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Efficient and selective Stille cross-coupling of benzylic and allylic bromides using bromobis(triphenylphosphine) (*N*-succinimide)palladium(II)

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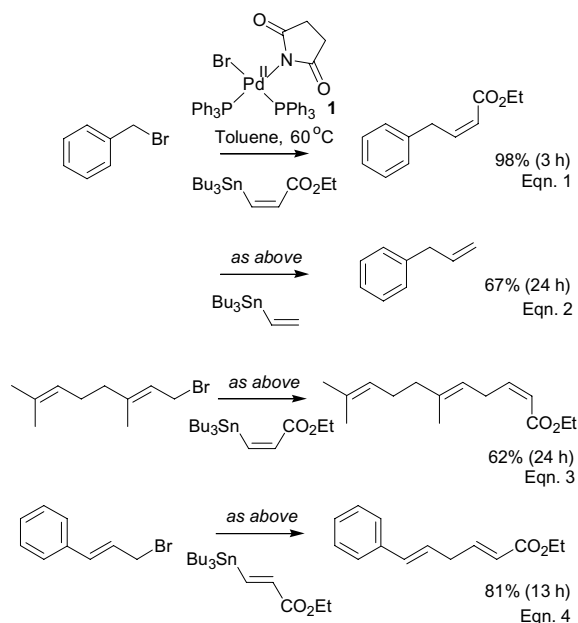
Abstract—Allylic and benzylic bromides are cross-coupled with organostannanes efficiently using the precatalyst [Pd(NCOC$_2$H$_4$CO)(PPh$_3$)$_2$Br] **1**. Significantly, these reactions do not require the use of hexamethylphosphoramide (HMPA) as the solvent, or additional ligands, such as trifurylphosphine or triphenylarsine. Selectivity for benzyl bromide over bromobenzene is observed for precatalyst **1**, against the precatalysts, bromobis(triphenylphosphine)(benzyl)palladium(II) and bis(triphenylphosphine)palladium(II) bromide.
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Stille cross-coupling[1] represents one of the most important reactions for the formation of carbon–carbon bonds.[2] The reaction, involving the coupling of organo-halides with organostannanes catalysed by palladium, has been employed in numerous syntheses of natural products, as well as other important compounds.[3] This creates an impetus to identify new and more efficient catalysts for this reaction and a number of major advances have been made in recent years.[4] We have interests in the identification and development of new palladium catalysts for carbon–carbon bond forming processes. In the Stille area, not only did we want to improve catalyst efficiency and associated reaction yields, but we were also interested in whether it was possible to couple selectively allylic or benzylic bromides in preference to aryl bromides. We recently reported a new precatalyst for Stille cross-coupling, namely [Pd(NCOC$_2$H$_4$CO)(PPh$_3$)$_2$Br] **1** (Scheme 1).[5] We now report more details of the scope of precatalyst **1** and present preliminary findings concerning selectivity studies.

Using a general procedure,[6] a range of allylic and benzylic bromides (1 equiv) were reacted with a number of organostannanes (1.2 equiv) employing the easily pre-
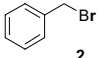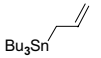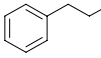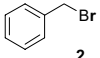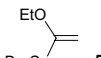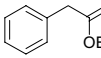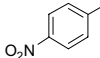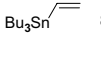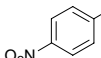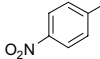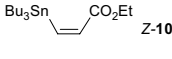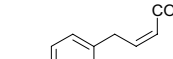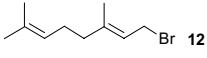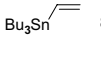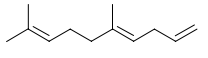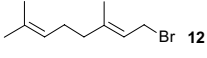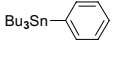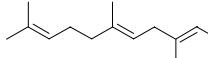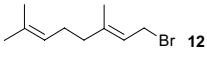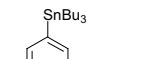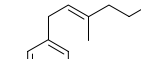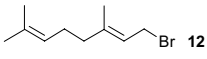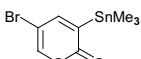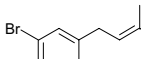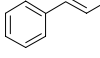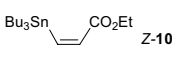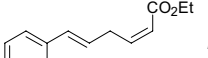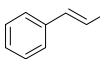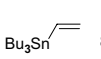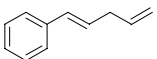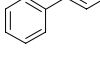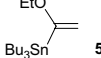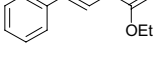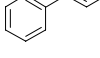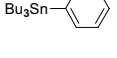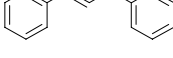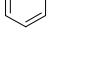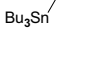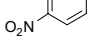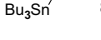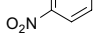

Scheme 1. Stille cross-coupling of allylic and benzylic bromides using precatalyst **1**.[5]

pared[5] precatalyst **1** (5 mol%) in dry, degassed toluene at 60 °C under an inert atmosphere of N$_2$. The cross-coupled products accessed using this method are shown in Table 1.

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Table 1. Products from the Stille cross-coupling of allylic or benzylic substrates with organostannanes, catalysed by **1**.[a,7]

Entry	RBr	R'SnBu₃	Coupled product	Yield (%)[b]	Reaction time (h)
1	**2** (benzyl bromide)	Bu₃Sn—allyl **3**	**4**	31[c]	48
2	**2** (benzyl bromide)	EtO / Bu₃Sn **5**	**6**	84	20
3	O₂N—benzyl **7**	Bu₃Sn— **8**	O₂N— **9**	67	6
4	O₂N—benzyl **7**	Bu₃Sn CO₂Et *Z*-**10**	O₂N— CO₂Et *Z*-**11**	67	24
5	**12**	Bu₃Sn— **8**	*E*-**13**	78	18
6	**12**	Bu₃Sn— **14**	*E*-**15**	34	18
7	**12**	SnBu₃ **16**	**17**	84	8
8	**12**	Br SnMe₃ **18**	Br **19**	72	24
9	**20**	Bu₃Sn CO₂Et *Z*-**10**	CO₂Et *E,Z*-**21**	86	13
10	**20**	Bu₃Sn— **8**	*E*-**22**	92	18
11	**20**	EtO / Bu₃Sn **5**	OEt *E*-**23**	79	20
12	**20**	Bu₃Sn— **14**	*E*-**24**	79	18
13	**20**	Bu₃Sn— **3**	*E*-**25**	70	24
14	O₂N— **26**	Bu₃Sn— **8**	O₂N— **27**	66	24

[a] Reaction conditions: allylic/benzylic bromide (0.25 mmol), organostannane (0.3 mmol), C₆H₅CH₃ (2.5 mL) at 60 °C, under an inert atmosphere of N₂.[6]

[b] Isolated yields after KF workup and chromatography.

[c] Conversion was >90% (by ¹H NMR). Compound **4** is extremely volatile, as noted previously.[8]

In the first example, benzyl bromide **2** was reacted with allyl stannane **3** to give **4** in 31% yield (entry 1). The overall conversion to **4** was very good (>90%, by ¹H NMR spectroscopic analysis of the crude material), although the high volatility of this compound reduced the isolated yield.[8] Cross-coupling of **2** with stannane **5** proceeds in an excellent 84% yield (entry 2). Migration of the double bond into conjugation with the aryl system

was not observed. It was expected that 4-nitrobenzyl bromide **7** might be more reactive than **2**, due to the electron withdrawing ability of the nitro group, which should favour the initial oxidative addition process. This was indeed the case for vinyltributyltin **8** (entry 3), which proceeds to completion in 6 h. This is substantially less than the reaction time needed for benzyl bromide and **8** (24 h, Eq. 2, Scheme 1).[5] Given that the yields from these reactions are identical, the particular type of tin reagent seems to affect the rate of reaction. On switching to *Z*-3-(tributylstannyl)propenoic acid ethyl ester *Z*-**10**, the reaction time with 4-nitrobenzyl bromide **7** is 24 h. Importantly, the rate of reactions with 4-nitrobenzyl bromide **7** and **8** or *Z*-**10** are reversed when compared to the corresponding reactions of benzyl bromide **2** (compare Eqs. 1 and 2 in Scheme 1 and entries 3 and 4 in Table 1).

Geranyl-based substrates have been frequently employed in Stille cross-coupling reactions.[2] This stems from the fact that two questions are addressed; namely, what are the regio (α or γ cross-coupled products are possible[9]) and stereo-selectivity consequences? Furthermore, the cross-coupled products can be useful as intermediates to natural products and terpenoid mimetics.[10] These substrates provide a useful test for precatalyst **1**. Cross-coupling of **12** with **8** provided *E*-**13** in 78% yield (entry 5). The reaction is regioselective for the α-position. Migration of the terminal double bond into conjugation was not observed and the *E*-stereochemistry was preserved. The reaction of phenyl stannane **14** also proceeded stereoselectively, but in a modest 34% yield (entry 6). The reactive 2-pyrone stannane **16**[11] reacted with **12** to give *E*-**17** in an excellent 84% yield (entry 7). The known 3-trimethylstannyl-5-bromo-2-pyrone[12] **18** reacted selectively[13] with **12** to give *E*-**19** in 72% yield (entry 8).

Cinnamyl bromide **20** poses a similar question to **12**, in terms of the regio- and stereo-selectivity issues. As with geranyl bromide **12**, the stereochemistry in the cross-coupled products is preserved and no double migration is detectable by ^{1}H NMR spectroscopy. The cross-coupling reactions of *Z*-**10** and **8** with **20**, to afford *E,Z*-**21** and *E*-**22** were particularly efficient, proceeding in 86% and 92% yields, respectively (entries 9 and 10). Similarly, stannanes **5** and **14** gave *E*-**23** and *E*-**24** in good yields (entries 11 and 12). Allyltributyltin **3** reacts well with **20** to give *E*-**25** in a respectable 70% yield (entry 13). In the final example, a well known[4] activated substrate for cross-coupling reactions was chosen, namely 1-bromo-4-nitrobenzene **26**, for reaction with **8**. Although the reaction gave the cross-coupled product **27** in good yield, the reaction time was slower than had been anticipated (entry 14). This was quite surprising and led us to question the reactivity of aryl halide substrates under the reaction conditions using precatalyst **1**.

We moved on to investigate whether selectivity for the benzylic carbon (Csp[3]) over the aryl carbon (Csp[2]) could be achieved. Generally, aryl bromides react faster and more smoothly than allylic and benzylic bromides, and therefore one would expect that a selective reaction might be difficult.

There are a number of reports on the cross-coupling of benzylic and allylic halides with various organostannanes.[2] A large proportion of the reactions with benzylic bromides[14] employ hexamethylphosphoramide (HMPA) as the solvent, or require the presence of additional ligands, such as P(2-furyl)$_3$ or AsPh$_3$,[15] as well as the precursor catalyst (usually Pd$_2$dba$_3$, dba = dibenzylidene acetone). For example, the transfer of methyl,[16] vinyl,[17] butyl,[9] benzyl[9] and tolyl[18] groups from organostannanes are reported to require HMPA. The toxicity of this reagent, the inherent handling problems and precautions required for waste disposal are clearly a limitation. The commercially available precatalyst chlorobis(triphenylphosphine) (benzyl)palladium(II) [Pd(Bn)(PPh$_3$)$_2$Cl] is useful for a number of benzylic substrates,[19] particularly in the presence of ZnCl$_2$,[20] although some limitations are known.[21] In order to make a fair comparison, a competition reaction between benzyl bromide **2** (1 equiv) and bromobenzene **28** (1 equiv) was performed with *Z*-**10** (1 equiv) under the previously used reaction conditions (Table 2). We also studied the use of two other palladium(II) based precatalysts containing bromide ligands,[22] namely bromobis(triphenylphosphine)(benzyl)palladium(II) **31**[23] and bis(triphenylphosphine)palladium(II) bromide **32**[24] in the competition reactions.

The results of these experiments demonstrate that in the presence of **1**, the reaction gives *Z*-**29**, exclusively and in high yield (entry 1, Table 2). The employment of precatalyst **31** gave a mixture of *Z*-**29** and *Z*-**30**, in a ratio of ~1:2.25 (entry 2), whereas precatalyst **32** gave the aryl coupled product **30**, as a mixture of *E/Z*-stereoisomers in poor yield (entry 3). The difference between **1** and **31** is the presence of the succinimide instead of the benzyl group; precatalyst **32** contains an additional bromide instead of succinimide. These results suggest that the succinimide is playing a crucial role in this reaction.

We next studied whether a benzylic substrate containing both Csp[2]-Br and Csp[2]-Br bonds could be selectively cross-coupled in the presence of precatalyst **1**. 4-Bromobenzyl bromide **33** (1 equiv) was chosen as the substrate for the reaction with vinyl stannane **8** (1 equiv) (Scheme 2).

The reaction occurred preferentially at the benzylic (Csp[3]) position to provide 84% of the sp[3]-coupled product **30**, as opposed to only 7% of the sp[2]-coupled product **35**. We did not observe the formation of product **36** in this reaction.

In summary, precatalyst **1** has been successively employed in a range of Stille cross-coupling reactions of allylic and benzylic halides with a variety of organostannanes. The results suggest that there are subtle electronic and/or steric differences that affect the rates of reaction. The isolated yields of the cross-coupled products are on the whole very good and selectivity for benzyl bromide **2** versus bromobenzene **28** has been observed. Here the succinimide ligand, which can be described as a pseudohalide,[25] seems to play an important role. Our mechanistic investigations are ongoing and our findings will be reported in due course.

Table 2. Competition reactions between **2** and **28** for cross-coupling with *Z*-**10**
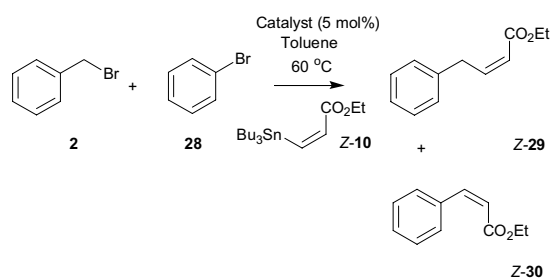
Entry	Precatalyst	Yield (%)	
		Z-**29**	*Z*-**30** (*E*-**30**)
1	Pd(NCOC$_2$H$_4$CO)(PPh$_3$)$_2$Br **1**	86	—
2	Pd(Bn)(PPh$_3$)$_2$Br **31**	16	36
3	Pd(PPh$_3$)$_2$Br$_2$ **32**	—	21 (15)
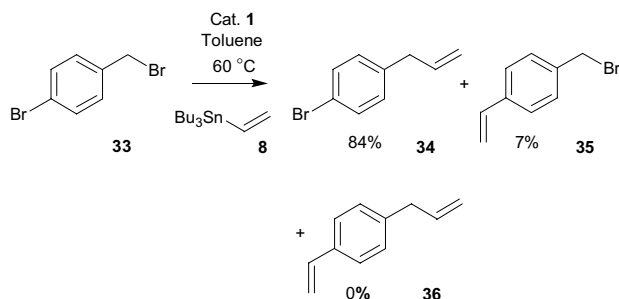
Scheme 2. Csp^3 cross-coupling versus Csp^2 cross-coupling.

Acknowledgements

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2. For a complete review of the Stille reaction, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.
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6. General procedure for Stille cross-coupling. The specified precatalyst (5 mol%) was added to a solution of benzyl bromide (0.25 mmol) and the stannane (0.3 mmol) in dry degassed toluene (2.5 mL) and heated to 60 °C in the dark, under a N$_2$ atmosphere, for the specified time. The reaction was allowed to cool to ambient temperature, then saturated aq KF (2.5 mL) was added and the mixture stirred vigorously for 1 h. The mixture was filtered through Celite, washed with saturated aq NaCl (2×2.5 mL) and dried (MgSO$_4$). Concentration in vacuo and subsequent purification by column chromatography using ethyl acetate/petroleum ether 40–60 °C mixtures (1:20 to 1:9, v/v) afforded the desired product as colourless oils. The employment of a DBU/I$_2$/Et$_2$O workup (see: Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140), to remove the organotin side products results in rapid regio- and stereo-isomerisation in the vast majority of examples. This should be avoided for these types of products.
7. All new compounds have been fully characterised (IR, ^{1}H, ^{13}C NMR, LRMS/HRMS and/or elemental analysis).
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23. Precatalyst **31** presents the initial oxidative addition intermediate from the reaction of $(PPh_3)_2Pd(0)$ and benzyl bromide.

24. Historically it has been assumed that $(PPh_3)_2PdX_2$ (where $X = Cl$ or Br) is reduced to $(PPh_3)_2Pd(0)$ in situ (overall two-electron reduction). However, Amatore and Jutand have recently demonstrated that the situation is much more complicated and that anionic $(PPh_3)_2Pd(0)-X(-)$ complexes are likely to be generated from $(PPh_3)_2PdX_2$, see Refs. 22b and 22c, and references cited therein.

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