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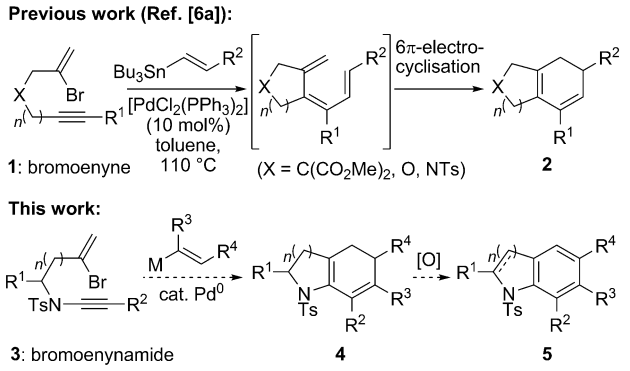
Palladium-Catalyzed Cascade Cyclization of Ynamides to Azabicycles

Rebecca L. Greenaway,[a] Craig D. Campbell,[a] Oliver T. Holton,[a] C. Adam Russell,[b] and Edward A. Anderson*[a]

Nitrogen-containing bicyclic heteroaromatics are ubiquitous in organic chemistry, featuring in countless natural products and drugs.[1] Their importance is evidenced by the multitude of synthetic routes that have been developed to access such structures,[2] the majority of which use a prefunctionalized benzene ring as a nucleus for heterocycle annulation—an approach that intrinsically suffers from a reduced ability to diversify the benzenoid portion of the heterocycle at a late stage of a synthesis. A solution to this problem would be the reversal of the order of annulation events,[3] or the formation of both rings in a single step.[4,5]

We[6] and others[7] have developed an efficient carbopalladation/Stille cross-coupling/electrocyclization route to bi- and tricyclic carbocycles from acyclic bromoenynes (**1**→**2**, Scheme 1).[8] We realized that the use of bromoenynamides **3** rather than bromoenynes **1** in this cascade process would lead to significantly more valuable azabicycles **4**. These aminodienes represent useful synthetic building blocks and could also serve as precursors to a wide range of heteroaromatics, such as indoles, quinolines, and benzazepines (**5**, $n=$ 1–3). This approach is complementary to the many classical (and palladium-catalyzed)[8b] routes to such bicycles and in particular imparts great substituent diversity on the nascent carbocycle.



Scheme 1. Cascade cyclization of bromoenynamides to azabicycles.

Witulski and others have reported the use of ynamides[9] as precursors to azacycles in elegant [2+2+2] cyclizations;[5,10] however, this process can be restricted in regioselectivity compared to our proposed carbopalladative route. Only a single study of ynamide carbopalladation/C–C bond formation has been reported,[11] in which terminal ynamides tethered to aryl halides were coupled with aryl boronic acids. Finally, as nitrogen-substituted trienes are relatively unusual electrocyclization substrates,[3d,12] we felt that the planned three-step cascade held significant appeal. Herein, we describe the realization of this powerful approach to functionalized bicyclic aminodienes and their selective oxidation to bicyclic heteroaromatics.

We began our studies using bromoenynamide **6a** (Table 1), which was prepared by using Hsung's efficient copper-catalyzed sulfonamide/bromoalkyne cross-coupling reaction.[13,14] Treatment of **6a** with stannane **7** and 10 mol% of $[PdCl_2(PPh_3)_2]$[6a] revealed that successful cascade cyclization occurred at 95 °C, and the aminodiene **8a** was isolated in 92% yield (entry 1). Pleasingly, the catalyst loading could be reduced to 1 mol% with no significant decrease in yield (entry 2).

Whilst vinyl stannanes were clearly competent coupling partners in the cascade, we realized that the use of vinyl boron derivatives, which avoid the aspects of toxicity associated with organotin reagents, would be of greater appeal. This reaction proved challenging to optimize, with application of Cossy's conditions to the coupling of ynamide **6a** with styrenylboronic acid **9a** (5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, THF/NaOH (aq.), reflux)[11] leading to incomplete consumption of starting material (Table 1, entry 3). In addition, we observed the unexpected formation of significant quantities of diene **10**, which likely arises from reduction of the intermediate dienylpalladium(II) complex.[15] We next tested conditions employed by Oh in a related Suzuki cascade reaction (10 mol% $[Pd(PPh_3)_4]$, Cs_2CO_3, anhydrous EtOH, 80 °C),[16] which improved conversion, but did not prevent the formation of diene **10** (Table 1, entry 4); indeed, in the absence of the boronic acid, **10** was isolated in 83% yield (Table 1, entry 5). We reasoned that hydroxylic sol-

[a] R. L. Greenaway, Dr. C. D. Campbell, O. T. Holton, Dr. E. A. Anderson
Chemistry Research Laboratory
University of Oxford, 12 Mansfield Road
Oxford, OX1 3TA (UK)
Fax: (+44) 1865-285002
E-mail: edward.anderson@chem.ox.ac.uk

[b] Dr. C. A. Russell
Syngenta Ltd, Jealott's Hill International Research Centre
Bracknell, Berkshire, RG42 6EY (UK)

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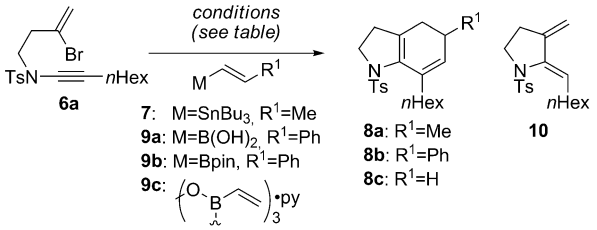
Table 1. Optimization of ynamide cascade cyclization.[a]



Entry	Coupling partner	Solvent, time [h]	Pd catalyst ([mol%])	Yield [%][b]	**8**:**10**
1	**7**	PhMe, 18[c]	$[PdCl_2(PPh_3)_2]$ (10)	92	1:0
2	**7**	PhMe, 18[c]	$[PdCl_2(PPh_3)_2]$ (1)	90	1:0
3	**9a**	THF, 5[d]	$Pd(OAc)_2$ (5), PPh_3 (10)	n.d.[i]	1:4:2[e]
4	**9a**	EtOH, 18	$[Pd(PPh_3)_4]$ (10)	n.d.	1:1.2
5	–	EtOH, 2	$[Pd(PPh_3)_4]$ (10)	83	–
6	**9b**	THF, 18	$[Pd(PPh_3)_4]$ (5)	80[f]	30:1
7	**9b**	DME, 4	$[Pd(PPh_3)_4]$ (5)	83	1:0
8	**9b**	DME, 18	$[PdCl_2(PPh_3)_2]$ (5)	70[f]	10:1
9	**9b**	DME, 18	$[PdCl_2(dppf)]$ (5)	25[g]	1:0
10	**9a**	THF, 18	$[Pd(PPh_3)_4]$ (5)	67[f]	20:1
11	**9a**	DME, 18	$[Pd(PPh_3)_4]$ (5)	79	1:0
12	**9c**	THF, 3[h]	$[Pd(PPh_3)_4]$ (5)	85	1:0

[a] Reactions conducted using **7** (1.6 equiv) or **9a** or **9b** (1.5 equiv) and Cs_2CO_3 (1.5 equiv) at reflux in degassed, anhydrous solvent. [b] Isolated yield. [c] Reaction conducted at 95 °C with no base added. [d] 1 M NaOH used as base. [e] Ratio of **6a**:**8b**:**10**. [f] Combined yield of **8b** and **10**. [g] Direct cross-coupling with the bromoalkene was also observed. [h] **9c** (0.5 equiv)/H_2O (1.5 equiv). [i] n.d. = not determined.

vents might be responsible for the formation of **10**,[15] and after some optimization we found that the use of anhydrous THF or DME eradicated this side reaction (Table 1, entries 6 and 7). A brief survey of alternative catalysts (entries 7–9) revealed the combination of $[Pd(PPh_3)_4]$ (5 mol%) and Cs_2CO_3 in anhydrous DME at reflux to be optimal, with **8b** being isolated in 83% yield from ynamide **6a** and boronic ester **9b**. Significantly, the nature of the vinylboron derivative did not affect the reaction efficiency, with boronic acid **9a** and the boroxine–pyridine adduct **9c** also giving excellent yields (Table 1, entries 10–12).

With an optimized set of conditions in hand, we investigated the scope of the cyclization reaction with a range of ynamides and coupling partners (Table 2). First, the effects of the ynamide substituents were examined using coupling partner **9b**, with both alkyl and aryl ynamides giving the 5,6-fused bicyclic products (entries 1 and 2). The preparation of ynamides derived from α-branched amines (**6d** and **6e**) proved unsuccessful when using copper-catalyzed methods,[17,18] however, the use of Witulski's alkynyl iodonium triflate methodology permitted the synthesis of these substrates.[5d,19] The electrocyclizations of **6d** and **6e** to the trisubstituted 5,6-bicyclic aminodienes **8f** and **8g** proceeded with moderate diastereoselectivity (Table 2, entries 3 and 4), suggesting a degree of remote stereocontrol to be imparted from the conformational influences of the tosyl group and its adjacent substituents.[12c,20] Access to larger ring sizes was investigated by using ynamides **6f** (which also required synthesis via the alkynyl iodonium triflate) and **6g** (which in contrast could be accessed by using copper catalysis). Both underwent successful cyclization to give the 6,6- and 7,6-fused frameworks **8h** and **8I**, respectively (Table 2, entries 5 and 6). The latter was isolated as a mixture of 1,3- and 1,4-diene isomers, which could both be oxidized to the benzazepine (see below).

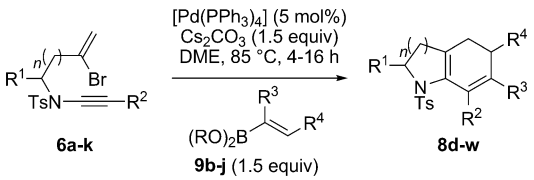
The scope of the reaction with respect to the vinylboron coupling partner was next evaluated. We were pleased to find that alkyl-, cycloalkyl- and electron-rich aryl-substituted vinylboronates all underwent successful coupling with ynamide **6a** (Table 2, entries 7–10), giving the corresponding aminodienes **8j–m** in good yields. The reactions of the electron-deficient and ester-containing boronic esters **9h** and **9i** were again complicated by the isolation of mixtures of diene isomers (Table 2, entries 11 and 12), and in these cases the products were oxidized to the indolines **8n** and **8o** (see below). The sterically challenging coupling of the disubstituted vinylboronic ester **9j** is of particular note (Table 2, entry 13), with the trisubstituted aminodiene **8p** being isolated in 63% yield. The use of electron-deficient ynamide **6h** resulted in successful cyclization to diene **8q** with alkyl boronic acid **9f**, but afforded the indoline **8r** using **9b**, presumably owing to in situ oxidation (Table 2, entries 14 and 15).

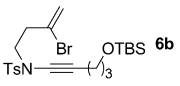
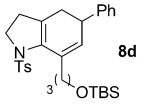
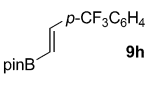
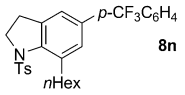
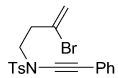
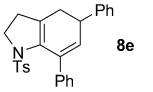
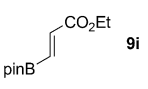
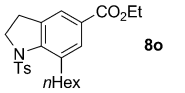
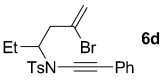
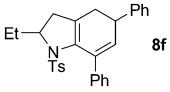
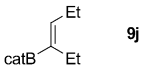
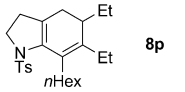
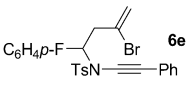
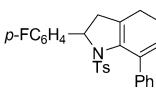
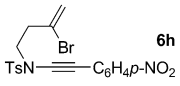
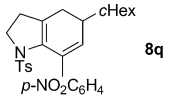
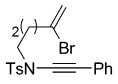
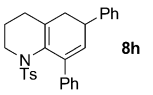
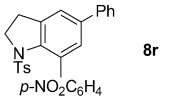
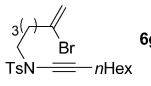
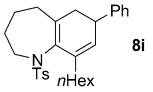
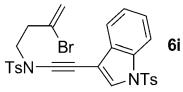
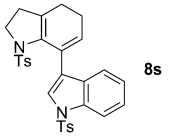
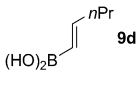
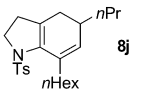
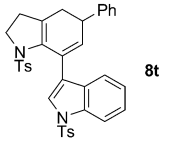
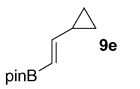
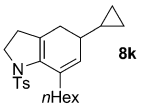
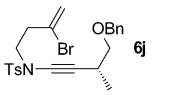
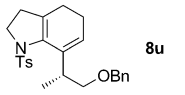
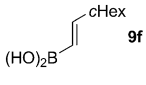
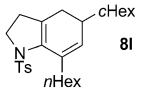
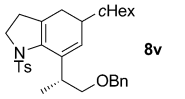
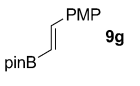
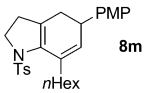
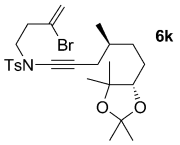
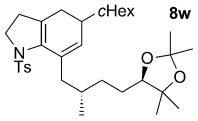
Satisfied with this initial exploration of product scope, we turned our attention to the preparation of aminodienes containing more elaborate sidechains, which would be more difficult to prepare by using other routes. For example, the indole-substituted ynamide **6i** underwent high-yielding cyclizations with **9c** and **9b** to provide the bis-heterocyclic indolylaminodienes **8s** and **8t** (Table 2, entries 16 and 17). The incorporation of chiral sidechains into the aminodiene could be readily achieved with ynamides **6j** and **6k**,[14] which cyclized equally efficiently with the unsubstituted boroxine **9c** or the cyclohexyl derivative **9f** to give products **8u–8w** (Table 2, entries 18–20). In the last two cases, as might be expected, little or no diastereoselectivity was observed.

The successful cyclization of a wide range of ynamides and coupling partners had delivered a variety of aminodiene frameworks, motifs of high synthetic potential. For the purposes of this work, we elected to subject our products to oxidative conditions, with the aim of accessing bicyclic heteroaromatics. Aminodiene **8b** was treated with a wide range of oxidants, with many giving incomplete reaction or byproducts,[21] but after some optimization we found activated MnO_2 to be the most effective oxidant. Whilst reaction in chlorinated solvents gave a 9:1 mixture of the tosylindoline **11** and the tosylindole **12**, the use of acetone as solvent led to the selective formation of **11** (86%, Scheme 2).

Pleasingly, detosylation of **11** to the indoline **13** could be achieved by using magnesium in methanol.[22] Combining these procedures in an oxidation/detosylation/oxidation sequence allowed the aminodiene **8b** to be converted to indole **14** in 64% yield with only a single purification step, thus providing a straightforward and selective access to both the indoline and indole oxidation states from the aminodiene. Application of this oxidation chemistry to other ami-

Table 2. Substrate scope for the cascade cyclization of ynamides and vinylboronates.[a]

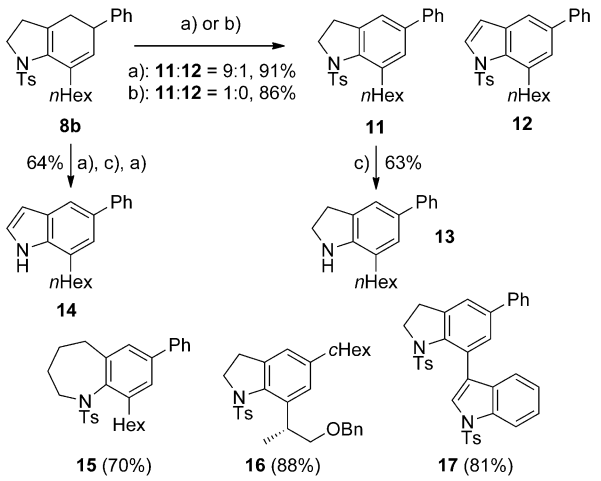


Entry	Ynamide	Coupling partner	Product	Yield [%][b] (d.r.)[c]	Entry	Ynamide	Coupling partner	Product	Yield [%][b] (d.r.)[c]
1	 **6b**	**9b**	 **8d**	55	11	**6a**	 **9h**	 **8n**	63[e]
2	 **6c**	**9b**	 **8e**	69	12	**6a**	 **9i**	 **8o**	61[e]
3	 **6d**	**9b**	 **8f**	68 (1.4:1)	13	**6a**	 **9j**	 **8p**	63
4	 **6e**	**9b**	 **8g**	77 (3:1)	14	 **6h**	**9f**	 **8q**	74
5	 **6f**	**9b**	 **8h**	61	15	**6h**	**9b**	 **8r**	61
6[a]	 **6g**	**9b**	 **8i**	74[d]	16	 **6i**	**9c**	 **8s**	87
7	**6a**	 **9d**	 **8j**	74	17	**6i**	**9a**	 **8t**	62
8	**6a**	 **9e**	 **8k**	72	18	 **6j**	**9c**	 **8u**	83
9	**6a**	 **9f**	 **8l**	70	19	**6j**	**9f**	 **8v**	70 (1.4:1)
10[e]	**6a**	 **9g**	 **8m**	55	20	 **6k**	**9f**	 **8w**	73 (1:1)

[a] See the Supporting Information for details of ynamide synthesis. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] Isolated as a 1.3:1 mixture of 1,3- and 1,4-diene isomers. [e] Isolated as a 3:1 (**8n**) and 1.2:1 (**8o**) mixture of 1,3- and 1,4-diene isomers, which were oxidized to the indolines using γ-MnO_2 (see text); yield over two steps. [e] PMP = *p*-methoxyphenyl.

nodienes provided the benzazepine **15**, indoline **16**, and indolinyl indole **17** (70–88%).

In conclusion, we have demonstrated that bromoenynamides can serve as substrates for the synthesis of a diverse range of bicyclic aminodienes using a palladium-catalyzed cascade cyclization. These reactions represent the first examples of ynamide carbopalladation/Stille or vinylic Suzuki cross-coupling reactions and also the first application of a Suzuki coupling in a carbopalladation cascade terminating in electrocyclization.[23] The resultant aminodienes, which are important frameworks in their own right, undergo selective and tunable oxidations to the corresponding heteroaro-



Scheme 2. Selective oxidation of aminodienes. Reagents and conditions: a) γ-MnO_2 (10 equiv), CH_2Cl_2, 2 h; b) γ-MnO_2 (10 equiv), acetone, 18 h; c) Mg (5 equiv), MeOH, sonication, 1.5 h.

matic bicycles, thus providing a general and flexible route to indoles, indolines, tetrahydroquinolines, and benzazepines. Of particular note is the ability of this route to install a variety of functionalized sidechains on the carbocyclic ring in a regiospecific manner in the course of the ring synthesis, thus providing a unique alternative to classical and contemporary methods. Ongoing work includes the extension of this methodology towards the synthesis of other heterocycles and the application of aminodienes in synthesis.

Experimental Section

Typical procedure for the cascade Suzuki cyclization—7-hexyl-5-phenyl-1-tosyl-2,3,4,5-tetrahydro-1*H*-indole (8b): A degassed solution of ynamide **6a** (50 mg, 0.12 mmol, 1.0 equiv) and boronic ester **9b** (41 mg, 0.18 mmol, 1.5 equiv) in anhydrous DME (2 mL) was added to [Pd(PPh_3)$_4$] (6.9 mg, 0.006 mmol, 0.05 equiv) and Cs_2CO_3 (58 mg, 0.18 mmol, 1.5 equiv) under Ar. The reaction mixture was heated to reflux under Ar until complete conversion, as analyzed by TLC (4 h), then it was cooled to room temperature and concentrated. Column chromatography (petroleum ether/Et_3N (1%) to petroleum ether/EtOAc (10:1)/Et_3N (1%)) gave aminodiene **8b** as a pale yellow oil (43 mg, 0.099 mmol, 83%). R_f = 0.38 (petroleum ether/EtOAc 10:1); IR (thin film): $\tilde{\nu}$ = 2926, 2856, 1598, 1493, 1452, 1351, 1164, 1089, 1019 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.69 (2H, d, J = 8.0 Hz; *o*-Ts*H*), 7.39–7.30 (5H, m; Ph*H*), 7.22 (2H, d, J = 8.0 Hz; *m*-Ts*H*), 5.62 (1H, s; H6), 3.94–3.89 (1H, m H2), 3.71–3.65 (1H, dt, J = 13.5, 9.5 Hz; H2′), 3.64–3.57 (1H, m; H5), 2.77–2.70 (1H, m; H10), 2.50–2.40 (1H, m; H10′), 2.44 (3H, s; TsCH_3), 2.36–2.27 (1H, m; H4), 2.24–2.16 (1H, m; H4′), 1.69–1.63 (2H, m; H3), 1.57–1.52 (1H, m; H11), 1.50–1.44 (1H, m; H11′), 1.41–1.27 (6H, m; H12–H14), 0.90 ppm (3H, t, J = 7.0 Hz; H15); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.0, 143.8, 138.8, 135.3, 133.0, 131.9, 129.2, 128.5, 128.4, 127.5, 126.5, 125.4, 51.5, 41.1, 32.4, 32.1, 31.8, 30.4, 28.9, 28.8, 22.7, 21.6, 14.1 ppm; HRMS (ESI): *m/z* calcd for $C_{27}H_{33}NNaO_2S$: 458.2124 $[M+Na]^+$; found: 458.2112. See the Supporting Information for specific reaction details and product characterization for other compounds, and for the preparation and characterization of the ynamides.

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Keywords: cascade reactions · cross-coupling · electrocyclic reactions · nitrogen heterocycles · ynamides

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