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Palladium-catalysed in situ zipper generation–cyclisation–anion capture. Synthesis of 3,3-disubstituted indolines and 2,3-dihydrobenzofurans

Ronald Grigg,* Edoardo Mariani and Visuvanathar Sridharan

Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, Leeds University, Leeds LS2 9JT, UK

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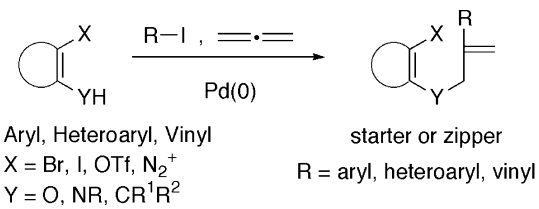
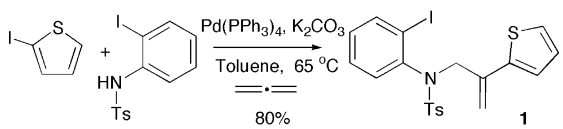
Abstract—A palladium-catalysed one-pot reaction for the in situ assembly of monocyclisation 'zippers' and subsequent cyclisation–anion capture with aryl/heteroaryl boronic acids produces 3,3-disubstituted indolines and 2,3-dihydrobenzofurans.

Palladium-catalyzed cascade reactions provide versatile and efficient methods for the assembly of a wide range of organic compounds via carbon–carbon and carbon–heteroatom bond formation. These cascades usually proceed under mild conditions and are tolerant of a wide variety functional groups.[1–4] They permit the attainment of a high degree of molecular complexity in a one-pot protocol where conventional methodology would require technically demanding multistep synthesis. Such reactions minimise reactor time and waste, whilst offering interesting synthetic solutions.



Scheme 1.



Scheme 2.

We have developed two powerful catalytic cascade protocols: cyclisation–anion capture[5] and relay switched molecular queuing processes.[6] Both of these involve formation of one or more rings and utilise a suitable starter species to achieve this. A typical example of a starter species ('zipper') is shown in Scheme 1.

Cascade zipper generation of the type illustrated in Scheme 1 is a challenging problem that potentially offers access to a wide variety of 'zippers' that could form the basis for expanded cascades in conjunction with a cyclisation–anion capture sequence.

In this communication we report successful cyclisation–anion capture cascade processes involving in situ synthesis of two families of monocyclisation zippers and their subsequent cyclisation–anion capture, using boronic acids as terminating species, leading to 3,3-disubstituted indolines and 2,3-dihydrobenzofurans.

Zipper **1** was synthesised in 80% yield from 2-iodothiophene (1 mol equiv.), allene (1 bar) and 2-iodo-*N*-tosylaniline (1 mol equiv.), using $Pd(PPh_3)_4$ (10 mol%) as catalyst and potassium carbonate (10 mmol) in toluene at 65°C (Scheme 2).

The Pd(0) reacts selectively with iodothiophene, probably because the oxidative insertion step is facilitated by coordination with the adjacent sulfur atom. The arylpalladium(II) species then reacts with allene giving a π-allylpalladium(II) species that is captured by the deprotonated 2-iodo-*N*-tosylaniline.

* Corresponding author. Tel.: +44-(0)113-233-6501; fax: +44-(0)113-233-6501; e-mail: r.grigg@chem.leeds.ac.uk

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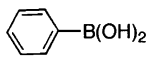
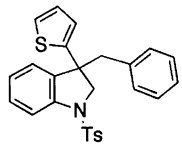
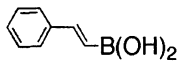
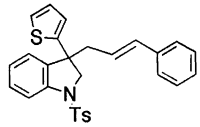
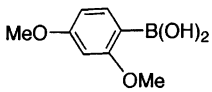
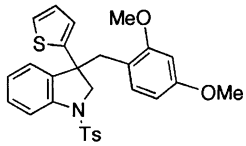
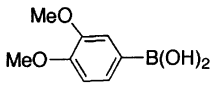
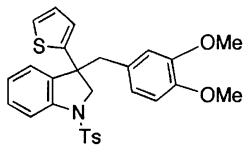
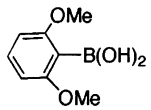
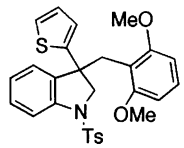
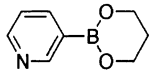
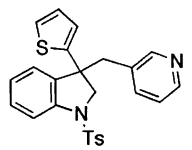
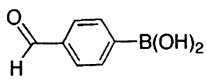
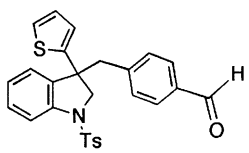
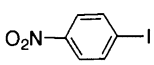
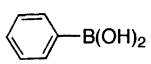
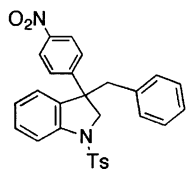
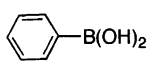
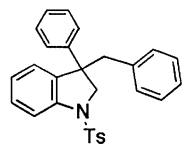
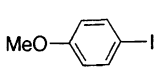
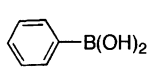
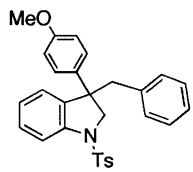
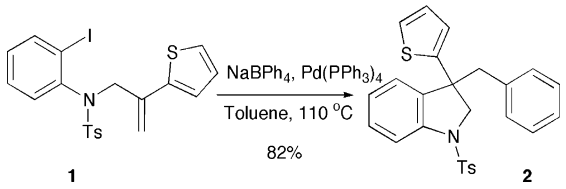
Table 1. One-pot zipper formation–cyclisation–anion capture from aryl iodides, 2-iodo-*N*-tosylaniline, allene (1 bar) and boronic acids[a]

Entry	Aryl Iodide	Boronic Acid	Product	Yield %[b]
1				70
2				95
3				61
4				84
5				0
6				67
7				58
8				56
9				78
10				85

[a]All reactions employed allene (1 bar), 5 mol% $Pd(PPh_3)_4$, iodothiophene or iodoarene (1 mmol), 2-iodo-*N*-tosylaniline (1 mmol) and K_2CO_3 (2 mmol) in toluene (8 ml) at 70°C for 16 h. Excess allene was then vented, the arylboronic acid (1.2 mmol) and water (0.2 ml) added and heating continued for 22 h.

[b]Isolated yield.



Scheme 3.

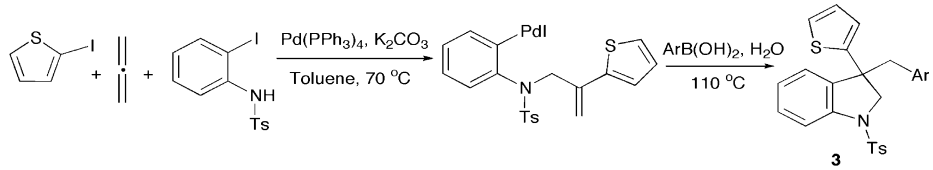
We first tested the isolated zipper **1** in a cyclisation–anion capture procedure using sodium tetraphenylborate as anion capture agent (Scheme 3). The desired product **2** was formed 82% yield.

Next we performed the entire sequence without isolation of the intermediate zipper, simply adding the capture agent at the end of the first step.[7] The overall yield of the one-pot protocol (66%) is about equal to that obtained previously by the two-step procedure, but there is the advantage of avoiding purification and recharging the solvent and the catalyst.

Subsequently we tested the generality of the reaction using commercially available boronic acids as capture agents (Scheme 4) (Table 1).[8]

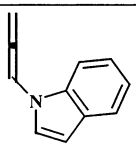
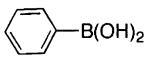
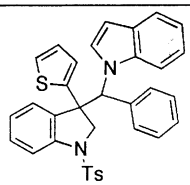
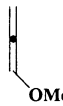
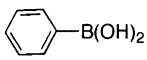
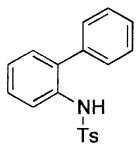
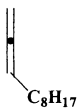
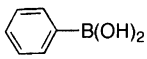
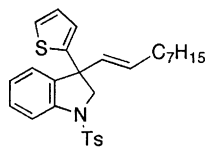
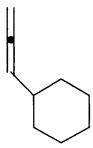
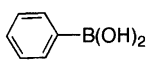
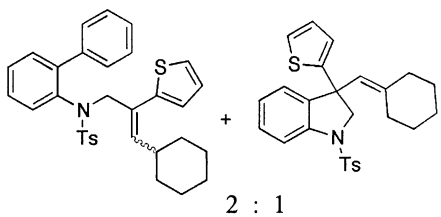
Good to excellent yields were obtained. Steric effects underlie the trend in the yield of product from the isomeric dimethoxyphenylboronic acids (Table 1, entries 3–5) and the nearly quantitative yield obtained with β-styrylboronic acid (entry 2).

We then synthesised several other zippers of the same family using substituted iodobenzenes in place of iodothiophene (Table 1). The reaction proved to be quite general, working with activated (entry 8) and non-activated (entry 9) iodoarenes in addition to 4-iodoanisole (entry 10), which interestingly, afforded the



Scheme 4.

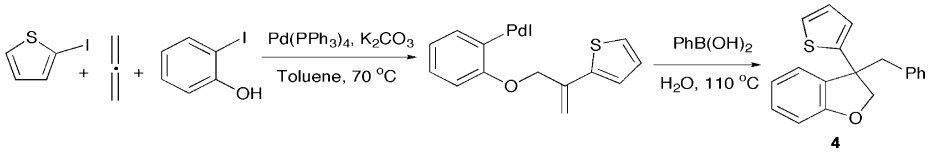
Table 2. One-pot synthesis from 2-iodo-*N*-tosylaniline, substitutes allenes and 2-iodothiophene

Entry	Aryl Iodide	Allene	Boronic Acid	Product	Yield %[a]
1					39
2					52[b]
3					35
4				 2 : 1	54[c]

[a]Isolated yield.

[b]From hydrolysis of the *O*-methyl hemiaminal intermediate and subsequent Suzuki reaction.

[c]Reaction performed at 140°C.



Scheme 5.

highest yield, whilst 4-nitroiodobenzene gave the poorest yield.

We have briefly investigated the reaction with 2-iodophenol in place of 2-iodo-*N*-tosylaniline. The corresponding 3,3-disubstituted 2,3-dihydrobenzofuran **4** was isolated in 40% yield (Scheme 5).

Finally, we also evaluated several substituted allenes in this reaction (Table 2). All the reported allenes gave the required intermediate with moderate to good yields, the alkyl-allenes generally requiring higher temperature of reaction. In all cases except one (entry 2) the nucleophilic attack of 2-iodo-*N*-tosylaniline was found to occur at the unsubstituted terminus of the allene; the exception, methoxyallene, reflects the enolic nature of this species. The subsequent cascade proved to be more problematic, with steric hindrance (entry 1) and competing processes like hydrolysis (entry 2), β-hydride elimination (entry 3) or direct capture (entry 4) preventing or diverting the desired outcome of the reaction.

Further studies of in situ assembly of 'zippers' as well as the use of substituted allenes are currently under investigation in our laboratories and the results will be published in due course.

Acknowledgements

We thank Leeds University and the EPRSC for support.

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6. Grigg, R.; Sridharan, V. *Pure Appl. Chem.* **1998**, *70*, 1047–1057.
7. Iodothiophene (2 mmol), 2-iodo-*N*-tosylaniline (2 mmol), potassium carbonate (4 mmol), $Pd(PPh_3)_4$ (10 mol%) and toluene (10 ml) were charged in a 100 ml glass pressure vessel, the mixture was degassed by two freeze–pump–thaw cycles and allene (1 bar) was finally added; the flask was immersed in an oil bath at 65°C and stirred for 16 h. After cooling to rt allene was vented and $NaBPh_4$ (2 mmol) added, the flask was immersed in an oil bath at 110°C and stirred for 22 h. Filtration and evaporation of the solvent in vacuo afforded the crude product, which was purified by column chromatography to afford **1** (66%).
8. Grigg, R.; Sansano, J. M.; Santhakumar, V.; Sridharan, V.; Thangavelanthum, R.; Thornton-Pett, M.; Wilson, D. *Tetrahedron* **1997**, *53*, 11803–11826.