entries 2 and 3 were more successful. Most unexpectedly, from the 5% of palladium used in the assay described in entry 2, we could isolate 4% of the bis(1-(pyridin-2-yl)-1*H*-pyrazol-5-yl)palladium II complex (**7a**) along with 51% of the target compound **6** and 40% of the reduced material **3a**. The ^{1}H NMR and LC/MS analysis of reaction samples also pointed out the occurrence of the dimeric compound **8** although we could not properly separate it from phosphine oxide derivatives in this trial. Finally, in a series of trials in DMF (entries 3–5) we could point out that a high temperature was detrimental

* Corresponding authors. Tel.: +33 (0) 145688297; fax: +33 (0) 1456888404; e-mail address: yves.janin@pasteur.fr (Y.L. Janin).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.01.019

Table 1
Coupling trials of compounds **4** and **5**[a]



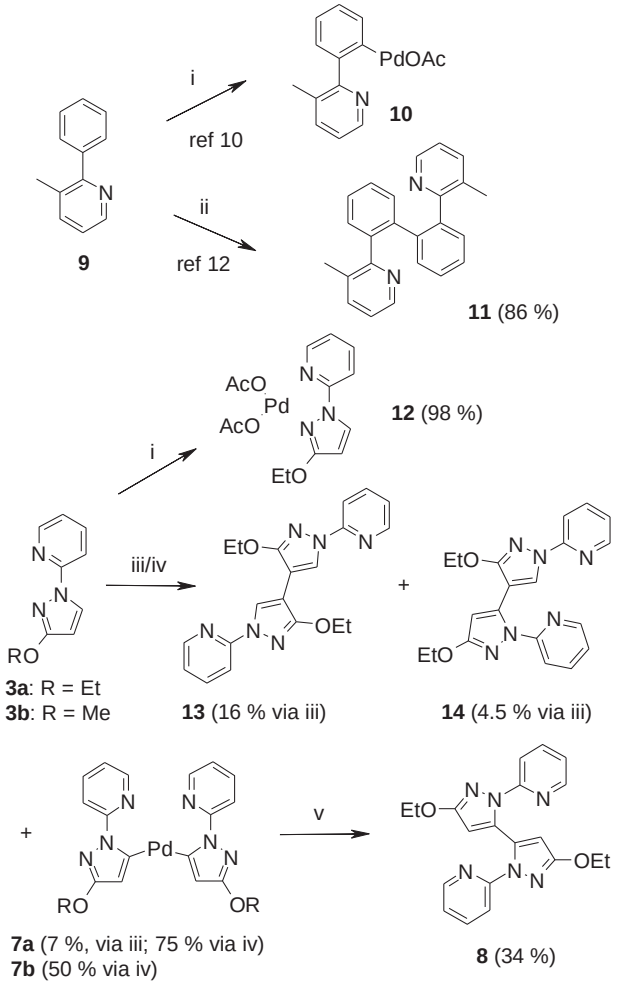


	Catalyst	Solvent	T/t[b]	%**6**	%**3a**	%**7a**	%**8**
1	$PdCl_2$, dppf	*n*-PrOH/H_2O 1:1	130/1.5	39	20	—	—
2	$Pd(OAc)_2$, 2XPhos	Dioxane/H_2O 3:1	100/12	51	40	4	<5
3	$Pd(OAc)_2$, 2XPhos	DMF	160/3	52	7	n.i.	<5
4	$Pd(OAc)_2$, 2XPhos	DMF	140/3	62	6	n.i.	<5
5	$Pd(OAc)_2$, 2XPhos	DMF	120/40	80	9	n.i.	—

[a] Isolated yield.
[b] In °C and hours.

to the reaction yield as the coupling reaction stalled and the corresponding starting material recovered. However, at 120 °C, the target 5-phenyl derivative **6** was obtained in 80% yield. We suggest that a temperature-dependant catalyst deactivation, leading to compound **7a**, is the source of this effect. A 120 °C temperature is appearing to be optimal in balancing this deactivation and the coupling reaction. At 100 °C, the latter turned out to be exceedingly slow (50% conversion in 3 days).

Beyond this optimization, the isolation of the uncommonly stable palladium derivative **7a** was of interest in itself. A literature search pointed out another case of a stable pyrazole-bearing palladacycle[10] and the remarkable chemistry of 2-phenylpyridine Pd^{II} derivatives involving reaction intermediates related to compound **7a**.[11–16] Indeed, the preparation of the cyclopalladated complex **10** (existing mostly as a bimetallic species[17]) was easily achieved by CH activation of 2-phenylpyridine **9** using palladium acetate at room temperature.[11] Moreover, still at room temperature and under catalytic conditions, the addition of oxone to this reaction gave 86% of compound **11**, resulting from the palladium-catalyzed oxidative dimerization of compound **9**.[13] Interestingly, the chemical behaviour of compound **3a** markedly differed from 2-phenylpyridine **9**. In our case, the reaction of **3a** with palladium acetate only gave the unmistakable liganded palladium salt **12** in a 98% yield. We also tried to achieve the oxidative dimerization of compound **3a** with oxone in the presence of catalytic amount of palladium acetate in isopropanol.[13] No reaction occurred at room temperature and—despite the inherent explosion risk of heating an oxidizer in an organic solvent—raising the reaction temperature to 110 °C in a microwave oven had little effect. We suggest that, in the case of **3a**, a strong chelation by the pyridine as well as the pyrazole nitrogens remove any carbon–hydrogen bond from the reach of the palladium atom. This could also explain why, although carbon 4 or 5 pyrazole CH arylation reactions have been reported,[18–24] our attempts to achieve a catalytic C-5 arylation of compound **3a** have so far met limited success. For instance, heating a stoichiometric mixture of **3a** and palladium acetate, in DMF at 160 °C in the presence of caesium carbonate gave the two other possible dimers **13** and **14** in 16% and 4.5% yield, respectively, along with 7% of palladium complex **7a** as well as 43% of unreacted material **3a**. The cyclopalladated derivatives **7a**,**b** were also obtained in much improved 75% and 50% yield via the deprotonation of **3a**,**b**, followed by the addition of a palladium acetate solution (conditions iv in Scheme 2).[25]



Scheme 2. i: $Pd(OAc)_2$, MeOH, 25 °C, 12 h. ii: 5% $Pd(OAc)_2$, oxone, *i*-PrOH, 25 °C. iii: 1 equiv $Pd(OAc)_2$, Cs_2CO_3, DMF, MW, 160 °C. iv: (a) BuLi, THF, −78 °C, (b) $Pd(OAc)_2$, THF. v: NCS, DMF 20 °C reflux.

Few attempts to achieve a simple Pd^{II} to Pd^0 reductive elimination with compound **7a**, to prepare the dimer **8** failed. On the other hand, as previously reported for 2-phenylpyridine-based cyclopalladated derivatives,[14] the oxidation of compound **7a** with *N*-chlorosuccinimide followed by heating at 130 °C led to an adequate amount of **8**. Interestingly, none of the other two possible dimers **13** and **14** were detected in this experiment. Finally, if compound **7a** failed to provide monocrystals suitable for X-ray diffraction, the methoxy analogue **7b** secured the solid state structure depicted in Fig. 1. This bispalladacycle thus adopts a symmetrical planar conformation, with an average carbon–palladium bond length of 1.97 Å and a nitrogen–palladium bond length of 2.15 Å.

Few experiments were conducted in order to investigate the reactivity of compound **7a** and attempt to explain the occurrence of the side compounds described in Table 1. Heating at up to 190 °C equal amount of complex **7a**, the 5-iodinated derivative **4** and caesium carbonate in DMF gave the reduced compound **3a** in 48% yield along with traces amount of the dimer **8**. Far more interestingly, 86% of the cyclopalladated compound **7a** were recovered from this trial. This experimental fact led us to suspect a palladium II-based catalytic process leading to the reduction of compound **4**. Accordingly, as depicted in Table 2 few reactions were conducted with compound **7a**. Heating at 160 °C a mixture of **7a**, 3 equiv of the less hindered iodobenzene and caesium carbonate in DMF (entry 1) gave compound **6** in a 22% yield along with 33% of unreacted **7a**, less than 6% of the reduced material **3a** as well as 20% of the volatile biphenyl (**15**). A trial with 1.5 equiv of phenylboronic

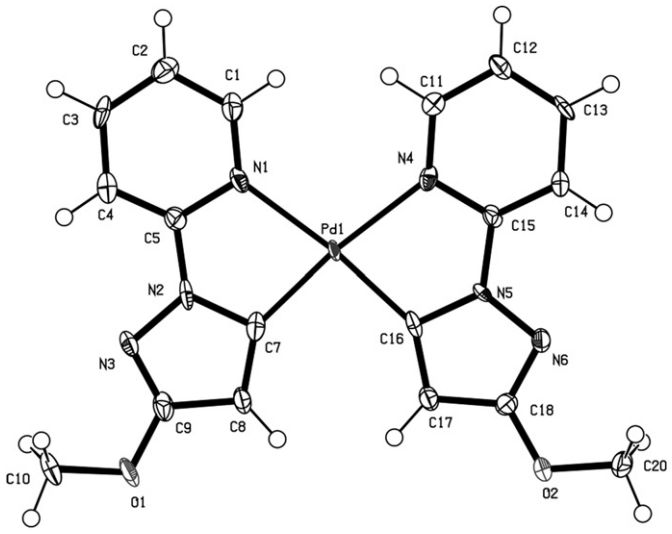
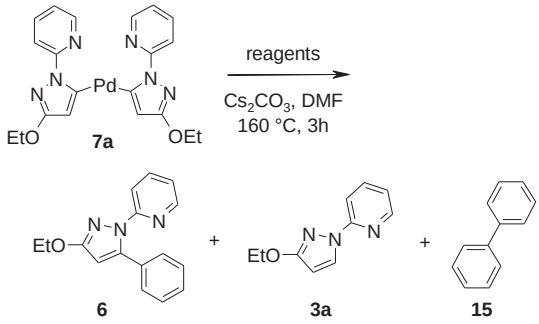


Fig. 1. X-ray derived ORTEP diagram of the biscyclopalladated compound **7b**.

Table 2
Reactivity of **7a** with PhX or $PhB(OH)_2$[a]



	Reagents	%**6**	%**3a**	%**15**	%**7a**
1	PhI[b]	21	<6	20	33
2	PhI[c]+$PhB(OH)_2$[c]	17	12	50	28
3	$PhB(OH)_2$[b]	<5	<5	—	>90
4	PhBr[b]	46	<5	24	6
5	PhCl[b]	—	<3	—	84

[a] Isolated yield.
[b] 3 equiv.
[c] 1.5 equiv.

acid and 1.5 equiv of iodobenzene (entry 2) resulted in 34% of **6**, 28% of unreacted **7a**, 12% of **3a** and an increased 50% of biphenyl (**15**). Slightly more unexpectedly, a trial with only phenylboronic acid under the same conditions (entry 3) actually led to detectable amount of compounds **6** and **3a**, although 90% of the cyclopalladated complex **7a** was recovered and the occurrence of phenol was noted. Remarkably, the arylation reaction with bromobenzene (entry 4) was far more efficient as a 46% yield of compound **6** was isolated (close to a theoretical maximum of 50% ?) along with traces of the reduced **3a**, 20% of biphenyl **15** and 6% of the starting material **7a**. In this somewhat cleaner reaction, we could also detect traces of the dimer **13**. Finally, no arylation with chlorobenzene was detected (entry 5) and the occurrence of less than 3% of **3a** was observed. All our attempts to isolate the water-soluble components of these reaction trials have, so far, only pointed out their instability.

3. Conclusion

This report is describing few side reactions involving nitrogen-bearing chelating substrates, such as **3a** or **4** and palladium. It is also providing insights in the behaviour of the biscyclopalladated compound **7a**, which markedly differs from other *N*-pyridylpyrazole palladium complexes previously suggested[26,27] or characterized.[10,28] Indeed, we are reporting here an instance of aryl–aryl coupling between bromo or iodobenzene and a cyclopalladated substance. What remains to be fully demonstrated is whether products **6** and **8** are occurring via an oxidative addition of iodobenzene on a palladium II entities to give a palladium IV intermediate, or by other more conventional mechanisms.[29–31] Reviews are actually describing cases where such oxidative insertions were suggested.[32–36] For that matter, recent work have reported palladium III reaction intermediates for, arguably, related CH oxidation reactions[16,37] and bis(2-pyridylphenyl)palladium IV sulfinate was demonstrated to undergo a reductive elimination.[38] The fact that phenyl bromide reacts more efficiently than phenyliodide with the biscyclopalladated compound **7a** to give compound **6** (Table 2 entry 1 and 4) is reminiscent of another case where a palladium IV intermediate is suspected.[39] Concerning the occurrence of biphenyl **15**, such palladium-catalyzed Ullmann reaction is far more documented.[40–42] In conclusion, we hope that all theses results are providing an original direction for the design of new (and remarkably stable) metallic entities potentially useful as tool for mechanistic studies.[31]

4. Experimental section

4.1. General

A Biotage initiator 2 microwave oven was used for reactions mentioning such heating method. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, respectively. Shifts (δ) are given in parts per million with respect to the TMS signal and coupling constants (J) are given in hertz. Column chromatographies were performed either on Merck silica gel 60 (0.035–0.070 mm) or neutral alumina using a solvent pump and an automated collecting system driven by a UV detector set to 254 nm unless required otherwise. Sample deposition was carried out by absorption of the mixture to be purified on a small amount of the solid phase followed by its deposition of the top of the column. The low resolution mass spectra were obtained on an Agilent 1100 series LC/MSD system using an atmospheric electrospray ionization system and the high resolution mass spectra (HRMS) were obtained using a Waters Micromass Q-Tof with an electrospray ion source.

*4.1.1. 3-Methoxy-1H-pyrazole (**1b**).* This compound was prepared in the two following steps. Step 1: dimethylmethoxymethylenemalonate (54.40 g, 0.31 mol) and hydrazine monohydrochloride (22.04 g, 0.32 mol) were refluxed in ethanol (600 mL) for 16 h. The solvents were removed under reduced pressure and the residue was dispersed in water (500 mL). The precipitate was filtered, washed with 1N hydrochloric acid. The filtrate was cautiously made basic with solid potassium carbonate, this was extracted with ethyl acetate and the organic layer was washed with a saturated solution of sodium hydrogencarbonate, brine, dried over sodium sulfate and concentrated to dryness. The resulting residue was recrystallized in toluene (130 mL) to yield methyl 3-methoxy-1*H*-pyrazole-4-carboxylate (8.51 g, 17%). Mp=125 °C. ^1H ($CDCl_3$): 3.83 (s, 3H); 4.02 (s, 3H); 7.92 (s, 1H); 10.25 (br s, 1H). ^{13}C ($CDCl_3$): 51.3; 56.6; 99.3; 134.3; 162.8; 163.3. HRMS: calcd for $C_6H_8N_2O_3$+H: 157.0613. Found: *m*/*z*, 157.0620. Step 2: the intermediate ester (3.3 g, 0.021 mmol) was dispersed in 6N hydrochloric acid (40 mL). This was heated to reflux until the end of the carbon dioxide evolution (1 h in the present case). The aqueous phase was diluted in water, slowly made basic by the addition of sodium hydrogencarbonate, saturated with sodium chloride and

extracted with ethyl acetate four times. The organic phase was washed with a 1N solution of sodium hydrogencarbonate once, with brine once, dried over sodium sulfate and concentrated to dryness to yield compound **1b** as a volatile oil (1.25 g, 60%). ^{1}H ($CDCl_3$): 3.92 (s, 3H); 5.73 (d, 1H, J=2.5 Hz); 7.37 (d, 1H, J=2.5 Hz). ^{13}C ($CDCl_3$): 56.6; 89.6; 130.4; 164.4.

4.2. General method for the preparation of 3a,b

In a 450 mL pressure steel reactor the considered 3-alkoxypyrazole (0.044 mol), caesium carbonate (20.2 g, 0.062 mol), 2-fluoropyridine (6.02 g, 0.062 mol) and acetonitrile (145 mL, dried over 4 Å molecular sieve) were heated at 140 °C for 72 h. After cooling, the suspension was diluted in water and extracted with ethyl acetate. The organic layer was washed with water, brine and concentrated to dryness to yield pure compounds **3a**,**b** as oils in the yield mentioned in the text.

*4.2.1. 2-(3-Ethoxy-1H-pyrazol-1-yl)pyridine (**3a**).* Spectroscopic data identical with the reported one.[5]

*4.2.2. 2-(3-Methoxy-1H-pyrazol-1-yl)pyridine (**3b**).* ^{1}H ($CDCl_3$): 4.01 (s, 3H); 5.93 (d, 1H, J=2.7 Hz); 7.10 (m, 1H); 7.76 (m, 1H); 7.83 (m, 1H); 8.35 (m, 1H); 8.38 (d, 1H, J=2.7 Hz). ^{13}C ($CDCl_3$): 56.3; 94.6; 111.4; 120.2; 128.3; 138.5; 147.9; 151.4; 165.5. HRMS: calcd for $C_9H_9N_3O$+H: 176.0824; found: 176.0804.

*4.2.3. 2-(3-Ethoxy-5-iodo-1H-pyrazol-1-yl)pyridine (**4**).* Under an argon atmosphere, a stirred solution of compound **6a** (3.5 g, 18.5 mmol) in dry tetrahydrofuran (35 mL, dried over 4 Å molecular sieve) was cooled to −78 °C. A 2 M *n*-butyllithium solution in cyclohexane (11.1 mL, 22.2 mmol) was slowly added with a syringe. The yellow mixture was then stirred at −78 °C for 40 min. The resulting reddish solution was quenched with a solution of iodine (7.04 g, 27.7 mmol) dissolved in dry tetrahydrofuran (25 mL, dried over 4 Å molecular sieve) and then allowed to warm to room temperature. This was treated with a sodium disulfite solution and extracted with ethyl acetate. The organic phase was washed with water, brine, dried over magnesium sulfate and the solvent was removed under vacuum to give a yellow oil. This was purified by a chromatography over silica gel (cyclohexane/ethyl acetate 6:1) to yield compound **4** (4.62 g, 79%) as a light yellow powder. Its spectroscopic data were identical with the reported one,[5] although one ^{13}C signal had slipped our attention; here is the corrected spectra: ^{13}C ($CDCl_3$): 14.7; 64.8; 77.7; 106.4; 116.8; 121.7; 138.2; 147.3; 152.3; 165.6. Another chromatography fraction yielded 2-(3-ethoxy-5-iodo-1*H*-pyrazol-1-yl)-3-iodopyridine (0.92 g, 11%) as a white powder. Mp=146 °C. ^{1}H ($CDCl_3$): 1.49 (t, 3H); 4.29 (q, 2H); 6.11 (s, 1H); 7.15 (m, 1H); 8.32 (m, 1H); 8.61 (m, 1H); 7.86 (m, 1H). ^{13}C ($CDCl_3$): 14.7; 64.8; 82.4; 93.8; 103.4; 125.6; 148.4; 148.9; 153.6; 165.2. HRMS: calcd for $C_{10}H_9N_3I_2O$+Na: 463.8733; found: 463.8723.

*4.2.4. 2-(3-Ethoxy-5-phenyl-1H-pyrazol-1-yl)pyridine (**6**) by the Suzuki–Miyaura reaction.* In a Biotage tube, compound **4** (0.31 g, 0.98 mmol), caesium carbonate (1.28 g, 3.92 mmol) and phenylboronic acid (0.26 g, 2.13 mol) were dispersed in dimethylformamide (16 mL, dried over 4 Å molecular sieve). The suspension was degassed with a slow stream of argon and a premilled 1:2 mixture of palladium(II) acetate and XPhos (0.058 g, 0.049 mmol) was added. This was sealed and heated in an oil bath at 120 °C for 40 h. The resulting suspension was diluted in ethyl acetate, the organic layer was washed with water and brine, dried over magnesium sulfate and concentrated under vacuum. The resulting residue was then purified by a chromatography over first over silica (cyclohexane/ethyl acetate 95–5 to 9/1) to give compound **6** (0.21 g, 80%) featuring spectroscopic data identical with the previously reported one.[5]

*4.2.5. Compound **3a**, complexed with palladium acetate (**12**).* A suspension of compound **3a** (0.41 g, 0.0021 mol) and palladium acetate (0.38 g, 0.0017 mol) were stirred overnight in methanol (5 mL). The resulting solution was dispersed in diethyl ether, the precipitate formed was filtered washed with diethyl ether and dried under vacuum to yield complex **12** (0.69 g, 98%). ^{1}H ($CDCl_3$): 1.42 (t, 3H, J=7.1 Hz); 2.05 (s, 3H); 2.14 (s, 3H); 3.98 (q, 2H, J=7.1 Hz); 5.99 (d, 1H, J=3.4 Hz); 7.05 (m, 1H); 7.78 (m, 1H); 8.10 (m, 1H); 8.55 (m, 1H); 9.37 (d, 1H, J=3.4 Hz). Note: this substance is not soluble enough in chloroform to obtain complete ^{13}C spectra and it partially decomplexes in DMSO.

4.3. General method for the preparation of 7a,b

Under an argon atmosphere, the considered alkoxypyrazole **3a** or **3b** (3.70 mmol) was dissolved in dry tetrahydrofuran (37 mL, dried over 4 Å molecular sieve). This was cooled to −78 °C and 2 M *n*-butyllithium solution in cyclohexane (1.8 mL, 3.70 mmol) was then slowly added with a syringe. The resulting yellow mixture was stirred at −78 °C for 30 min before adding a solution of palladium (II) acetate (0.33 g, 1.48 mmol) dissolved in dry tetrahydrofuran (20 mL, dried over 4 Å molecular sieve). This was stirred at −78 °C for 30 min and then allowed to warm to room temperature. The resulting solution was diluted in ethyl acetate, washed successively with water and brine. The organic phase was dried over magnesium sulfate and the solvent removed under vacuum. The resulting residue was dispersed in boiling cyclohexane and the cold suspension filtered to yield compounds **7a** or **7b** as yellow powders in the yield mentioned in the text.

*4.3.1. Bis(3-ethoxy-1-(pyridin-2-yl)-1H-pyrazol-5-yl)palladium (**7a**).* Mp>260 °C. ^{1}H ($CDCl_3$): 1.47 (t, 3H, J=7.1 Hz); 4.28 (q, 2H, J=7.1 Hz); 5.87 (s, 1H); 6.94 (m, 1H); 7.47 (m, 1H); 7.74 (m, 1H); 8.14 (m, 1H) ^{13}C ($CDCl_3$): 26.9; 64.7; 100.7; 110.6; 117.5; 140.1; 145.9; 154.0; 154.7; 166.7. HRMS: calcd for $C_{20}H_{20}N_6O_2Pd$+H: 483.0761; found: 483.0775. Micro-analysis: calcd for $C_{20}H_{20}N_6O_2Pd$+1/11th toluene C: 50.46%; H: 4.25%; N: 17.11%; found: C: 50.37%; H: 4.50%; N: 17.49%.

*4.3.2. Bis(3-methoxy-1-(pyridin-2-yl)-1H-pyrazol-5-yl)palladium (**7b**).* Mp>260 °C. ^{1}H ($CDCl_3$): 4.00 (s, 3H); 5.90 (s, 1H); 6.98 (m, 1H); 7.52 (m, 1H); 7.78 (m, 1H); 8.20 (m, 1H). ^{13}C ($CDCl_3$): 56.2; 100.7; 110.6; 117.6; 140.6; 146.0; 154.1; 154.8; 167.5. HRMS: calcd for $C_{18}H_{17}N_6O_2Pd$+H: 455.0448; found: 455.0487. A sample of **3b** was dissolved in an excess of boiling toluene and left in an open flask to crystallize inside a large dessiccator over a month to yield monocrystals, containing some toluene but suitable for X-ray analysis.

*4.3.3. 5,5′-Diethoxy-2,2′-di(pyridin-2-yl)-2H,2′H-3,3′-bipyrazole (**8**).* Compound **7a** (0.15 g, 0.31 mmol) was dissolved in dry DMF (20 mL, dried over 4 Å molecular sieve). *N*-chlorosuccinimide (0.039 g, 0.29 mmol) was added and the solution was stirred at room temperature for 30 min before heating it to reflux for 15 min. The resulting dark solution was diluted in ethyl acetate, washed five times with water, brine, dried over magnesium sulfate and concentrated to dryness. The residue was further purified by a chromatography over silica gel (cyclohexane/ethyl acetate 5:1) to yield compound **8** as white powder (0.04 g, 34%). Mp=218 °C. ^{1}H ($CDCl_3$): 1.46 (t, 3H, J=7.1 Hz); 4.36 (q, 2H, J=7.1 Hz); 6.07 (s, 1H); 6.83 (m, 1H); 7.50 (m, 2H); 7.93 (m, 1H). ^{13}C ($CDCl_3$): 14.9; 64.9; 97.3; 114.6;

120.1; 134.4; 137.6; 147.5; 152.3; 163.3 HRMS: calcd for $C_{20}H_{20}N_6O_2$+H: 377.1726; found: 377.1741.

4.4. Preparation of compounds 13 and 14

In a Biotage tube, compound **3a** (0.44 g, 0.0023 mol), palladium acetate (0.52 g, 0.0023 mol) and caesium carbonate (1.6 g, 0.0046 mol) were dispersed in dimethylformamide (12 mL, dried over 4 Å molecular sieve). This was sealed and heated in a microwave oven at 160 °C for 4 h. The resulting suspension was dispersed in ethyl acetate and water, the organic layer was washed with water five times, with brine, dried over magnesium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel (cyclohexane/ethyl acetate from 95:5 to 1:2) to yield, in order of elution, compound **3a** (0.19 g, 43%), compound **13** as a white powder (0.07 g, 16%), compound **14** as an oil (0.02 g, 4.5%) and compound **7a** as a yellow powder (0.04 g, 7%).

*4.4.1. 3,3′-Diethoxy-1,1′-di(pyridin-2-yl)-1H,1′H-4,4′-bipyrazole (**13**).* Mp=214 °C. ^{1}H ($CDCl_3$): 1.57 (t, 3H, *J*=7.1 Hz); 4.53 (q, 2H, *J*=7.1 Hz); 7.08 (m, 1H); 7.75 (m, 1H); 7.81 (m, 1H); 8.39 (m, 1H); 8.73 (s, 1H) ^{13}C ($CDCl_3$): 14.9; 65.0; 101.6; 111.3; 119.7; 124.6; 138.3; 147.9; 151.6; 161.8. HRMS: calcd for $C_{20}H_{20}N_6O_2$+H: 377.1726; found: 377.1717.

*4.4.2. 3′,5-Diethoxy-1′,2-di(pyridin-2-yl)-1′H,2H-3,4′-bipyrazole (**14**).* ^{1}H ($CDCl_3$): 1.16 (t, 3H, *J*=7.1 Hz); 1.46 (t, 3H, *J*=7.1 Hz); 4.20 (q, 2H, *J*=7.1 Hz); 4.35 (q, 2H, *J*=7.1 Hz); 6.13 (s, 1H); 7.11 (m, 1H); 7.19 (m, 1H); 7.66 (m, 1H); 7.78 (m, 3H); 8.35 (m, 1H); 8.40 (m, 1H); 8.53 (s, 1H). ^{13}C ($CDCl_3$): 14.4; 14.9; 64.7 (two signals); 95.5; 101.8; 111.4; 117.6; 120.3; 121.3; 127.1; 135.0; 138.1; 138.4; 147.7; 147.9; 151.2; 153.3; 161.4; 163.9. HRMS: calcd for $C_{20}H_{20}N_6O_2$+H: 377.1726; found: 377.1717.

4.5. Typical procedure used for the trials described in Table 2

In a Biotage vial, compound **7a** (0.245 g, 0. 50 mmol), (0.24 g, 1.52 mmol) and caesium carbonate (0.51 g, 1.57 mmol) in DMF (3 mL, dried over 4 Å molecular sieve) were heated with micro waves at 160 °C for 3 h. The resulting suspension, containing insoluble black material, was dispersed in a mixture of water and ethyl acetate. The organic layer was washed five times with water, once with brine, dried over magnesium sulfate and concentrated to dryness. The resulting residue was purified by a chromatography over silica gel (cyclohexane/ethyl acetate, from 95:5 to 1:2) to yield, in order of elution, compound **15** (0.03 g, 24%), compound **3a** along with detectable amount of compound **13** (0.009 g, less than 5%) compound **5** (0.125 g, 46%) and the starting material **7a** (0.012 g, 6%). Biphenyl (**15**) displayed ^{1}H and ^{13}C NMR spectra identical with a commercially available sample.

4.6. X-ray structure of compound 7b

The crystal structure was solved from a colourless squared thick plate suitable to X-ray single crystal diffraction, obtained by slow concentration in a toluene solution. Crystallographic data were collected at the PX-3 beamline of the Swiss Synchrotron Light Source (SLS), Villigen, Switzerland at 100(2) K on mar225ccd using a 360°-unique Phi scan with 1° per oscillation. Diffraction data were integrated with XDS.[43] Although completeness dropped dramatically beyond 1 Å, high resolution data measured up to the edge of the detector with an overall $I/\sigma(I)>7$ in the last resolution bin were conserved to keep a reasonable ratio data over parameters albeit leading to a low overall completeness (barely superior to 70%). The structure was solved by charge-flipping methods using the Superflip program,[44] and refined on F^2 by means of full-matrix least-squares methods (SHELXL-97).[45] All non-hydrogen atoms were refined anisotropically whereas all H atoms were located in difference maps and then treated as riding atoms in geometrically idealized positions. Despite efforts to model the toluene molecule disordered over a centre of inversion satisfactorily, decision was taken to resort to the squeeze procedure as implemented in the PLATON[46] suite was used to treat the solvent disorder. Its contribution to the diffraction pattern was removed and modified F_o^2 written to a new HKL file. The number of electrons thus located, 54 per unit cell, was approximately assigned to one molecule of toluene solvent per unit cell corresponding to a void of 154 Å. This was taken into account in the formula, formula weight, calculated density, and *F*(000).

Results for compound **7b**: $C_{18}H_{16}N_6O_2$ Pd, 0.5(C_7H_8) M_r=500.83, 0.30×0.25×0.05 mm, triclinic, space group *P*−1, *a*=8.269(2) Å, *b*=10.966(2) Å, *c*=11.960(4) Å, *α*=68.326(4)°, *β*=79.224(6)°, *γ*=89.443(7)°, *V*=988.0(4) Å^3, *Z*=2, ρ_{calcd}=1.684 g cm^{-3}, *F*(000)=506, *λ* (PX-3=0.8266 Å, 2*θ*max=59.54° (d_{min}=0.83 Å), $-8\le h\le 8$, $-11\le k\le 12$, $-13\le l\le 13$, 5068 measured reflections, 2546 independent, *R*(int)=0.0759, 246 parameters were refined against all reflections, *R*1=0.0568, *wR*2=0.1395 (using all data) based on observed *F* values, *R*1=0.0557, *wR*2=0.1382 (2438 reflections with $I>2\sigma(I)$), $\Delta\rho_{min}$ and $\Delta\rho_{max}$=−1.146 and 1.612 e Å^{-3}, *GOF*=1.038 based on F^2.

The file CCDC-847343 contains the supplementary crystallographic data for compound **7b**. These data can be obtained free of charge on application to the Director, CCDC 12 Union Road, Cambridge CB2 1EZ, UK (fax (+44) 1223 336033; or e-mail deposit@ccdc.cam.uk) or via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

The initial project, leading to this work, was supported by the Medicen initiative (Chemical Library Project; grants of the Région Ile de France no I 06-222/R and I 09-1739/R). We also acknowledge Synchrotron SLS (Villigen, Switzerland) for the provision of synchrotron radiation facilities, and we would like to thank Martin Fuchs for assistance with the use of the beamline X06DA.

References and notes

1. Guillou, S.; Bonhomme, F. J.; Janin, Y. L. *Synthesis* **2008**, 3504–3508.
2. Guillou, S.; Nesme, O.; Ermolenko, M. S.; Janin, Y. L. *Tetrahedron* **2009**, *65*, 3529–3535.
3. Guillou, S.; Bonhomme, F. J.; Janin, Y. L. *Tetrahedron* **2009**, *65*, 2660–2668.
4. Guillou, S.; Janin, Y. L. *Chem.—Eur. J.* **2010**, *16*, 4669–4677.
5. Guillou, S.; Bonhomme, F. J.; Chahine, D.; Nesme, O.; Janin, Y. L. *Tetrahedron* **2010**, *66*, 2654–2663.
6. Guillou, S.; Bonhomme, F. J.; Ermolenko, M. S.; Janin, Y. L. *Tetrahedron* **2011**, *67*, 8451–8457.
7. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
8. Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440.
9. Suzuki, A. Coupling Reactions of Areneboronic Acid and Esters with Aromatic Electrophile In *Boronic Acids*; Wiley-VCH: Weinheim, 2005; pp 123–170.
10. Tretyakov, E. V.; Knight, D. W.; Vasilevsky, S. F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3713–3720.
11. Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331.
12. Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790–12791.
13. Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047–14049.
14. Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142–15143.
15. Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974–10983.
16. Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050–17051.
17. Ryabov, A. D. *Inorg. Chem.* **1987**, *26*, 1252–1260.
18. Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 3042–3048.
19. Mateos, C.; Mendiola, J.; Carpintero, M.; Minguez, J. M. *Org. Lett.* **2010**, *12*, 4924–4927.
20. Fall, Y.; Doucet, H.; Santelli, M. *Synthesis* **2010**, 127–135.
21. Shibahara, F.; Yamaguchi, E.; Murai, T. *J. Org. Chem.* **2011**, *76*, 2680–2693.
22. Beladhria, A.; Beydoun, K.; Ben Ammar, H.; Ben Salem, R.; Doucet, H. *Synthesis* **2011**, 2553–2560.

23. Laidaoui, N.; Rogers, J.; Miloudi, A.; El Abed, D.; Doucet, H. *Eur. J. Org. Chem.* **2011**, 4373–4385.
24. Gaulier, S. M.; McKay, R.; Swain, N. A. *Tetrahedron Lett.* **2011**, *52*, 6000–6002.
25. Jolliet, P.; Gianini, M.; von Zelewsky, A.; Bernardinelli, G.; Stoeckli-Evans, H. *Inorg. Chem.* **1996**, *35*, 4883–4888.
26. Sun, X.; Yu, Z.; Wu, S.; Xiao, W. J. *Organometallics* **2005**, *24*, 2959–2963.
27. Bin, H. R.; Bae, Y. S.; Kim, G.; Lee, K. I. *Synthesis* **2011**, 1783–1791.
28. Budzisz, E.; Malecka, M.; Keppler, B. K.; Arion, V. B.; Andrijewski, G.; Krajewska, U.; Rozalski, M. *Eur. J. Inorg. Chem.* **2007**, 3728–3735.
29. Canty, A. J. Palladium Complexes Containing Pd(I), Pd(III), or Pd(IV) In; Negishi, E., Ed. . *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, NY, 2002; Vol. 1, pp 189–211.
30. Canty, A. J. *Dalton Trans.* **2009**, 10409–10417.
31. Maestri, G.; Motti, E.; Della Ca', N.; Malacria, M.; Derat, E.; Catellani, M. *J. Am. Chem. Soc.* **2011**, *133*, 8574–8585.
32. Catellani, M. *Top. Organomet. Chem.* **2005**, *14*, 174–190.
33. Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512–1522.
34. Martins, A.; Mariampillai, B.; Lautens, M. *Top. Curr. Chem.* **2010**, *292*, 1–33.
35. Xu, L. M.; Li, B. J.; Yang, Z.; Shi, Z. J. *Chem. Soc. Rev.* **2010**, *39*, 712–733.
36. Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824–889.
37. Powers, D. C.; Xiao, D. Y.; Geibel, M. A. L.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14530–14536.
38. Zhao, X.; Dong, V. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 932–934.
39. Faccini, F.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2004**, *126*, 78–79.
40. Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.
41. Zawisza, A. M.; Muzart, J. *Tetrahedron Lett.* **2007**, *48*, 6738–6742.
42. Wang, L.; Lu, W. *Org. Lett.* **2009**, *11*, 1079–1082.
43. Kabsch, W. *Acta Crystallogr.* **2010**, *D66*, 125–132.
44. Palatinus, L.; Chapuis, G. *J. Appl. Crystallogr.* **2007**, *40*, 786–790.
45. Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.
46. Spek, A. L. *J. Appl. Crystallogr.* **2003**, *36*, 7–13.