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Tandem intermolecular Suzuki coupling/intramolecular vinyl triflate–arene coupling†

Michael C. Willis,* Christelle K. Claverie and Mary F. Mahon

Department of Chemistry, University of Bath, Bath, UK BA2 7AY. E-mail: m.c.willis@bath.ac.uk; Fax: (44) 01225 386231; Tel: (44) 01225 386568

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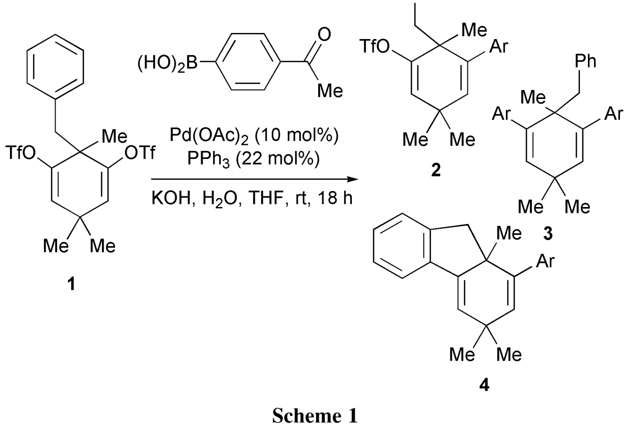
Treatment of a benzyl substituted *meso*-ditriflate with boronic acids in the presence of palladium acetate, triphenylphosphine and caesium fluoride results in intermolecular Suzuki coupling followed by vinyl triflate–arene cyclisation to provide, in high yields, single regioisomers of tricyclic-carbocycles.

The Suzuki coupling reaction is one of the most reliable and frequently used palladium catalysed cross-coupling procedures. Its widespread use in the synthesis of both natural and unnatural products is testament to its utility and practicability.[1,2] Conversely, the direct palladium catalysed coupling between unfunctionalised arenes and aryl halides or triflates is not well represented in the literature although the intramolecular version of this process has been utilized in the synthesis of a variety of cyclic systems including dibenzofurans,[3] 5- and 6-membered lactones[4,5] and lactams,[6] and a range of aromatic carbocyclic frameworks.[7–11] This class of coupling reaction is attractive from a synthetic point of view as it has the advantage of requiring only a hydrogen atom as the leaving group on one of the aryl rings, thus significantly simplifying the synthesis of the substrates. This utility does however introduce a complication in that the formation of regioisomeric products is possible in many cases. To the best of our knowledge the related reaction, the palladium catalysed intramolecular coupling of a *vinyl halide or triflate* with an unfunctionalised arene has not been reported. In this communication we disclose our studies combining intermolecular Suzuki cross coupling reactions with an intramolecular arene–vinyl triflate coupling to provide a tandem reaction route to the regioselective synthesis of tricyclic-carbocycles.

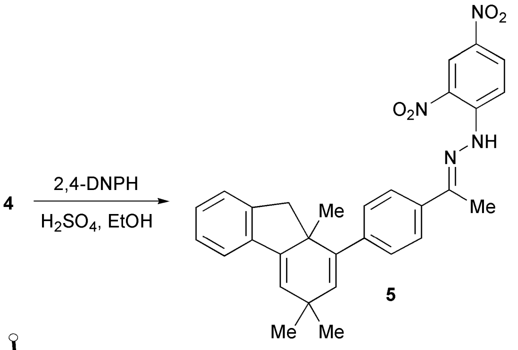
We recently reported the efficient preparation of a range of *meso*-ditriflates such as **1** (Scheme 1).[12] In the course of studying the reactivity of these highly functionalised substrates we discovered that when **1** was treated with 4-acetylbenzene boronic acid under standard Suzuki coupling conditions ($Pd(OAc)_2$, PPh_3, KOH) we observed, as well as the expected mono- and dicoupled products **2** and **3**, the formation of a third compound that was being produced at the expense of the mono-coupled material. This final compound was eventually shown to be the tricyclic-carbocycle **4**.



Scheme 1

The formation of **4** presumably occurs by an initial intermolecular Suzuki coupling to generate **2** followed by an intramolecular arene–vinyl triflate coupling. Although the related catalysed arene–aryl triflate couplings are known they generally require much harsher conditions (typically temperatures > 120 °C) to achieve good yields of the desired cyclised compounds. The mild conditions (rt) employed in the preparation of **4** therefore deserve particular note. To confirm the identity of this unprecedented product the ketone functionality present in **4** was derivatised to produce the 2,4-dinitrophenylhydrazone derivative **5**. Recrystallisation of **5** from methylene chloride–hexane generated crystals suitable for diffraction studies. The ensuing structure,[13] shown in Fig. 1, confirms the formation of the 5-membered carbocycle containing a defined quaternary centre.

Optimized reaction conditions for the selective formation of **4** involved exchanging the base to caesium fluoride, increasing the dilution to 0.025 M (previously 0.10 M), increasing the catalyst loading to 15 mol% palladium and conducting the reactions at 50 °C. Using these new conditions tricycle **4** could be isolated in 88% yield along with only small amounts of the mono- and dicoupled products (< 5%).[14] The system could be extended to include a variety of boronic acid coupling partners (Table 1). Boronic acids substituted with both electron rich (X = OMe, Ph) and electron poor (X = CN, C(O)Me) groups are



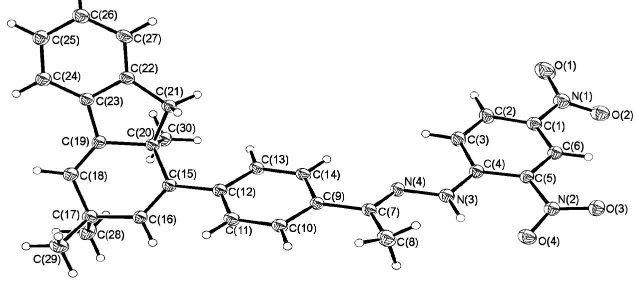


Fig. 1 The asymmetric unit for the crystal structure of **5**. Ellipsoids are depicted at 30% probability.

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† Electronic supplementary information (ESI) available: experimental and crystallographic data for compound **5**. See http://www.rsc.org/suppdata/cc/b2/b200692h/

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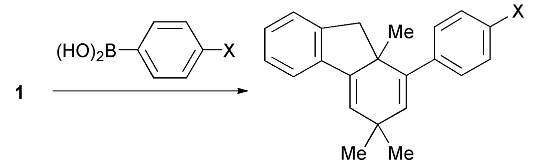
Table 1 Reaction of **1** with substituted boronic acids

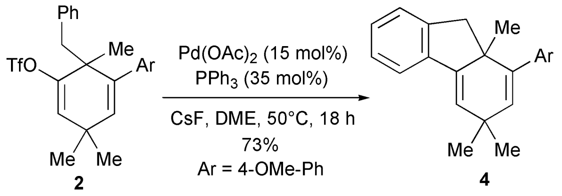


Entry	X	Time/h	Yield (%)
1	C(O)Me	20	88
2	CN	20	82
3	OMe	20	80
4	Ph	20	72
5	H	20	65

Conditions: Pd(OAc)$_2$ (15 mol%), PPh$_3$ (35 mol%), boronic acid (1.8 eq.), CsF, DME (0.025 M), 50 °C, 18 h.

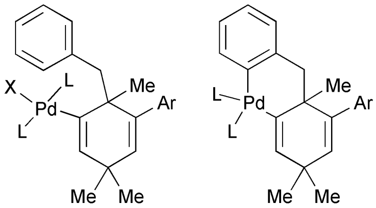
tolerated well and provide the corresponding carbocycles, as single regioisomers, in good to excellent yields.

Tandem or sequential reaction sequences represent a powerful strategy for the efficient and selective synthesis of complex organic architectures.[15,16] The definition of a tandem process usually involves a series of sequential reactions in which functionality generated in the first step is involved in the subsequent reaction; the two reactions combined in the formation of **4** do not immediately appear to satisfy these conditions. However, treatment of ditriflate **1** under identical reaction conditions but excluding the boronic acid resulted in no reaction, thus indicating that an aryl substituent from the initial Suzuki cross coupling is required before the arene–vinyl triflate cyclisation can take place. Given the electronic isolation of the two vinyl triflate units we speculate that the introduction of the aryl substituent causes a conformational adjustment that favours cyclisation. This is supported by the observation that resubjection of mono-coupled product **2** to the reaction conditions, excluding the boronic acid, delivers the cyclised material in good yield (Scheme 2).



Scheme 2

In analogy to the reported arene–aryl triflate cyclisations we expect the formation of **4** to proceed *via* an initial oxidative addition to generate Pd(II) species **6** followed by insertion into the *ortho*-C–H bond to generate palladacycle **7** (Fig. 2). Reductive elimination from **7** then generates the required 5-membered carbocycle. All of the cyclised compounds obtained are formed as single regioisomers, this is presumably due to the unfavourable formation of the corresponding 7-membered palladacycle.[17] The use of additives such as LiCl in palladium catalysed vinyl- and aryl triflate coupling reactions is well documented and in early experiments we explored the effect of added LiCl on the formation of **4**.[18] Interestingly, when LiCl was added only mono- and dicoupled Suzuki products were obtained with no cyclisation products being observed. We attribute this selectivity to the inability of intermediate **8**, containing the more strongly donating Cl- ligand, to undergo the required C–H insertion.



6 X = OTf
8 X= Cl

7

Fig. 2

In summary, we have described a novel intramolecular palladium catalysed arene–vinyl triflate coupling that can be combined with an initial Suzuki cross coupling in a tandem sequence to generate tricyclic-carbocycles. The reactions are conducted under mild conditions and yield only single regioisomers of products in good yields. Studies to probe the exact requirements for arene–vinyl triflate coupling and to fully explore the scope of this process are under way and will be reported in due course.

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13 *Crystal Data*: $C_{30}H_{28}N_4O_4$, M = 508.5, orthorhombic, λ = 0.71073 Å, a = 9.2040(1), b = 16.1930(2), c = 34.3440(5) Å, U = 5118.64(11) Å^3, T = 150(2) K, space group = *Pbca*, Z = 8, D_c = 1.320 g cm^{-3}, μ(Mo-Kα) = 0.089 mm^{-1}, F(000) = 2144, size = 0.30 × 0.30 × 0.13 mm. 40645 reflections collected, 6112 unique (Rint = 0.091), Final R_1 = 0.0594, wR_2 = 0.1352 (observed data [$I > 2\sigma(I)$]). CCDC 178159. See http://www.rsc.org/suppdata/cc/b2/b200692h/ for crystallographic files in .cif or other format.
14 The procedure for the formation of compound **4** serves as a general procedure; a dry 25 mL flask equipped with a condenser was charged with ditriflate **1** (102 mg, 0.2 mmol), 4-acetylphenylboronic acid (59 mg, 0.36 mmol), Pd(OAc)$_2$ (6.7 mg, 0.03 mmol), PPh$_3$ (17 mg, 0.07 mmol) and caesium fluoride (91 mg, 0.6 mmol). The solid mixture was dried under vacuum for 1 h before DME (8 mL) was added. The solution was stirred at rt for 10 min and then heated at 50 °C for 20 h. The solution was cooled to rt and partitioned between water (5 mL) and EtOAc (5 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL) and the combined organic portions were then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 2% EtOAc–petrol) to give *tricyclic diene* **4** (57.2 mg, 88%) as a colourless oil; ν_{max} (neat)/cm^{-1} 3030, 2959, 2925 and 2857, 1682, 1603; δ_H (400 MHz, $CDCl_3$) 7.95–7.93 (2H, m), 7.53–7.47 (3H, m), 7.24–7.17 (3H, m), 5.98 (1H, d, J 1.6), 5.76 (1H, d, J 1.6), 2.94 (1H, d, J 14.8), 2.71 (1H, d, J 14.8), 2.64 (3H, s), 1.43 (3H, s), 1.31 (3H, s), 1.26 (3H, s); δ_C (100 MHz, $CDCl_3$) 197.5 (C=O), 146.7 (C), 146.0 (C), 142.0 (C), 141.7 (C), 138.9 (C), 137.3 (CH), 135.4 (C), 128.1, 128.0, 127.7, 126.7,125.5, 125.3 and 120.7 (CH), 46.9 (C), 43.9 (CH_2), 36.6 (C), 30.9 (CH_3), 30.7 (CH_3), 29.4 (CH_3), 26.7 (CH_3C=O); m/z (CI$^+$) 329.3 (100%, M + H$^+$); Found M^+, 328.1825, $C_{24}H_{24}O$ requires 328.1827.
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