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Unusual (*Z*)-Selective Palladium(II)-Catalysed Addition of Aryl Boronic Acids to Vinylaziridines

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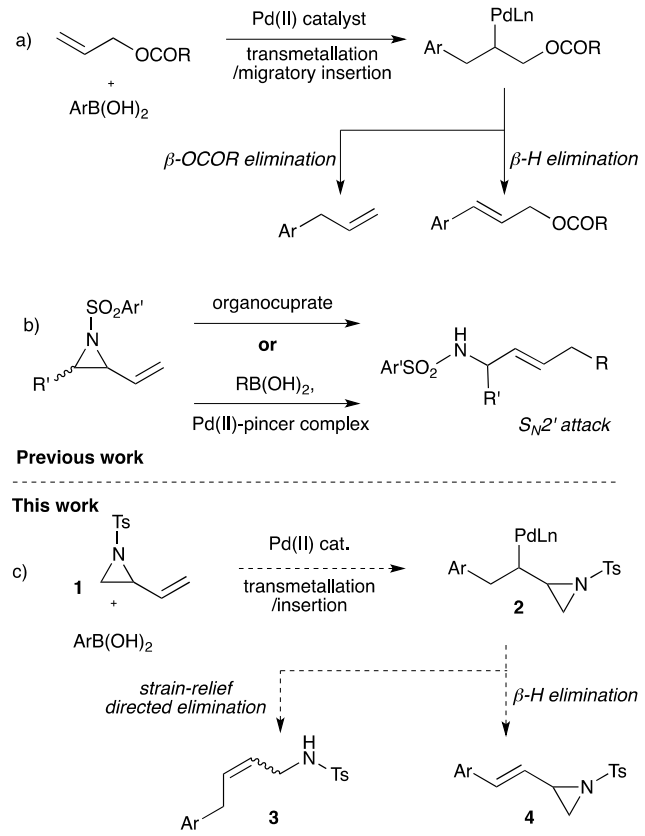
The palladium(II)-catalysed addition of arylboronic acids to vinylaziridines has been developed. This reaction proceeds via an insertion/ring-opening process to provide *(Z)*-allylsulfonamides preferentially. This stereoselectivity is complimentary to existing methods that typically proceed via a S_N2' mechanism to yield (*E*)-allylsulfonamides. Electron-deficient arylboronic acids were the optimum substrates for this reaction, while electron-donating groups on the aromatic ring of the boronic acids resulted in moderate yields.

The palladium(0)-catalysed alkylation of allylic esters is a powerful C-C bonding forming reaction that has been widely used in the synthesis of complex organic molecules.[1] Typically the nucleophile in these reactions is a stabilized carbanion, which undergoes attack on an intermediate Pd(II)-η^3-allyl complex. However, recently the reaction of organoboronic acids with allylic esters under Pd(II)-catalysis has emerged as a complementary C-C bond forming reaction. These reactions are proposed to proceed via migratory insertion of the allylic ester to Ar-Pd(II)-X, followed by either *β*-H and *β*-OCOR elimination (Figure 1, a). Despite the potential *β*-H and β-OCOR selectivity issues, recent advances have been made in controlling the reactivity of allylic esters with aryl boronic acids. Notably, Sawamura and co-workers have developed a *γ*-selective process, which proceeds via *β*-acetoxy elimination.[2] On the other hand, Jiao and co-workers have developed a reaction that is selective for *β*-hydride elimination, which occurs in the presence of a Pd(II) catalyst and a silver re-oxidant.[3]

Vinylaziridines are readily accessible, alternative electrophilic species for alkylation and arylation reactions. These electrophiles can undergo regioselective ring-opening addition via their double bond[4,5] or directly to the aziridine ring.[6-9] In addition, Trost and co-workers have developed the asymmetric addition of vinylaziridines to isocyanates and pyrroles, proceeding via *π*-allyl palladium intermediates.[10] Interestingly, Szábo and co-workers have reported that palladium pincer complexes can catalyse the reaction of boronic acids with *N*-sulfonyl vinylaziridines to give (*E*)-allylic sulfonamides (Figure 1b).[11] The authors proposed that this reaction proceeds via transmetalation of the boronic acids to the palladium-pincer complex, followed by an S_N2'-type opening of the vinylaziridine substrate. Similar S_N2'-additions of organocuprates to vinylaziridines have been developed and also yield predominantly the (*E*)-allylic sulfonamides.[4,5]

We felt that given the single coordination site on the palladium pincer complex there would be little chance for coordination of the transmetallated palladium complex to the vinylaziridine. As such, in the context of our investigations into stereo- and regio-selective transition-metal-catalysed ring-opening of aziridines, we identified that the $Pd(OAc)_2$/phenanthroline/$AgSbF_6$ catalyst system employed by Sawamura should afford the opportunity to coordinate to the *N*-sulfonyl group and aid in controlling the stereochemical outcome of the addition reaction. Notably, Sawamura[2] and co-workers invoked intramolecular coordination of the carbonyl oxygen of the acetoxy group to a cationic Pd centre as being key in assisting with the stereo- and regiochemical outcome of their *γ*-selective coupling between allylic esters and arylboronic acids.[2] Mechanistically, using this catalyst system with a vinylaziridine would also allow an alternative method for control of *β*-H vs *β*-heteroatom elimination based on the propensity of these systems for ring-opening (Figure 1, c). Specifically, we anticipated that the insertion product 2 would favour a ring-opening/elimination process over *β*-H elimination due to the concomitant relief of ring-strain.

Herein, we demonstrate the simple $Pd(OAc)_2$/phenanthroline/$AgSbF_6$ catalyst system, is both effective for the addition boronic acids to *N*-tosyl vinylaziridine to provide allylic amines *and* displays unusual stereoselectivty to provide (*Z*)-allylic sulfonamides in compliment to Szabo's palladium pincer complex.



Scheme 1. Oxidative Heck reactions of allylic esters, ring-opening of vinylaziridines and proposed reactions of vinylaziridines.

1-Tosyl-2-vinylaziridine **1** was chosen as a substrate for the proposed reaction due its ready availability from the direct aziridination[12] of 1,3-butadiene and for the activating effect of the tosyl group, which should further favouring ring-opening over *β*-H elimination.[13] The addition of phenylboronic acid to 1-tosyl-2-vinylaziridine was initially investigated using conditions based on those reported by Sawamura and co-workers for the addition of boronic acids to allylic acetates (Table 1, entry 1).[2] It was pleasing to find that under these conditions the addition of phenylboronic acid occurred with ring-opening to yield allylic sulfonamide **3a** in good yield, as a 4.2:1 mixture of *Z:E* isomers.†

It was found that the reactions with substituted arylboronic acids required the addition of 0.5 equivalents of potassium acetate (entries 2 to 9). If the base was omitted for the electron-poor boronic acids then the reaction was not clean (entry 3) and for electron-rich boronic acids the conversion was low (entry 2). In addition, the conversion and stereoselectivity was significantly lowered if the silver salt was omitted but potassium acetate was present (entry 2). It was found that highly electron-deficient arylboronic acids were the optimum substrates for this reaction (entries 3-6, Table 1). Notably, aryl chlorides and esters, which provide handles for further functionalisation, were tolerated by the reaction. Electron-rich aryl boronic acids resulted in only moderate yields, however, these reactions were very clean and the lower yield predominantly resulted from incomplete conversion of the starting material (entries 2, 7 and 9). The reaction was sensitive to steric hindrance, with ortho-substitution either shutting down the reaction; (entry 10) or providing undesired products resulting from hydrolysis of the aziridine and ring-opening by acetate (entry 11). In some cases, trace quantities of the styrenyl system observed, as evidenced by the presence of distinctive down-field olefinic signals. The trace amount of styrenyl product could either be due to base-induced isomerisation during the reaction or competing *β*-H elimination.

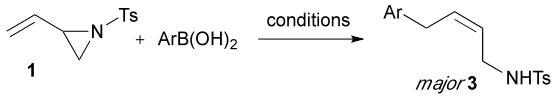
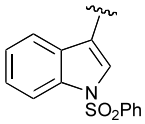
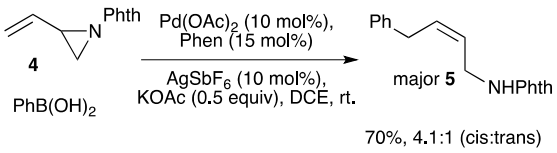


Table 1 Reaction scope and optimisation

Entry	Ar	Product	Yield[b]	(*Z:E* ratio)
1	C_6H_5	**3a**	79%[c]	4.2:1
2	4-MeC_6H_4	**3b**	17% conversion (no KOAc)	
			40% (0.5 eq. KOAc)	3.5:1
			17% (0.5 eq. KOAc no $AgSbF_6$)	1.6:1
3	4-EtO_2C-C_6H_4	**3c**	decomp. (no KOAc)	
			94% (0.5 eq. KOAc)	2.7:1
4	4-ClC_6H_4	**3d**	57%	2.8:1
5	3-$NO_2C_6H_4$	**3e**	90%	2.2:1
6	4-FC_6H_4	**3f**	75%	2.5:1
7		**3g**	38%	1.8:1
8	3-OMe-C_6H_4	**3h**	42%	4.5:1
9	3,4-OMe-C_6H_4	**3i**	25%	3.1:1
10	2-OMe-C_6H_4	-	N.R.	
11	2-ClC_6H_4	-	aziridine hydrolysis[e]	

[a] Conditions: vinylaziridine (1.0 eq), boronic acid (1.5 eq), $Pd(OAc)_2$ (10 mol%), Phen (15 mol%), $AgSbF_6$ (10 mol%), KOAc (0.5 eq), 70 °C, 22 h.[b] Isolated yields.[c] No addition of KOAc. [d]product derived from attack of acetate on aziridine also observed.

In addition to *N*-Ts vinylaziridine, we also found that more the more electron-rich *N*-phthalimide aziridine **4** was able to undergo ring-opening with phenylboronic acid in good yield and stereoselectivity. (Scheme 1).



Scheme 1 Ring-opening of *N*-phthalimide vinylaziridine.

We tentatively propose that the mechanism for the reaction may be similar to that reported by Sawamura and co-workers for the coupling of allylic esters and arylboronic acids.[2] As suggested by Sawamura, the 1,10-phenanthroline-ligand, $Pd(OAc)_2$ and $AgSbF_6$ react to form the active cationic palladium complex, which can then undergo transmetalation with the boronic acid (Figure 2). Conformation **6** of 1-tosyl-2-vinylaziridine, which minimises 1,3-allylic strain,[14] can coordinate to this cationic palladium-aryl complex through is double bond and the *N*-protecting group. It is possible that this ancillary coordination through the *N*-protecting group regioselectively directs migratory insertion to the lower face of conformation **6** to provide **7**. The subsequent insertion product **7** preferentially adopts an anti-periplanar configuration for elimination, which leads to the *cis*-allylic amide **3**. A *syn*-elimination, which would yield the *trans*-allylic amide, is likely less favoured, because a high level of strain likely hampers coordination between the *N*-protecting group of the aziridine and the cationic Pd-centre in **8**. We speculate that the additional potassium acetate may play a role in the final elimination step to regenerate the cationic palladium catalyst, which undergoes transmetalation. The boronic acid is a plausible proton source following elimination and this is supported by the lack of reactivity of boronic esters in the reaction. Notably, the reaction was much more efficient with electron-deficient boronic acids. This trend suggests that transmetalation may not be the rate-determining step in our transformation, as electron-poor arylboronic acids undergo transmetalation at a slower rate than electron-neutral arylboronic acids due to their decreased nucleophilicity.[15,16]

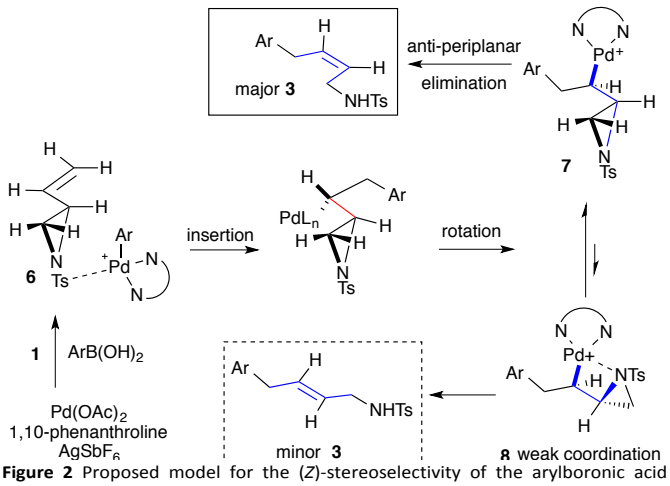


Figure 2 Proposed model for the (*Z*)-stereoselectivity of the arylboronic acid addition to 1-tosyl-2-vinylaziridine.

In conclusion, we have shown that arylboronic acids undergo palladium(II)-catalysed addition to 1-tosyl-2-vinylaziridine to yield allylic sulfonamides. The allylic amine products are useful precursors for the synthesis of nitrogen containing bioactive molecules.[17] While the products are obtained as a mixture of (*Z*:*E*) the *Z*-isomer is dominant, representing an intriguing reversal of stereoselectivity in comparison to related reactions catalysed by palladium-pincer complexes.[11] In addition, the procedure does not require rigorous exclusion of air and uses a simple palladium acetate catalyst in combination with readily available nitrogen-based ligands. Further investigation into the substrate scope and reaction mechanism is now underway.

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Notes and references

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† 1D NOESY was used to confirm the *cis* stereochemistry of **3e**, this data can be found in the ESI.

Electronic Supplementary Information (ESI) available: Full experimental details for the preparation of new compounds along with copies of the ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c000000x/

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