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AscCat and FurCat: new Pd catalysts for selective room-temperature Stille cross-couplings of benzyl chlorides with organostannanes†

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Two novel succinimide-based palladium complexes, AsCat and FurCat, are highly efficient catalysts for room-temperature Stille cross-coupling of organostannanes with benzyl chlorides. The air- and moisture-stable catalysts are prepared in one step, and the coupling reactions proceed with a high selectivity for the benzyl position under mild conditions without the need for additives.

The Pd-catalysed cross-coupling reaction between organostannanes and halides or pseudohalide electrophiles, known as the Stille cross-coupling (SCC) reaction,[1] finds widespread use in the synthesis of complex organic molecules.[2] Its inherent mildness and functional group compatibility are borne out by its frequent use at a late stage in the total synthesis of complex natural products.[3] Moreover, mechanistic investigations have led to significant developments in the catalytic systems and conditions employed to effect the Stille coupling, permitting ever more efficient reactions.[4]

Diarylmethanes are useful substructures present in many biologically active compounds.[5] Palladium catalysis has emerged as a useful method to access these types of structural units,[6] but despite its potential, the SCC reaction has received relatively little attention in this regard, with only limited reports of couplings between organostannanes and benzyl halides.[7] These typically require the use of elevated temperatures and/or a Lewis basic additive to achieve efficient reaction. Although room-temperature SCC reactions are established with certain electrophiles,[8] less reactive substrates can require specially designed catalyst systems.[9] There have been only sporadic reports of room-temperature SCC reactions between organostannanes and benzyl bromides,[10] and are no dedicated reports with benzylic chlorides. The ability to carry out these transformations mildly on a range of substrates under simple conditions would be of great value to synthetic chemistry.

In previous studies, we have shown that Pd catalysts bearing one or more imidate ligands exhibit an unusually high efficiency in Stille and Suzuki–Miyaura cross-couplings involving allylic and benzylic electrophiles.[7b–e,11] Imidate ligands have a number of different coordination modes and similar electronic properties to halide ligands, and are proposed to play a key part in this observed selectivity.

As part of our endeavours to develop new catalysts for SCCs, we proposed that succinimide-containing Pd catalysts incorporating the labile triphenylarsine and tri(2-furyl)phosphine ligands, which have been shown to offer dramatic rate enhancements in Stille couplings,[12] could be efficient new catalysts. We report herein two novel succinimide-containing Pd complexes, Pd(*N*-succ)Br$(AsPh_3)_2$ (**1**, AsCat) and Pd(*N*-succ)Br(P(2-Fu)$_3$)$_2$ (**2**, FurCat) (Fig. 1, depicted with a *cis*-geometry), which are effective catalysts for SCC reactions with benzyl halides at ambient temperature.

Both complexes were synthesised by treating $Pd_2dba_3 \cdot CHCl_3$ with the appropriate ligand (L, 2 equiv. per Pd) in CH_2Cl_2, followed by oxidative addition of *N*-bromosuccinimide (NBS, 1 equiv. per Pd) (Scheme 1).

The desired complexes were obtained in moderate-to-high yields as pale brown solids, and although labile in solution, they were found to be air- and moisture-stable in the solid state. Complex **1** exists in a *ca.* 4 : 1 *cis*/*trans*-ratio on isolation (^{1}H NMR spectroscopy), with complete isomerisation to the *trans*-isomer seen after 24 h at RT in $CDCl_3$ or CD_2Cl_2 solution (Scheme 1). Complex **2** exhibits a similar behaviour, with both the ^{1}H and ^{31}P NMR spectra indicating an approximately 9:1 *cis*/*trans*-ratio on isolation. Isomerisation is slower in the case of **2** (1 : 1, *cis*/*trans* after 24 h at RT in $CDCl_3$ solution).

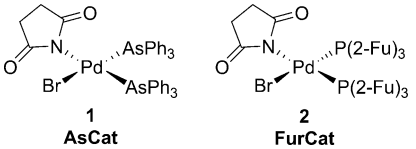

Fig. 1 Structures of the two novel succinimide-based catalysts, **1** and **2**.

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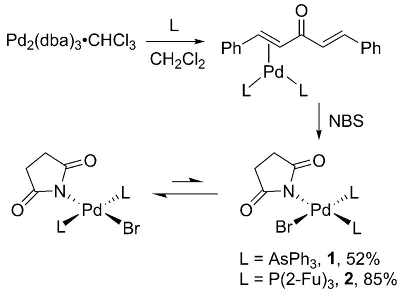


Scheme 1 Synthesis of complexes **1** (AsCat) and **2** (FurCat).

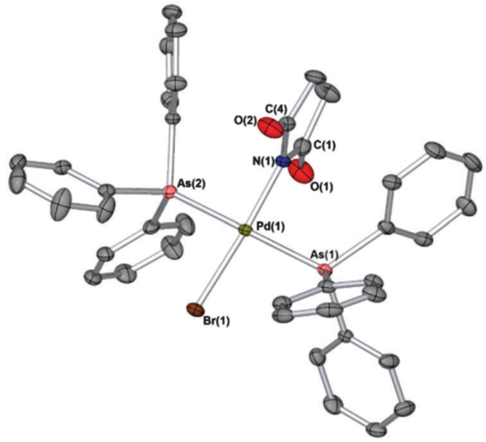
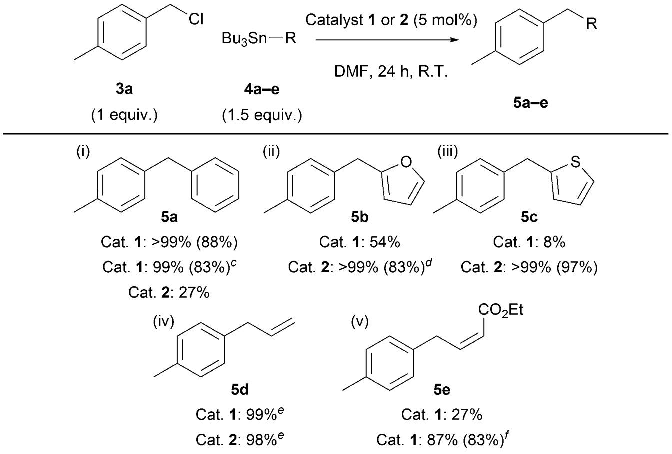


Fig. 2 The crystal structure of complex **1**. Hydrogen atoms have been removed and only selected atoms are numbered for clarity. Thermal ellipsoids are shown with a probability of 50%. Selected bond lengths (Å): Pd(1)–As(1): 2.4229(4), Pd(1)–Br(1): 2.4338(4), Pd(1)–As(2): 2.3914(4), Pd(1)–N(1): 2.025(2). Selected bond angles (°): N(1)–Pd(1)–As(1): 90.69(7), As(1)–Pd(1)–Br(1): 92.969(13), Br(1)–Pd(1)–As(2): 87.471(13).

A single crystal X-ray diffraction structure of *trans*-**1** was obtained (Fig. 2), with the crystals grown by vapour diffusion of pentane into a saturated solution of the complex in CH_2Cl_2.

Catalyst screening showed that **1** and **2** are highly active catalysts, being able to mediate the coupling of 4-methylbenzyl chloride (**3a**) with a variety of stannanes in DMF at room temperature (Table 1). Product conversions were dependent on both the catalyst and stannane used, but the catalytic ability of the complexes appears to be complementary. The triphenylarsine-based catalyst **1** was efficient at mediating coupling with tributylphenylstannane **4a** in both DMF and propylene carbonate (entry i, Table 1), whilst the tri(2-furyl)phosphine-based catalyst **2** gave only modest conversion (the analogous triphenylphosphine-based succinimide catalyst, Pd(*N*-succ)Br(PPh_3)$_2$, gave no conversion at room temperature). Conversely, coupling of the electron-rich heteroaromatic stannanes **4b** and **4c**, based on furan and thiophene respectively, was efficiently mediated by complex **2**, but not by **1** (entries ii and iii, Table 1). Both catalysts were efficient with tributylvinylstannane **4d** (entry iv, Table 1). Note that, when required, pure products could be readily obtained following a simple aqueous workup and flash chromatography using SiO_2–K_2CO_3 (9 : 1, w/w) as the stationary phase in order to remove organotin impurities.[13]

Table 1 Stille cross couplings of 4-methylbenzyl chloride **3a** with various stannanes using catalysts **1** and **2**[a,b]



(i) **5a**: Cat. **1**: >99% (88%); Cat. **1**: 99% (83%)[c]; Cat. **2**: 27%

(ii) **5b**: Cat. **1**: 54%; Cat. **2**: >99% (83%)[d]

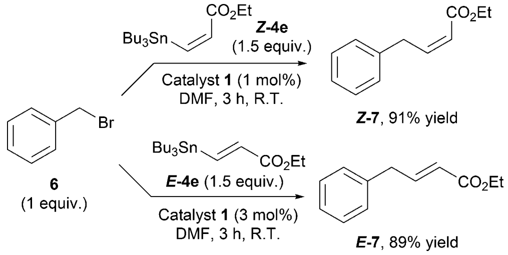
(iii) **5c**: Cat. **1**: 8%; Cat. **2**: >99% (97%)

(iv) **5d**: Cat. **1**: 99%[e]; Cat. **2**: 98%[e]

(v) **5e**: Cat. **1**: 27%; Cat. **1**: 87% (83%)[f]

[a] Percentages refer to conversion to product as judged by ^{1}H NMR spectroscopy. [b] Percentages in parentheses refer to yields of isolated product following purification on SiO_2–K_2CO_3. [c] Reaction conducted using propylene carbonate solvent as a substitute for DMF. [d] Reaction time 3 h. [e] Product not isolated due to volatility. [f] Reaction time 72 h.

The electron-deficient stannane ***Z*-4e** could also be coupled using the more reactive catalyst **1**, although a longer reaction time was required for higher product conversions (entry v, Table 1). By contrast, stannanes ***E*-** and ***Z*-4e** could be coupled rapidly with benzyl bromide (**6**) catalysed by complex **1** at lower catalyst loadings and ambient temperature (Scheme 2), affording products ***E*-** and ***Z*-7**.

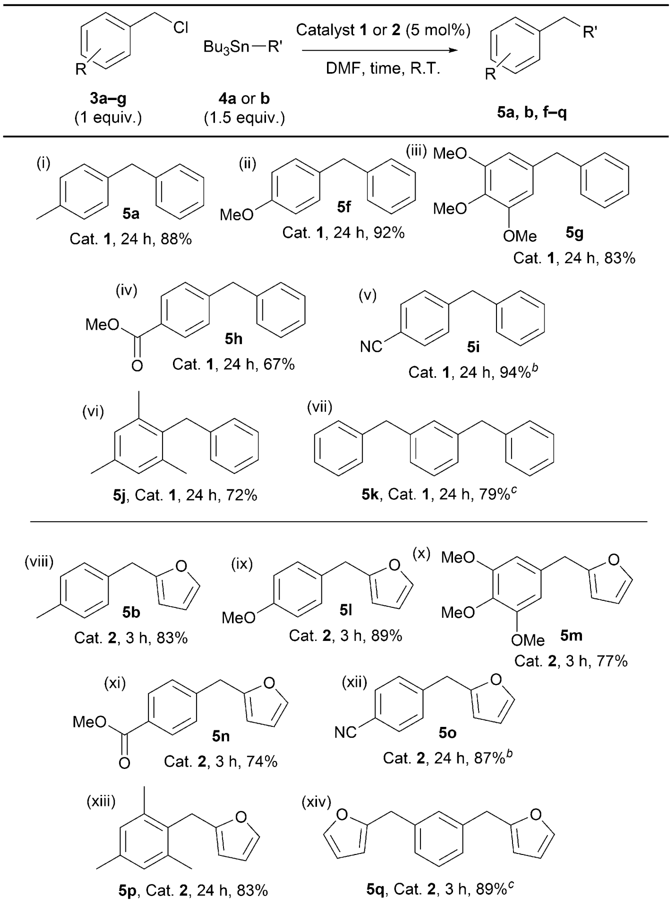


Scheme 2 Coupling of benzyl bromide (**6**) with electron deficient stannanes ***E*-** and ***Z*-4e** using catalyst **1**.

The scope of benzyl chloride coupling partners was explored next (Table 2), and both catalysts are found to be fully compatible with a range of substitution on the aryl group. Electron-rich (entries ii, iii, ix and x, Table 2) and electron-deficient (entries iv and xi, Table 2) substrates were coupled effectively with both catalysts, although very electron-poor benzyl chlorides (entries v and xii, Table 2) required gentle heating for efficient reaction. We interpret this observation as being due to a difference in transmetallation rates of the oxidative addition Pd^{II} intermediates, or a different mechanism to the traditional Pd^0/Pd^{II} catalytic cycle.[4a] Substitution *ortho*- to the benzyl position was also tolerated (entries vi and xiii, Table 2), as was a double coupling on a bis-benzyl chloride (entries vii and xiv, Table 2).

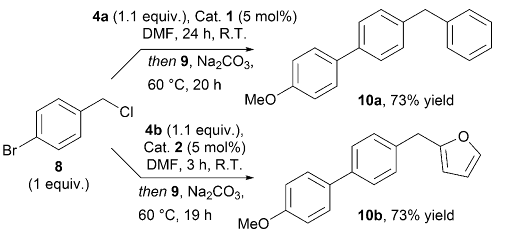
One of the most useful aspects of our new catalysts is the high selectivity which they display for coupling of benzyl electrophiles

Table 2 Coupling of stannanes **4a** and **4b** with various benzyl chlorides **3** using catalysts **1** and **2** respectively[a]



[a] Percentages refer to yields of isolated product following purification on SiO_2–K_2CO_3. [b] Reaction carried out at 40 °C. [c] Reaction carried out with 3 equiv. of stannane and 6 mol% catalyst.

over aryl electrophiles. Selectivity for a benzyl bromide over an aryl bromide has been previously demonstrated with similar complexes,[7c] however, there is no instance in the literature of the SCC with a benzyl chloride in the presence of an aryl bromide. In order to illustrate this selectivity, we carried out the reaction of 4-bromobenzyl chloride (**8**) with stannanes **4a** and **4b** using catalysts **1** and **2** respectively (Scheme 3). The intermediates (not isolated) were subjected to a Suzuki–Miyaura coupling with 4-methoxyphenylboronic acid (**9**), without the further addition of catalyst, and this allowed the isolation of the desired products **10a** and **10b**, both in 73% yield, effectively demonstrating the unusual selectivity of these catalysts.



Scheme 3 Tandem Stille–Suzuki cross-coupling reactions demonstrating the selectivity of both catalysts for the benzyl chloride over an aryl bromide.

In conclusion, two novel catalysts, AsCat (**1**) and FurCat (**2**), exhibit remarkable activity in the first reported examples of room-temperature SCC reactions with benzyl chlorides. Both catalysts show a useful selectivity for benzyl chlorides over aryl bromides, tolerating a range of functionality including electron-deficient and electron-rich benzyl chlorides, and exhibit an intriguing complementarity with respect to the structure of the organostannane. The SCC reactions greatly benefit from being mild, simple and highly efficient; their broader use in the synthesis of complex organic molecules is anticipated. Detailed mechanistic investigations are ongoing and will be reported in due course.

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