Aryl bromide/triflate selectivities reveal mechanistic divergence in palladium-catalysed couplings; the Suzuki–Miyaura anomaly†

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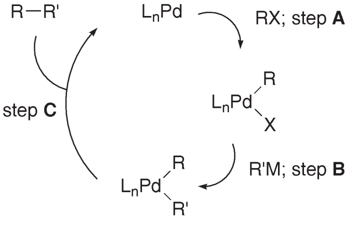
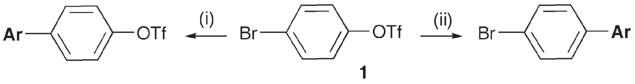
In palladium-catalysed cross-coupling reactions, the outcome of competition between aryl bromides and aryl triflates depends on the nucleophilic partner; Suzuki couplings with R–B generally follow a different pattern from other R–M species.

The original nickel-catalysed cross-coupling reactions reported by Kumada[1] and Corriu[2] involved the reaction of vinyl- and arylmagnesium halides with unsaturated halides; palladium catalysts followed rapidly thereafter.[3] A high level of generality has been achieved through extension in scope of both the electrophilic and nucleophilic components. In particular, organoboron, organozinc and organotin reagents are all regularly employed as nucleophiles.[4] Heck-type reactions involve an alkene as the nucleophilic component.[5] All such palladium-catalysed reactions are considered to involve a stepwise process from a low-valent metal complex that first activates the electrophile in a formal oxidative addition step **A**. The resulting complex then undergoes nucleophilic attack in step **B**. This permits C–C bond formation in step **C**, and direct or indirect return to the original state with product liberation. It is widely assumed that the addition of the electrophile to Pd[0] is commonly the turnover-limiting step.[6]



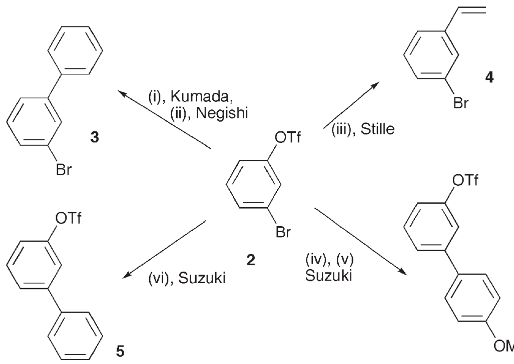
In studies of S_N reactions at sp^3 carbon, the relative reactivity of halide and tosylate as leaving groups has been widely used as a mechanistic tool.[7] Since both triflate and halide are commonly employed as electrophilic leaving groups in palladium catalysis, the opportunity for related studies exists. The only systematic work along these lines is due to Hayashi and co-workers,[8] involving an internal competition as recorded in Scheme 1. For Kumada (RMgX) coupling, a bulky monophosphine induces preferential displacement of bromide over triflate in compound **1**; a chelating aryldiphosphine does the reverse, and PPh_3 as ligand is unselective. The selectivity shown in Scheme 1 (ii) was demonstrated to occur for a wide range of bromoaryl triflates. Stoichiometric reactions with the appropriate Pd[0] precatalysts afforded the same trends, with dppp preferring insertion into C–OTf and $(PPh_3)_2$ preferring C–Br. The favouring of C–Br over C-OTf cleavage with catalysts that operate by a monophosphine mechanism has been more generally observed.[9] It is worth noting that the effect of added halide on chemoselectivity was noted in Hayashi's work, and the effect on reactivity[10] has been a consistent feature of coupling chemistry.



Scheme 1 Some previous results obtained for intramolecular bromide/triflate competition in Kumada coupling; (i) $Cl_2Pd(monophosphine)_2$, (ii) Cl_2Pd(diphosphine), added LiBr.

This protocol seemed to have general value in distinguishing between mechanistic pathways for the addition step. In particular, questions about the generality of coupling mechanisms can be addressed, comparing the variation of either the electrophile RX or the nucleophile R′M. With this in mind a preliminary screen of several palladium-catalysed coupling reactions was carried out, employing the bromotriflate **2** and varying the nucleophile; the results are shown in Scheme 2.

This set of data immediately confirms the main conclusion of Hayashi's work and extends it to both Negishi (Zn) and Stille (Sn) coupling; in all these cases the nucleophile reacts preferentially to



Scheme 2 Triflate/bromide selectivity in coupling reactions; preliminary results: (i) PhMgBr, LiBr, 5 mol% Cl_2Pd(dppp), Et_2O, 0 °C, 2 h, 60%, *ca.* 20% *m*-terphenyl; (ii) PhZnBr, 4 mol% Cl_2Pd(dppp), thf, 60 °C, 11 h, 90%; (iii) $CH_2{=}CHSnBu_3$, 3 eq. LiCl, 2 mol% Cl_2Pd(dppp), DMF, 25 °C, 39 h, 25%; (iv) $4\text{-}MeOC_6H_4B(OH)_2$, 3 eq. KF, 0.5 mol% $Pd(dba)_2$, 1.2 mol% PBu^t_3, thf, 25 °C, 3 h, 76%; (v) as (iv) with 5 mol% Cl_2Pd(dppp) as catalyst, 4 h, 52%; (vi) $PhB(OH)_2$, 3 eq. KF, 1.5 mol% $Pd(dba)_2$, 3.6 mol% PBu^t_3, thf, 25 °C, 4 h, 80%.

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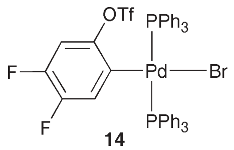
displace triflate rather than bromide when a palladium chelate or diphosphine complex is employed. The reverse result was observed in Suzuki coupling, where Br-displacement was observed irrespective of whether the ligand was dppp, or $P(Bu^t)_3$ under Fu's conditions – see entries (iv), (v), Scheme 2.[9] Indeed, no evidence for competing electrophilic reactivity of the triflate group was observed in these cases.

The unusual nature of these results encouraged us to extend them with a different reactant **7**,[11] designed to provide rapid ^{19}F NMR screening of the reaction course in diverse Pd couplings. Under a variety of conditions, Suzuki coupling of compound **7** using either 2 × PPh_3 or dppp as ligand led predominantly to the product of Br-displacement (Table 1). At lower temperatures, the reaction was slow and unspecific with these ligands and both possible monosubstituted products were formed, with bromide replacement dominant; entry 1 is typical. At higher temperatures, and in the non-polar solvent toluene following literature precedent, the reaction course was more selective. With either catalyst, the triflate-bearing monosubstitution product was formed near-exclusively at high conversion.

In keeping with these results, the complex **14** isolated in high yield from the reaction of bromotriflate **7** with $Pd(PPh_3)_4$ in hot toluene involves only C–Br insertion.‡ Employing this complex as the catalyst (5 mol%) in reaction of further reactant **7** with $PhB(OH)_2$ afforded complete conversion with biaryl **11** as the major product accompanied by traces of compound **13**, but with no detectable **12**.



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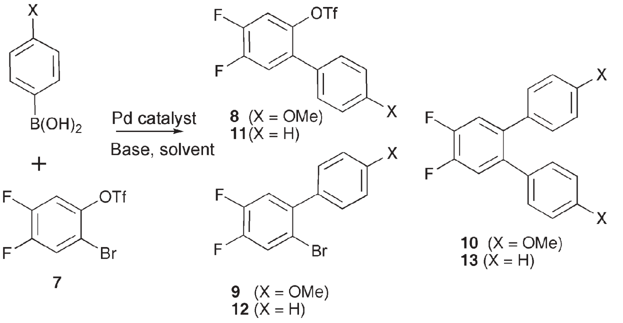
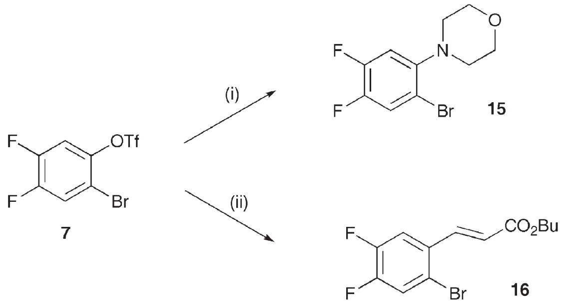
In order to check further the generality of this anomalous set of observations, reactant **7** was also subjected to a Pd-catalysed amination and a Pd-catalysed Mizoroki–Heck reaction (Scheme 3) under typical conditions, without optimisation. In both cases it is triflate that functions preferentially as the electrophilic leaving group, although the latter reaction gives a significant proportion of disubstituted product even at low conversion. In addition, the preference for triflate displacement in Kumada coupling with reactant **7** using 5 mol% $Cl_2Pd(dppp)_2$ was confirmed (PhMgBr, dioxane, 90 °C, 22 h; 100% conversion 2 : 1 **12** : **13**).

Table 1 Suzuki reactions with triflate **7**, 5 mol% catalyst. Reactions **I** involve boronic acid (X = OMe); reactions **II** (X = H). **A** refers to L_2 = dppp in Cl_2PdL_2, **B** refers to L_2 = 2 PPh_3

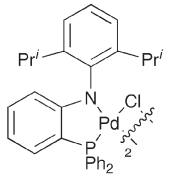
Entry	Reaction	Conditions	% Conversion *(**8** : **9** : **10**)* or *(**11** : **12** : **13**)*
1	**IA**	KF–thf; 23 °C, 4 h	28 *(65 : 35 : –)*
2	**IA**	K_3PO_4–C_7H_8; reflux 22 h	54 *(90 : – : 10)*
3	**IB**	As entry 2	88 *(> 95 : – : < 5)*
4	**IIA**	As entry 2	57 *(60 : 25 : 15)*
5	**IIA**	As entry 2/added LiBr	78 *(> 90 : – : < 10)*
6	**IIB**	As entry 2	66 *(100 : – : –)*
7	**IIB**	As entry 5	89 *(> 95 : – : < 5)*





Scheme 3 Amination and Heck reactions with reactant **7**; (i) 10 mol% catalyst ex. $Pd_2(dba)_3$/dppp, $NaOBu^t$, C_7H_8, 80 °C, 22 h, 50% as only amination product; (ii) same catalyst, Na_2CO_3, C_7H_8, 80 °C, 22 h, 25% with 15% disubstitution product.

Hence triflate is reluctantly displaced by boronate nucleophiles under the conditions of palladium coupling, but is otherwise the reactive partner. This puts Suzuki coupling out of line with all other common cross-coupling reactions in the present survey. In a more general sense, the activity of aryl triflates is ligand dependent, supporting Hayashi's observations. Hence lower reactivity has been observed here for monophosphine catalysts by Fu and co-workers. They demonstrate that when PBu^t_3 is employed as ligand, even aryl chlorides are more reactive than aryl triflates.[9] What is the explanation of the anomalous behaviour of the aryl triflate bond in Suzuki couplings? Differences as profound and general as the ones observed here require a radical explanation. Two of the three original papers on the Suzuki coupling of triflates comment on the lowered reactivity of –OTf relative to –Br, based on qualitative comparisons.[12] The oxidative addition step between various Ar–OTf and *in situ* generated $Pd(PPh_3)_2$ in DMF has a Hammett ρ value of 2.55, in line with an earlier value of $\rho = 2.0$ for aryl iodides.[13] A reactivity order of PhI ≫ PhOTf > PhBr was established for DMF. Since the aryl triflate oxidative addition generates a cationic product directly, it must be irreversible under the conditions of Suzuki coupling where more powerful oxygen nucleophiles (*e.g.* PO_4^{3-}) are present. Hence the oxidative addition step appears to be perfectly normal for Ar–OTf, in line with aryl halides. This must indeed be the case, given the large number of successful Suzuki reactions that have been performed with aryl triflates.[14] It is preferable to consider ways in which Suzuki couplings of aryl bromides might be subject to enhanced reactivity. Although data are limited, and confined to two particular palladacyclic catalysts, it appears that the activity of *m*-, *p*-substituted aryl bromides towards coupling with $PhB(OH)_2$ is insensitive to electronic effects, with recorded ρ-values of 0.48 for catalyst **17** and *ca.* 1.0 for catalyst **18**.[15] The authors suggest that under their conditions oxidative addition is not the turnover-limiting step in catalysis, but alternative suggestions are lacking and this one requires reversibility of the Ar–Br addition to palladium, which has only been observed under high steric stress up to now.[16]



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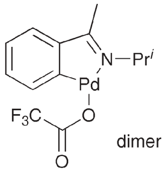

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We suggest possible explanations with direct involvement of the boronic acid, compatible with the observed facts and not requiring a change in turnover-limiting step. $ArB(OH)_2$ could feasibly be involved in one of two ways. It is known that boranes have an affinity for Br^-,[17] and possible that the association of trigonal boron with the halide could facilitate its departure, providing a pathway of lowered energy that is not available to the triflate. If correct, electrophilic assistance of this type could provide a novel feature of catalyst design capable of enhancing chemoselectivity.[18] For the second and more plausible alternative, we consider recent DFT calculations on the ArX addition step to Pd, studied in detail by several authors.[19] These reinforce the viability of the Amatore–Jutand pathway, where the oxidative addition step is facilitated by pre-coordination of an anion (Cl^-, OAc^-) to the palladium catalyst, either PdL or PdL_2.[19a,b] Specific coordination of a 3- or 4-coordinate boronate anion is thus feasible as an activation pathway, and one which permits the β-transfer of the aryl group to Pd. A similar pathway has been demonstrated for the Rh-catalysed conjugate addition of $ArB(OH)_2$ to electrophilic alkenes, which the authors indicate may have relevance to Suzuki coupling.[20] Further experimental work is required to distinguish between a modified oxidative addition step and a turnover-limiting boronate transmetallation.

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Notes and references

‡ The X-ray structure of complex **14** has been obtained and will be described in detail elsewhere because of the interesting dual π-stacking involved; G. Espino, A. R. Cowley and J. M. Brown, in preparation.

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