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Bromobis(triphenylphosphine)(*N*-succinimide)palladium(II) as a novel catalyst for Stille cross-coupling reactions

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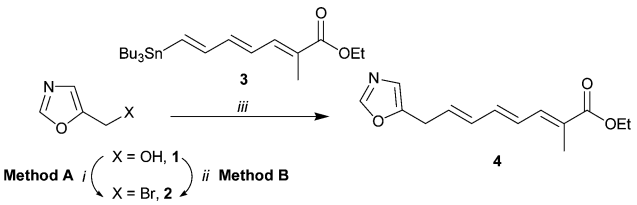
A new palladium catalyst is reported for Stille cross-coupling, namely [Pd(NCOC$_2$H$_4$CO)(PPh$_3$)$_2$Br].

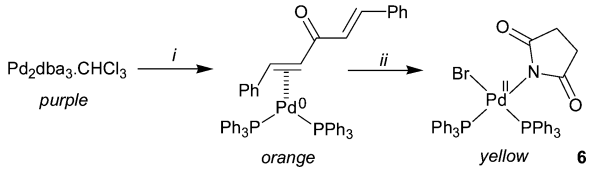
Originally reported by Kosugi, Shimizu and Migita[1] in 1977 and then comprehensively developed by Stille,[2] the Stille cross-coupling reaction of organohalides and organostannanes, catalysed by Pd, represents an extremely powerful synthetic tool for C–C bond formation[3] which has become increasingly popular in natural product synthesis.[4] The design of new, efficient catalysts[5] for this process has seen notable contributions from Bedford,[6] Fu,[7] Nolan[8] and others[3] over the past few years, allowing a range of aryl halides (including aryl chlorides) and related systems to be used as substrates. We have also been interested in the development of new catalysts for the Stille reaction, particularly for couplings involving allylic and benzylic halides. Herein we report the preparation and utilisation of a bromosuccinimido-based Pd-catalyst in such Stille coupling reactions.

During the course of synthetic studies towards the Inthomycins,[9] oxazole bromide **2** was coupled to organostannane **3** to give **4** (Scheme 1).



Scheme 1 *i*, NBS, PPh_3, THF, rt, 1 h; *ii*, CBr_4, PPh_3, CH_2Cl_2, 0 °C 1 h; *iii*, $Pd(PPh_3)_4$ (5 mol%), $C_6H_5CH_3$, reflux, 20 h (see text for yields).

It was eventually found that when **2** was prepared from the oxazole alcohol **1** using *N*-bromosuccinimide (NBS)–triphenylphosphine (PPh_3) (Method A), the subsequent Stille reaction with $Pd(PPh_3)_4$ **5** proceeded to give the coupled product **4** in 78% yield. However, when **2** was formed using carbon tetrabromide–Ph_3P (Method B), the coupling reaction failed. The unstable bromide **2** (light, heat >0 °C and moisture sensitive) was always semi-purified by passage through a small plug of silica washed with CH_2Cl_2 and used immediately. Trace quantities of starting materials or side products could therefore accompany **2**. At this point the question arose as to whether an impurity was inhibiting the reaction when Method B was used, or whether an impurity carried through using Method A was promoting the reaction. We felt that the side products arising from Method B, bromoform and triphenylphosphine oxide, would not inhibit the coupling reaction. It was conceivable that NBS was carried through using Method A and thus the effect of adding NBS to these reactions was studied. Reaction of **2** and **3** using $Pd(PPh_3)_4$ **5** (5 mol%) as the catalyst with added NBS (5 mol%), after 19 h at reflux, gave **4** in 75% yield. Bromide **2**, prepared *via* method B, was then reacted with $Pd(PPh_3)_4$ and added NBS (5 mol%), which provided **4** in 76% yield after 18 h at reflux. It was clear that the addition of NBS to the Stille reaction had a beneficial effect on the yields of the oxazole product **4**. The oxidative addition of NBS to Pd(0) and Pt(0) precursors has been reported by Serrano and co-workers[10] to give Pd(NCOC$_2$H$_4$CO)(PPh$_3$)$_2$Br **6**. Using a modified procedure,† **6** was synthesised by initial reaction of [Pd_2dba_3·$CHCl_3$] (1 eq.) with PPh_3 (4 eq.), followed by addition of recrystallised NBS (2 eq.) in CH_2Cl_2 at 25 °C in 74% yield (Scheme 2).



Scheme 2 *i*, CH_2Cl_2, PPh_3 (4 eq.), 25 °C, 0.2 h; *ii*, NBS (2 eq.), 0.2 h.

The ^{31}P NMR (202 MHz) spectrum of **6** shows a pair of doublets at δ 23.96 and 32.91 ($^2J_{PP}$ = 8.49 Hz), which suggests a *cis*-geometry for the Ph_3P ligands around the Pd-centre. Single crystals were obtained from CH_2Cl_2 by slow vapour diffusion with Et_2O (at 0 °C, 2 days) and their structure determined by X-ray analysis (Fig. 1), confirming the *cis*-geometry. It was then established that **6** catalyses the reaction of **2** and **3** to give **4** in 78% yield.

We next undertook a series of experiments where the effect of adding *N*-halosuccinimides to $Pd(PPh_3)_4$ **5**, on the Stille coupling of benzyl bromide **7** to organostannane *Z*-**8**, was compared (Table 1). With **5** alone, a 17% yield of *Z*-**9** was obtained after 24 h (entry 1). To establish whether the number of PPh_3 around palladium was having an effect, "$(PPh_3)_2Pd(0)$" was generated *in situ* from $Pd(OAc)_2$–3 PPh_3 **10**, but only a slight improvement in yield was seen and isomerisation occurred (entry 2, *E*:*Z*, 3:2). The addition of the *N*-halosuccinimides had a remarkable effect on the yields (entries 3–5). *N*-Chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS) both promote the reaction but the best additive was indeed NBS, which gave *Z*-**9** in 83% yield.

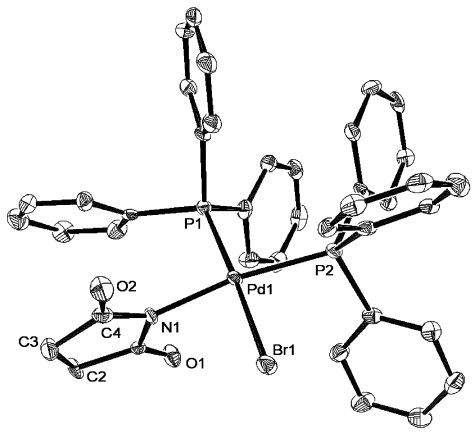


Fig. 1 ORTEP diagram of [Pd(NCOC$_2$H$_4$CO)(PPh$_3$)$_2$Br] **6**. Hydrogen atoms have been omitted for clarity. Ellipsoids drawn at 50% probability. Selected bond lengths (Å) and angles (°): Pd(1)–P(1) 2.2794(12), Pd(1)–P(2) 2.2928(13), Pd(1)–N(1) 2.052(4), Pd(1)–Br(1) 2.4687(6), P(1)–Pd(1)–P(2) 97.18, P(2)–Pd(1)–Br(1) 85.37, N(1)–Pd(1)–Br(1) 87.83, N(1)–Pd(1)–P(2) 89.50.

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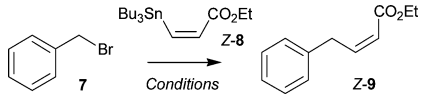
A common catalyst system for the Stille reaction is Pd_2dba_3·dba (dba = dibenzylideneacetone) with added PPh_3 (**14**). The reaction catalysed by **14** provided *Z*-**9** in 41% yield after 24 h, as a mixture of isomers (*E* : *Z*, 1 : 2.15) (entry 6). Changing the catalyst to Pd_2dba_3·dba–PPh_3 with added NBS provided *Z*-**9** exclusively in 76% yield (entry 7). Pd(Bn)$(PPh_3)_2$Br **16** was screened, providing *Z*-**9** in 54% yield, as an isomeric mixture (entry 8). The isolated catalyst **6** gave *Z*-**9** in 98% yield after only 3 h (entry 9). The synthesis of Pd$(NCOC_2H_4CO)$(dppe)Br **17** (dppe = diphenylphosphinoethane) was carried out in a similar manner to **6**.[10] Complex **17** was also shown to catalyse the reaction of **7** + *Z*-**8** → *Z*-**9** in 90% yield after 24 h (*E* : *Z*, 1 : 29).

Table 1 Effect of Pd-catalyst and succinimide additives[a]



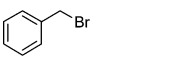
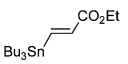
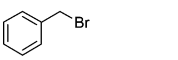
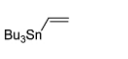
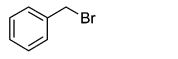
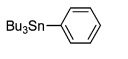
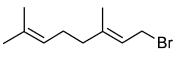
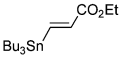
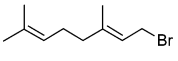
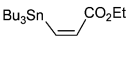
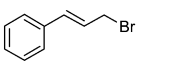
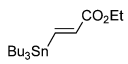
Entry	Catalyst[b]	Time/h	Yield (%)[e]
1	Pd$(PPh_3)_4$ (**5**)	24	17
2	Pd$(OAc)_2$ + PPh_3 (**10**)	24	46[f]
3	Pd$(PPh_3)_4$ + NCS (**11**)	24	61
4	Pd$(PPh_3)_4$ + NBS (**12**)	18	83
5	Pd$(PPh_3)_4$ + NIS (**13**)	24	33
6	Pd_2dba_3·dba + PPh_3 (**14**)[c]	24	41[f]
7	Pd_2dba_3·dba + PPh_3 + NBS[d] (**15**)	18	76
8	Pd(Bn)$(PPh_3)_2$Br (**16**)	24	54[g]
9	Pd$(NCOC_2H_4CO)(PPh_3)_2$Br (**6**)	3	98

[a] Reaction conditions: **7** (0.5 mmol), *Z*-**8** (0.6 mmol), $C_6H_5CH_3$ (5 mL) at 60 °C, under an inert atmosphere of N_2. [b] 5 mol% [Pd] unless stated otherwise. [c] Pd_2dba_3·dba (2.5 mol%) and PPh_3 (10 mol%). [d] As for entry 5 with added NBS (5 mol%). [e] Isolated yield after KF workup and chromatography. [f] Isomeric mixture: see text. [g] Diene (*E*:*Z*, 1.6:1) : skip-diene, 1.0 : 0.9 (by ^{1}H NMR).

The substrate scope of **6** and related catalysts with several allylic and benzylic substrates and organostannanes were studied (Table 2). One of the well-known drawbacks of the Stille reaction is the removal of tin halide by-products.[3] We generally use a KF workup,[2a] although for certain substrates a DBU–I_2–Et_2O workup[11] proved beneficial. It is important to note that in reactions of *Z*-**8** or *E*-**8** the latter workup resulted in a rapid regio- and stereo-isomerisation (< 2 min).

The yields of the cross-coupled products from reactions employing **6**, compare well to **5** and **16** in entries 1, 5 and 6. For entry 5, catalyst **5** gave only a 11% yield of the coupled product as an isomeric mixture (*Z*-C5 : *E*-C5, 1.2 : 1). An increase in yield occurred using **16**, and no isomerisation was observed. Here **6** is noticeably superior to **5** and **16**, providing the *Z*-isomer exclusively in 62% yield.

Table 2 Allylic and benzylic substrate screening with organostannanes[a]

Entry	RBr	R′$SnBu_3$	Cat.	Yield (%)[b]
1			**5**	73
			6	95 (4.5 h)
			16	71
2			**5**	9[c]
			6	67[c]
3			**5**	90
			6	93
4			**5**	51
			6	56
5			**5**	11[d]
			6	62
			16	32
6			**5**	56[e]
			6	81 (13 h)
			16	58

[a] Reaction conditions as for Table 1: 24 h unless other stated in brackets. [b] Isolated yields after KF workup and chromatography. Numbers in brackets are reaction times. [c] A DBU–I_2–Et_2O workup was used. [d] Isomeric mixture: see text. [e] Diene (*E* only) : skip-diene, 1.2 : 1 (by ^{1}H NMR).

It should be noted that on completion of each reaction using **6**, the colour of the solution remains yellow, which presumably indicates a Pd(II) catalytic resting state. Collodial palladium black was produced with all the other catalyst systems **5**, **10**, **14** and **16**. The Pd(II) resting state was confirmed by following the reaction of **7** + *Z*-**8** → *Z*-**9** using **6** in d_8-toluene at 70 °C by ^{31}P NMR (202 MHz) which shows one signal at δ 25.34 (singlet), which remains at the end of reaction. This species is not **6**, nor is it Pd(Bn)$(PPh_3)_2$Br. Furthermore **6** was not detected at the start, during or at the end of the reaction. Therefore **6** is a precatalyst. Mechanistic studies to identify the active catalyst are underway.

In summary, we have discovered that **6** can be used to effect the Stille reaction. Complex **6** can be synthesised in one step from Pd_2dba_3·$CHCl_3$, PPh_3 and NBS, which should facilitate its mainstream use. The catalytic activity of other monomeric and dimeric succinimido-based Pd(II) complexes will be reported in due course.

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Notes and references

† Modified synthetic procedure for **6**: to a Schlenk tube containing vacuum dried Pd_2dba_3·$CHCl_3$ (100 mg, 0.097 mmol) in dry CH_2Cl_2 (2 mL), under N_2, was added a solution of PPh_3 (101.4 mg, 0.387 mmol) in dry CH_2Cl_2 (2 mL). The mixture was stirred for 0.2 h, after which time an orange colour persisted. A solution of recrystallised *N*-bromosuccinimide (34.5 mg, 0.194 mmol) in dry CH_2Cl_2 (2 mL) was added in one portion and the mixture stirred for a further 0.2 h. The resulting yellow solution was concentrated *in vacuo* to a third of its original volume and petroleum ether added to precipitate complex **6**. The creamy yellow solid was filtered and washed with small quantities of hexane (104 mg, 74% yield). A small quantity of **6** was recrystallised. Single crystals were obtained from CH_2Cl_2 by slow vapour diffusion with Et_2O (1 : 5, *v*/*v*) at 0 °C for 2 d. ν_{max} (KBr)/cm^{-1} 1631 (C=O); δ_H (CD_2Cl_2, 400 MHz) 1.61 (2H, m, 2 × CH_A), 2.27 (2H, m, 2 × CH_B), 7.1–7.6 (30H, m, Ph–H); δ_P (CD_2Cl_2, 202 MHz) 23.96 (1P, $^2J_{PP}$ 8.49 Hz) and 32.91 (1P, $^2J_{PP}$ 8.49 Hz). **Crystal data.** $C_{40}H_{34}BrNO_2P_2Pd$, M = 808.93, monoclinic, a = 12.3222(11), b = 19.880(2), c = 13.6371(13) Å, U = 3340.6(6) Å^3, T = 115(2) K, space group $P21/n$, Z = 4, μ(Mo–K_a) = 1.885 mm^{-1}, 18654 reflections measured, 5990 unique (R_{int} = 0.0733) which were used in all calculations. Final $R1$ = 0.0849 and $wR(F^2)$ = 0.0905 (all data). CCDC 209523. See http://www.rsc.org/suppdata/cc/b3/b304960d/ for crystallographic data in .cif or other electronic format.

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