Palladium-catalysed biscyclisation of allenic bromoalkenes through a zipper-mode cascade†

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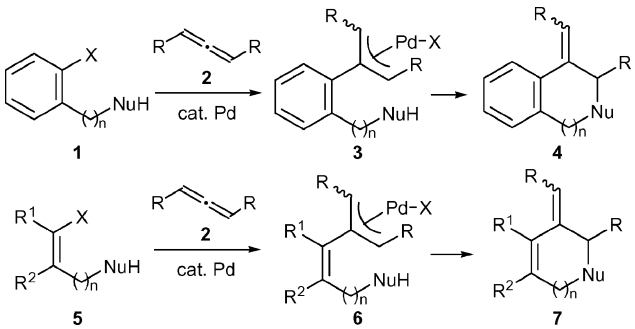
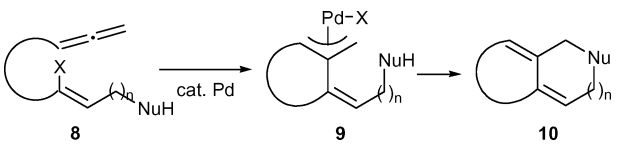
Treatment of allenic bromoalkenes bearing a nucleophilic moiety with a catalytic amount of palladium(0) in the presence of TBAF or Cs_2CO_3 in MeCN affords bicyclic heterocycles in good to high yields, through zipper-mode cascade cyclisation.

Palladium-catalysed cyclisation of allenic compounds has become an extremely useful method for construction of hetero- and carbocycles of significant biological importance.[1] It has been well documented that carbopalladation of allenes with an aryl- or alkenylpalladium halide easily occurs to afford π-allylpalladium intermediates, which readily undergo inter- or intramolecular nucleophilic substitution with various nucleophiles. Accordingly, the reaction of allenes **2** with aryl halide derivatives **1**, bearing a nucleophilic functional group such as 2-halophenols/anilines, 2-halobenzyl alcohols/amines and related compounds, provides a straightforward access to benzene-fused heterocyclic compounds **4** (Scheme 1).[2–4] In contrast, the reaction of allenes with haloalkene derivatives is relatively limited. Larock *et al.* reported regio- and stereoselective annulation of cyclic or acyclic allenes **2** with vinylic halides **5**, possessing a nucleophilic hydroxy, amino, sulfonamide, or carboxylic group, to produce five- or six-membered heterocycles **7**.[2b,c,5] However, there have been no precedents for cascade intramolecular reaction of allenic haloalkene derivatives with an internal nucleophile. We envisioned that allenic haloalkenes **8**, containing an appropriate nucleophilic moiety, could undergo domino cyclisation by successive intramolecular reactions (Scheme 2). Herein we wish to report the zipper-mode cyclisation[6] of allenic haloalkenylamine derivatives **8** to produce diazabicycloalkene derivatives **10**, which include medium-sized rings (n = 1–3).[7] The domino cyclisation involving oxygen and carbon nucleophiles is also described.

Requisite substrates for the biscyclisation were prepared from protected known amino allene derivatives **11** (Scheme 3), which, in turn, were readily obtained through diethylzinc-mediated allene synthesis catalysed by palladium(0).[8] Thus, allenes **11** were converted to allenic bromoalkenylamines **12** by a sequence of reactions including N-alkylation with *tert*-butyldimethylsilyl (TBS)-protected (*Z*)-3,4-dibromobut-2-en-1-ol[9] and Mitsunobu-type amination.



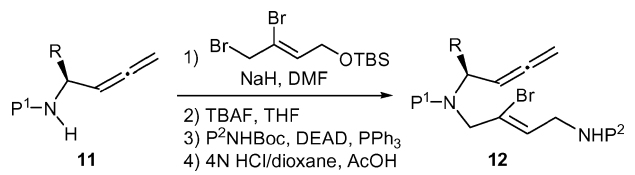
Scheme 1 Reaction of allenes with aryl or alkenyl halides bearing a nucleophilic moiety.



Scheme 2 Zipper-mode domino cyclisation of allenic haloalkenes.

We started our investigation with the domino cyclisation of L-valine-derived allenic bromoalkenylamine **12a** (Table 1). As we expected, the reaction of **12a** catalysed by $Pd(PPh_3)_4$ (10 mol%) in the presence of K_2CO_3 (2.5 equiv.) in MeCN afforded the desired hexahydro-2,6-naphthyridine derivative **13a**, although in low yield (37%, entry 1). Among palladium catalysts examined (entries 1–4), $Pd_2(dba)_3{\cdot}CHCl_3$ (dba = dibenzylideneacetone)proved promising, yielding 72% of **13a** with 5 mol% catalyst loading (entry 4). After experiments using various bases (2.5 equiv., entries 5–7) and solvents (entries 9–12), we found that a combination of tetrabutylammonium fluoride (TBAF)–MeCN gave the desired bicyclic product **13a** in 91% yield with 2.5 mol% of the palladium catalyst (entry 8).

Next, the domino cyclisation of several bromoalkenylamine derivatives **12b**–**12e** was investigated (Table 2). Results with **12a** (91%, entry 1) and bis-tosylamide derivative **12b**



Scheme 3 Preparation of allenic haloalkenylamines **12**.

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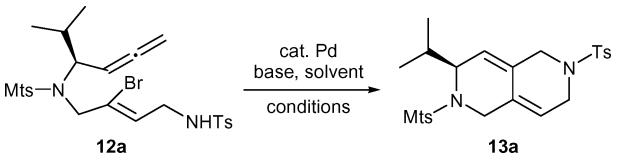
Table 1 Domino cyclisation of **12a** under various reaction conditions[a]



12a **13a**

Entry	Pd catalyst (mol%)	Solvent	Base	Temperature/ °C	Time/ h	Yield (%)[b]
1	$Pd(PPh_3)_4$ (10)	MeCN	K_2CO_3	70	0.75	37
2	$Pd(OAc)_2$ (10)	MeCN	K_2CO_3	70	2	53
3	$Pd(dppf)Cl_2$ (10)	MeCN	K_2CO_3	70	16	43
4	$Pd_2(dba)_3$·$CHCl_3$ (5)	MeCN	K_2CO_3	70	0.6	72
5	$Pd_2(dba)_3$·$CHCl_3$ (5)	MeCN	Cs_2CO_3	70	0.1	71
6	$Pd_2(dba)_3$·$CHCl_3$ (5)	MeCN	NaOAc	70	42	Trace
7	$Pd_2(dba)_3$·$CHCl_3$ (5)	MeCN	TBAF	70	0.1	87
8	$Pd_2(dba)_3$·$CHCl_3$ (2.5)	MeCN	TBAF	50	3.5	91
9	$Pd_2(dba)_3$·$CHCl_3$ (2.5)	THF	TBAF	50	5	Trace
10	$Pd_2(dba)_3$·$CHCl_3$ (2.5)	Dioxane	TBAF	50	2.5	77
11	$Pd_2(dba)_3$·$CHCl_3$ (2.5)	DMF	TBAF	50	10	70
12	$Pd_2(dba)_3$·$CHCl_3$ (2.5)	EtOH	TBAF	50	8	67

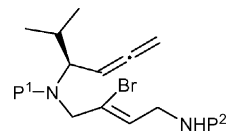
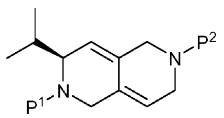
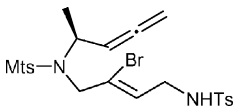
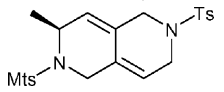
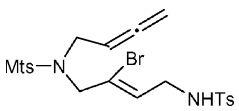
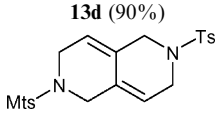
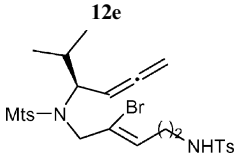
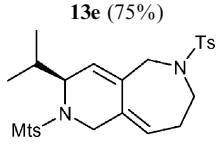
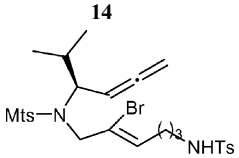
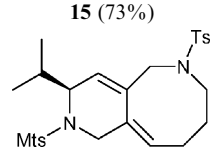
[a] Abbreviations: Mts = 2,4,6-trimethylphenylsulfonyl; dppf = 1,1'-bis(diphenylphosphino)ferrocene. [b] Isolated yields.

(89% yield, entry 2) were comparably successful. Similarly, nosylamide **12c** was smoothly cyclised into **13c** in 91% yield under identical reaction conditions. The substituent at the α-position of the allenic moiety affects the reactivity of the substrates. Thus, while the reaction of substrate **12d**, bearing a methyl group, afforded **13d** in 90% yield (entry 4), a slightly lower yield of the bicyclic product **13e** was obtained in the reaction of α-unsubstituted allene **12e** (75%, entry 5). It should be noted that this domino cyclisation is also applicable to construction of fused medium-sized heterocycles **15** and **17**, containing seven (**15**, 73%, entry 6) and eight-membered rings (**17**, 62%, entry 7).[10]

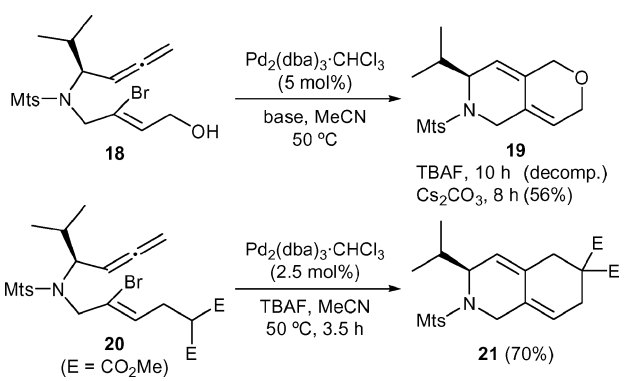
The cyclisation using other nucleophiles (oxygen and carbon) was then examined (Scheme 4). Unfortunately, treatment of bromoalkenol derivative **18** under the standard reaction conditions employed with the amine substrates [$Pd_2(dba)_3$·$CHCl_3$ and TBAF in MeCN at 50 °C] did not afford any biscyclised product and led to a complete decomposition of the substrate. In contrast, with the use of Cs_2CO_3 as the base, the alcohol **18** was converted to the expected pyranopyridine derivative **19** in 56% yield. Domino carbocyclisation of malonate derivative **20** was successfully promoted using the standard conditions, using TBAF as a base, to afford hexahydroisoquinoline dicarboxylate **21** in 70% yield.

Finally, construction of a fused benzoazepine framework using the domino cyclisation was investigated. Bromoalkenylaniline **22** (Scheme 5) was prepared in a similar manner as described previously (Scheme 3) from amino allene **11** (P^1 = Mts) and 2,3-dibromoprop-1-ene, derived from 2-aminobenzyl alcohol. The cyclisation of **22** using the standard procedure cleanly gave the expected product **23** in 89% yield as the sole isolable product.

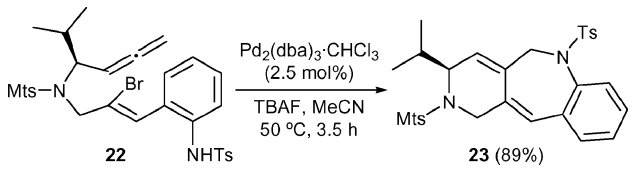
Table 2 Domino cyclisation of bromoalkenylamine derivatives[a]

Entry	Substrate	Time/ h	Product (% yield[b])
			
1	**12a** (P^1 = Mts, P^2 = Ts)	3.5	**13a** (P^1 = Mts, P^2 = Ts; 91%)
2	**12b** (P^1 = P^2 = Ts)	3.5	**13b** (P^1 = P^2 = Ts; 89%)
3	**12c** (P^1 = Mts, P^2 = Ns)	2.5	**13c** (P^1 = Mts, P^2 = Ns; 91%)
4		3.5	
	12d		**13d** (90%)
5		2.0	
	12e		**13e** (75%)
6		3.0	
	14		**15** (73%)
7		3.5	
	16		**17** (62%)

[a] All reactions were carried out using $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol%) and TBAF (2.5 equiv.) in MeCN at 50 °C. Abbreviation: Ns = 2-nitrophenylsulfonyl. [b] Isolated yields.



Scheme 4 Reaction involving oxygen and carbon nucleophiles.



Scheme 5 Construction of a fused benzoazepine framework.

In conclusion, we have developed a zipper-mode cascade cyclisation of allenic bromoalkenes catalysed by palladium(0). This reaction is widely applicable to cyclisations using nitrogen, oxygen, and carbon nucleophiles as well as the construction of fused medium-sized heterocycles. Further studies directed toward the application of this method to the synthesis of various heterocycles of biological importance is currently underway.

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Notes and references

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8. Chiral amino allenes **11** were prepared in an enantiomerically pure form starting from L-amino acids, see: (*a*) H. Ohno, A. Toda, S. Oishi, T. Tanaka, Y. Takemoto, N. Fujii and T. Ibuka, *Tetrahedron Lett*., 2000, **41**, 5131–5134; (*b*) H. Ohno, K. Miyamura, T. Tanaka, S. Oishi, A. Toda, Y. Takemoto, N. Fujii and T. Ibuka, *J. Org. Chem*., 2002, **67**, 1359–1367.
9. The protected (*Z*)-3,4-dibromobut-2-en-1-ol was prepared by Wittig olefination of 2-(*tert*-butyldimethylsiloxy)acetaldehyde with $Ph_3P{=}C(Br)CO_2Me$ followed by DIBAL-H reduction and bromination with CBr_4–PPh_3–imidazole. See also A. G. Steinig and A. de Meijere, *Eur. J. Org. Chem*., 1999, 1333–1344.
10. Formation of the five- or six-membered rings in the second cyclisation of **14** and **16** was not observed. Such cyclisation would be disfavoured because of highly restricted conformations of the alkenylamine intermediates of the type **9**.

