Palladium-Catalysed Cyclisation–Anion Capture Processes: In situ 'Zipper' Generation via Intramolecular Nucleophilic Capture of π-Allylpalladium Species

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Received 27 April 2006

Abstract: A palladium-catalysed one-pot reaction for the in situ generation of 'zippers' and subsequent cyclisation–anion capture with phenyl boronic acid produces tricyclic heterocycles with the formation of three C–C bonds, one C–N bond, two rings, two stereocentres and one tetrasubstituted C-centre.

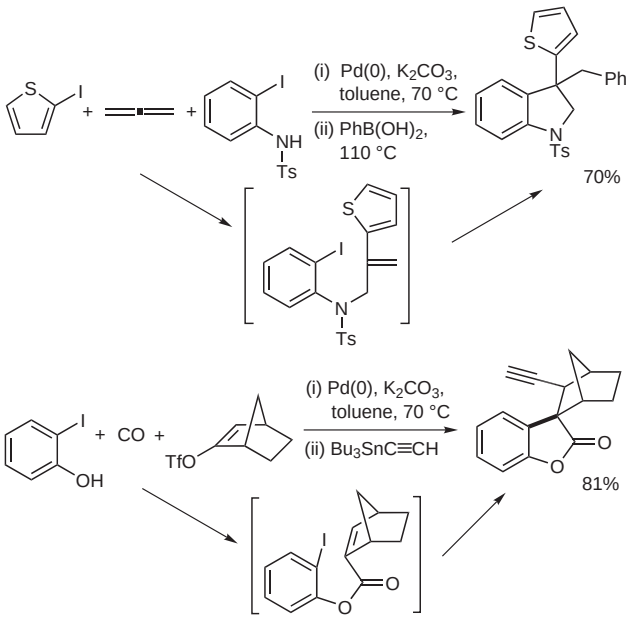
Key words: organopalladium chemistry, one-pot sequential reaction, heterocycles

The seminal contributions of Richard Heck to organopalladium chemistry are wide-ranging but it is the Heck Reaction that, in particular, struck a resonating chord with a wide spectrum of researchers and process chemists.[1,2] The popularity of this classic reaction shows no signs of diminishing its rapid growth as judged by the output of papers and it is a great pleasure to contribute some of our work to this tribute to Richard.

Over the past decade we have developed powerful, widely applicable, highly regio- and stereoselective palladium-catalysed cyclisation–anion capture methodology.[3,4] Recently two new starter species or 'zippers' (carbamoyl and oxy-carbonyl) have been developed and their cyclisation–anion capture explored.[5,6] Our basic methodology would advance to a higher level of sophistication if the starter or 'zipper' species could be created in situ as part of extended cascades or sequential one-pot processes. This is a challenging and novel area that will greatly expand the synthetic flexibility of the cascades whilst increasing the molecular diversity of the products. A key strategy for in situ 'zipper' generation is to employ what we termed relay-switch components such as CO and allenes.[3] Such components allow the cascade to be switched between inter- and intramolecular processes.

In situ 'zipper' generation utilising allene as the relay switch can be classified into four distinct classes depending on whether the formation of the π-allyl species (from aryl iodide and allene) and its subsequent nucleophilic capture is inter- or intramolecular (Table 1)

We have recently reported the palladium-catalysed (Table 1, class 1) in situ 'zipper' generation using CO[7] and allene[8] as relay switches and their subsequent cyclisation–anion capture processes (Scheme 1). Thus, Pd(0) reacts selectively with 2-iodothiophene/vinyltriflate. The arylpalladium(II)/vinyl-palladium(II) species then reacts with allene/CO to give π-allylpalladium(II)/acylpalladium(II) species which are captured intermolecularly by the nitrogen/oxygen nucleophile to generate the zippers. These processes resulted in the formation of one new heterocyclic ring, one C–O/C–N bond, two C–C bonds and one tetrasubstituted C-centre. Others have also recently reported a related in situ 'zipper' generation and subsequent cyclisation–anion capture processes.[9,10]



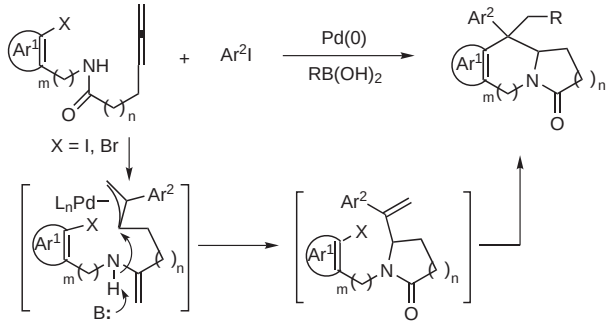
Scheme 1

Table 1 Synthetic Strategies for in situ 'Zipper' Generation via Allene Relay Switches

Class	π-allyl formation	Nucleophilic capture
1	intermolecular	intermolecular
2	intermolecular	intramolecular
3	intramolecular	intermolecular
4	intramolecular	intramolecular

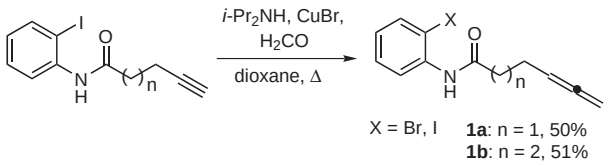
SYNLETT 2006, No. 18, pp 3021–3024
Advanced online publication: 25.10.2006
DOI: 10.1055/s-2006-951525; Art ID: S10006ST

In this communication we report successful cyclisation–anion capture cascade processes involving in situ class 2 'zipper' generation via intramolecular nucleophilic attack on the π-allylpalladium species and their subsequent cyclisation–anion capture, using boronic acids as anion capture agents (Scheme 2). A key feature of Scheme 2 is that the relative rates of oxidative addition of Pd(0) to the halides must be $Ar^2I > Ar^1X$ for a successful outcome.[7,8,11]



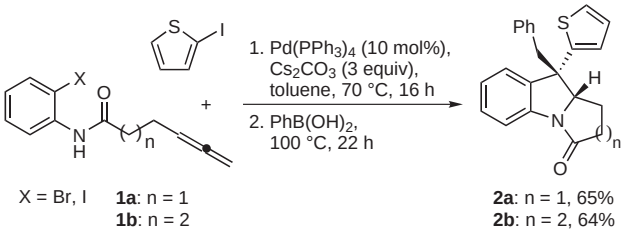
Scheme 2

For our initial studies, we selected **1a**,**b** as trifunctional aryl iodide/allene/nucleophile substrates. These were successfully synthesised via the Crabbe reaction[12] of the corresponding alkynes (Scheme 3) and were obtained as a 1:1 mixture of bromo and iodo allenes. The bromo species arises from halogen exchange with copper(I) bromide used as the catalyst for the Crabbe reaction.



Scheme 3

First we studied the one-pot sequential 'zipper' generation–cyclisation–anion capture process of **1a** (1 mmol) with 2-iodothiophene (1 mmol), $Pd(PPh_3)_4$ (10 mol%) and Cs_2CO_3 (3 mmol) in toluene (10 ml) at 70 °C for 16 hours, at which stage phenyl boronic acid (1 mmol) was added and the mixture heated at 110 °C for a further 22 hours to afford the tricyclic compound **2a** as a single diastereomer in 65% yield (Scheme 4). The structure of **2a** was established by NOE studies (Figure 1, **A**). Thus, irradiating one of the benzylic diastereotopic protons H_b caused enhancement of H_a (8%) and H_c (30%). The structure was confirmed by a subsequent X-ray crystal structure (Figure 2). Molecular models indicate the transition state develops a slight bowl shape as the second C–C bond forms and the sp^3 C–PdL_n bond is cleaved. Subsequently, following Suzuki coupling, the benzyl group is located on the least hindered outer face (Figure 1, **B**). Next, we varied the chain length between the allene and the nucleophile. Compound **1b** underwent a similar palladium-catalysed in situ 'zipper' generation–cyclisation–anion capture process to give tricyclic product **2b** in 64% yield.[14] The stereochemistry of the product **2b** was again confirmed by NOE studies analogous to those reported for **2a**.



Scheme 4

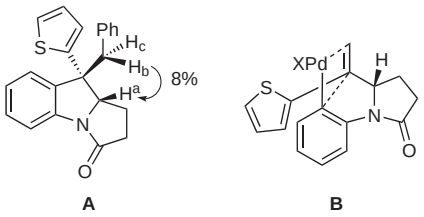


Figure 1

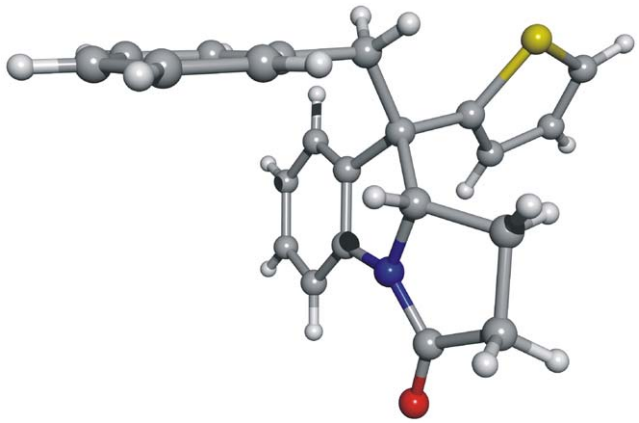
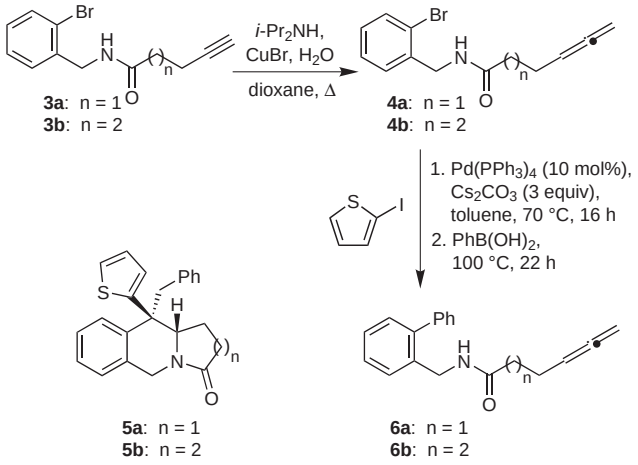


Figure 2

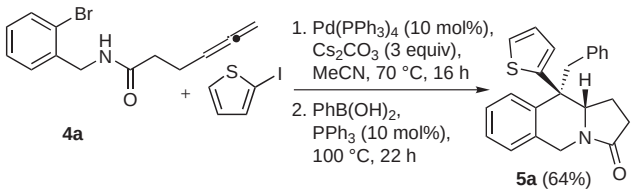
Finally, we varied the chain length between the nucleophile and the aryl iodide. Compounds **4** were synthesised from **3** via the Crabbe reaction.[12] However, under the previously developed palladium-catalysed conditions **4a** and **4b** failed to produce the desired products **5a** and **5b** in the presence of 2-iodothiophene (1 mmol). Instead, products **6a** and **6b**, derived from direct capture of boronic acid, were isolated in 50–67% yield (Scheme 5).

Failure to observe the cyclisation may reflect, we believe, the faster rate of the oxidative addition onto the C–Br bond, probably by the more efficient coordination of the oxygen atom of the amide due to the difference in electronegativity of the N atoms in **1** compared to **4**. Excess phosphine has been found to be beneficial in breaking the undesired coordination of palladium to a proximate donor.[13] This strategy was applied to **4a** (1 mmol) which was reacted with 2-iodothiophene (1 mmol), $Pd(PPh_3)_4$



Scheme 5

(10 mol%) and Cs_2CO_3 (3 mmol) in MeCN (10 mL) at 70 °C for 16 hours, then phenyl boronic acid (1 mmol) and PPh_3 (10 mol%) were added and the mixture was heated at 110 °C for a further 22 hours to afford the tricyclic compound **5a** as a single diastereomer in 64% yield (Scheme 6). The stereochemistry of **5a** was tentatively assigned based on NOE studies (Figure 3). Thus, irradiating one of the benzylic diastereotopic protons H_b caused enhancement of H_c (9%) but no enhancement of H_a. Similarly irradiation of the other benzylic diastereotopic proton H_c caused enhancement of H_b (20%) and but again had no effect on H_a indicating the *trans* relationship. We presume the stereochemical outcome reflects the more relaxed tether length in the case of **7** the precursor of **5a**.



Scheme 6

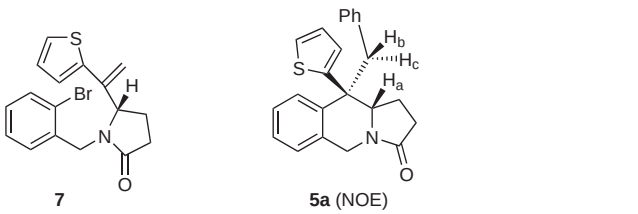


Figure 3

Overall these new processes generate three C–C bonds, one C–N bond, two rings, two stereocentres and one tetrasubstituted C-centre.

In conclusion, we have demonstrated a novel palladium-catalysed one-pot in situ 'zipper' generation coupled to sequential cyclisation–anion capture processes to access tricyclic heterocycles.

Acknowledgement

We thank Leeds University and ORS for support.

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(14) Compound **2b**: A mixture of **1b** (1 mmol), Cs_2CO_3 (3 mmol), $Pd(Ph_3)_4$ (10 mol%), and 2-iodothiophene (1 mmol) in toluene (10 mL) was stirred and heated at 70 °C for 16 h at which stage phenyl boronic acid (1 mmol) was added. The mixture was heated at 110 °C for 22 h, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography, (petroleum

ether–Et_2O, 1:3), to give the product in 64% yield as a single diastereomer, which crystallised from (EtOH–H_2O) as colourless prisms; mp 170–171 °C. IR (film): 2947, 1652 (CO), 1597, 1479,1462, 1428, 1402, 1284, 909 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.03 (qd, *J* = 13.2, 3.4 Hz, 1 H, HC*H*CHN), 1.62 (qdd, *J* = 13.2, 6.0, 3.2 Hz, 1 H, *H*CHCHN), 1.88 (m, 1 H, HC*H*CH_2C=O), 1.95 (m, 1 H, *H*CHCH_2C=O), 2.24 (m, 1 H, *H*CHC=O), 2.44 (ddt, *J* = 18.0, 5.9, 1.5 Hz, 1 H, HC*H*C=O), 3.62, 3.85 (2 × d, *J* = 14.2 Hz, 2 H, CH_2Ph), 4.08 (dd, *J* = 11.8, 3.7 Hz, 1 H, CHN), 6.47 (dd, *J* = 3.6, 1.1 Hz, 1 H, thienyl-H), 6.91 (dd, *J* = 5.1, 3.6 Hz, 1 H, thienyl-H), 7.06–7.08 (m, 2 H, ArH), 7.14–7.25 (m, 5 H, ArH), 7.31 (td, *J* = 7.8, 1.3 Hz, 1 H, ArH), 7.34 (dd, *J* = 7.8, 1.3 Hz,1 H, ArH), 8.19 (d, *J* = 7.8 Hz, 1 H, ArH). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 20.70, 24.90, 32.70, 41.90, 54.70, 66.80, 118.10, 124.70, 125.00, 125.20, 125.80, 127.30, 127.40, 128.80, (2 × C), 129.20, 131.20 (2 × C), 135.90,137.10, 143.00, 148.60, 169.10. MS (FAB): *m*/*z* (%) = 360 (M^+ + H, 100), 268 (86), 212 (7), 91 (11). Anal. Calcd for $C_{23}H_{21}NOS$: C, 76.85; H, 5.90; N, 3.90; S, 8.90. Found: C, 76.60; H, 5.80; N, 3.85; S, 8.80.