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Reaction of Vinylaziridines with Arynes: Synthesis of Benzazepines and Branched Allyl Fluorides

Sherif J. Kaldas,[a] Eva Kran,[b] Christian Mück-Lichtenfeld,[b] Andrei K. Yudin[a,*] and Armido Studer [b,*]

Abstract: We report the cycloaddition between vinylaziridines and arynes. Depending on the reaction conditions and the choice of the aryne precursor, the aziridinium intermediate can be trapped through two distinct mechanistic pathways. The first one proceeds through a formal [5+2] cycloaddition to furnish valuable multi-substituted benzazepines. In the second pathway, the aziridinium is intercepted by fluoride ion to afford allylic fluorides in good yields. Both reactions proceed stereospecifically and furnish enantiopure benzazepines and allylic fluorides.

The ongoing resurgence in aryne chemistry can be attributed to the development of modern methodologies that enable the efficient generation of arynes *in situ* under mild reaction conditions.[1] This advancement has allowed the scope of aryne chemistry to expand significantly into the areas of transition metal catalysis and multicomponent reactions, among others.[2] Amination reactions are an area in which aryne chemistry has been particularly successful. As a result, aminations of arynes have found great utility in the total synthesis of alkaloids.[3] As a part of our ongoing programs in aryne chemistry[4] and the synthesis of aza-heterocycles from aziridines,[5] we were interested in exploring the reactivity of vinylaziridines toward arynes. We envisioned that the [5+2] cycloaddition between an aryne and a vinylaziridine could proceed through formal cycloaddition[6] reaction to furnish valuable benzazepines (Figure 1a).[7] The 7-membered aza-heterocycle is an important scaffold in medicinal chemistry and is found in a wide range of bioactive compounds,[8] natural products,[9] dipeptide mimics,[10] and dyes[11] (Figure 1b). Due to the importance of this class of heterocycle, several methods have been developed for the synthesis of this and similar scaffolds.[12]

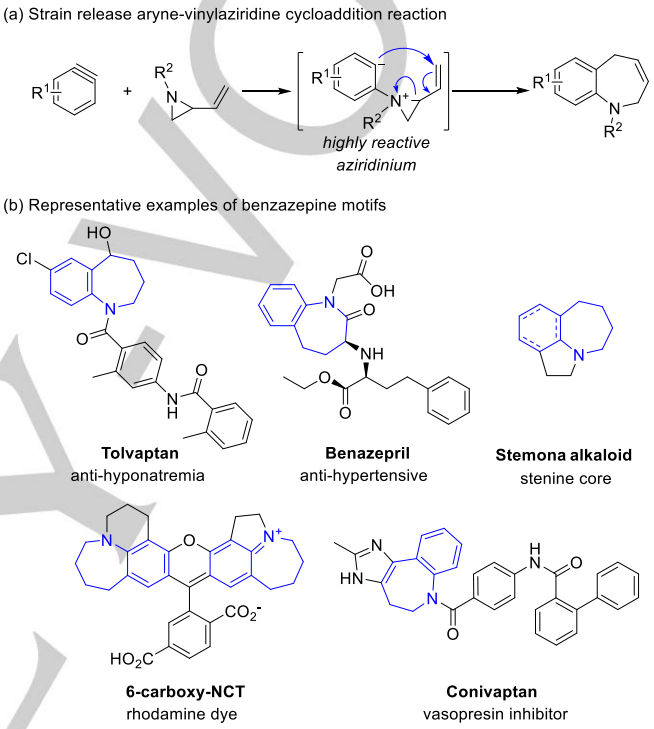

Figure 1. (a) Reaction of vinylaziridines with arynes. (b) Examples of benzazepine-containing pharmaceuticals, natural products and dyes.

We initiated our study by screening different conditions for benzyne generation in the presence of 1-benzyl-2-vinylaziridine (**2a**) as a model vinylaziridine (Scheme 1). Utilizing the conditions developed by Kobayashi[13] we only observed a trace amount of the desired benzazepine **3a**. However, we did record the formation of allylic fluoride **6a**, which is most likely formed from an attack of the fluoride anion onto the internal allylic position of the electrophilic aziridinium cation. This led us to screen methods for fluoride-free aryne generation. Utilizing aryne precursor **1b** and *i*PrMgCl•LiCl[14] we only recovered **2a**. It has been reported that magnesiated **1b** is highly reactive and decomposes to the aryne at -78 °C, presumably before nucleophilic attack of **2a**. We were pleased to see that by utilizing the same conditions, but switching to the more stable aryne precursor **1c**,[15] we were able to observe the formation of benzazepine **3a** in encouraging 45% yield.[16]

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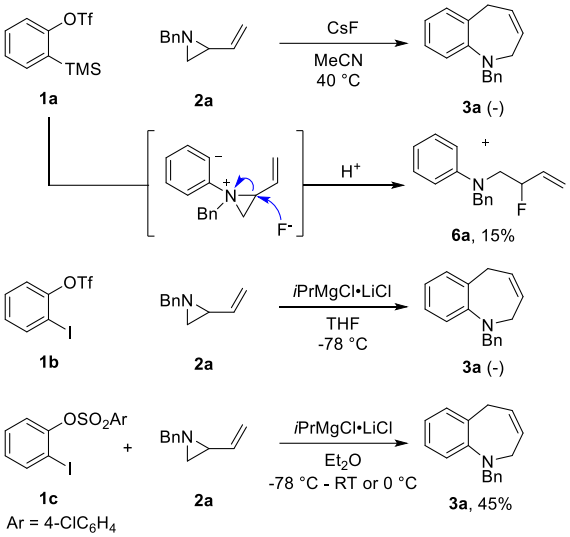
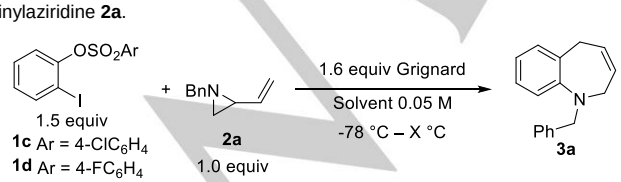


Scheme 1. Initial reaction screen utilizing various aryne precursors with vinylaziridine **2a**.

With the initial hit in hand, we began optimization of the annulation reaction (Table 1). Switching the solvent from Et_2O to THF had a deleterious effect (34%, Entry 1). Exchanging *i*PrMgCl•LiCl for *i*PrMgCl (2.0 M in Et_2O or THF) resulted in the recovery of both starting materials (Entries 2 and 3), while a combination of THF as solvent and *i*PrMgCl (2.0 M in THF) furnished **3a** in modest 30% yield (Entry 4). Toluene or a 4:1 mixture of Et_2O/1,2-dimethoxyethane[17] resulted in the formation of **3a** in 41% and 36% yield, respectively (Entries 5 and 6). We then explored the order of addition. Mixing Grignard reagent and **1c** at -78 °C followed by taking up the resulting solution and adding it dropwise to **2a** at room temperature was unsuccessful (Entry 7). Likewise, adding **2a** to a pre-mixed solution of Grignard reagent and **1c** at room temperature did not form the desired product (Entry 8). Gratifyingly, adding Grignard reagent to a solution of **1c** and **2a** at -78 °C before warming to room temperature significantly improved the yield to 80% (Entry 9). Changing the leaving group on the arene to 4-FC_6H_4 (Entry 10) or adding the Grignard reagent at room temperature to a mixture of **1c** and **2a** (Entry 11) resulted in slightly lower yield. To determine the stability of vinylaziridine to basic conditions, **2a** was treated with 2 equivalents of *i*PrMgCl•LiCl at room temperature. After 24 hours, only minimal decomposition of the vinylaziridine was observed.

Table 1. Optimization of the reaction between aryne precursors (**1c** or **1d**) and vinylaziridine **2a**.



Entry	Procedure	Ar	Solvent (0.05 M)	Grignard reagent	Yield (%)[a]
1	1	4-ClC_6H_4	THF	*i*PrMgCl•LiCl[b]	34
2	1	4-ClC_6H_4	Et_2O	*i*PrMgCl[c]	0
3	1	4-ClC_6H_4	Et_2O	*i*PrMgCl[d]	0
4	1	4-ClC_6H_4	THF	*i*PrMgCl[d]	30
5	1	4-ClC_6H_4	PhMe	*i*PrMgCl•LiCl	41
6	1	4-ClC_6H_4	4:1 Et_2O:1,2-DME	*i*PrMgCl•LiCl	36
7	2	4-ClC_6H_4	Et_2O	*i*PrMgCl•LiCl	0
8	3	4-ClC_6H_4	Et_2O	*i*PrMgCl•LiCl	0
9	4	4-ClC_6H_4	Et_2O	*i*PrMgCl•LiCl	80
10	4	4-FC_6H_4	Et_2O	*i*PrMgCl•LiCl	73
11[e]	4	4-ClC_6H_4	Et_2O	*i*PrMgCl•LiCl	65

Procedure 1: A solution of vinylaziridine was added after stirring Grignard reagent with aryne precursor at -78 °C for 30 min. Procedure 2: Aryne solution was added to vinylaziridine solution at 0 °C. Procedure 3: Vinylaziridine in solution was added at room temperature after stirring Grignard reagent with aryne precursor at -78 °C for 30 min. Procedure 4: Grignard reagent added to solution of vinylaziridine and aryne precursor at -78 °C before warming to room temperature. [a]NMR yield. [b]1.3 M in THF. [c]2.0 M in Et_2O. [d]2.0 M in THF. [e]Reaction carried out at room temperature.

After optimization, the scope of the reaction was investigated (Scheme 2). Overall, a variety of aryne precursors and vinyl aziridines could be matched to furnish benzazepines (**3a** – **3p**). Electron-rich arynes such as those substituted by *o*-methoxy and *m*-methoxy engaged efficiently in the reaction (**3b**, **3d**, **3m** and **3o**). This is likely due to the increased nucleophilicity of the aryne aiding in the second step of cyclization. Electron-poor arynes such as *o*-fluorinated and *m*-carboxymethyl ester-substituted derivatives also reacted with a variety of vinylaziridines (**3c**, **3e**, **3g**, **3j**, **3k** and **3n**). However, highly electron-deficient aryne precursors such as those substituted by trifluoromethyl, nitro or nitrile groups were not tolerated, likely due to the poor aryne generation from the corresponding stabilized anions.[18] Electron-neutral arynes also furnished the desired benzazepines in good yields (**3a**, **3f**, **3h**, **3i**, **3l** and **3p**). Selected *ortho*-substituted arynes reacted to form benzazepines (**3b**, **3e**, **3g**, **3i**, **3k** and **3m** – **3o**) in greater than 20:1 regioselectivity.[19] As expected, *meta*-substituted arynes provide both product regioisomers without any selectivity (**3c, 3d** and **3j**), indicating the free aryne is generated in solution. Various groups such as benzyl (**3a** – **3f**, **3i**, **3o** and **3p**), cyclohexyl (**3g**) and *p*-methoxybenzyl (PMB) (**3h**, **3j**, **3k** and **3l** – **3n**) were tolerated on the vinylaziridine nitrogen (R^2) without significant impact on the yield or regioselectivity. Furthermore, the reaction also proceeded when R^4 was replaced by a methyl group (**3f** – **3h**, **3j** and **3k**). The reaction also proceeded when R^5 was substituted with a phenyl group (1:1 *E/Z* mixture) to furnish benzazepines **3l** – **3n**. Utilizing enantiopure *trans*-vinylaziridine **2b**, the reaction proceeded with complete stereoretention to afford chiral benzazepines **3o** and **3p** in 99% *ee.* On the other hand, the corresponding *cis*-vinylaziridine stereoisomer was unreactive. Finally, the reaction was amenable to scale up with compound **3a** being isolated in 69% yield on a 1 mmol scale.[20]

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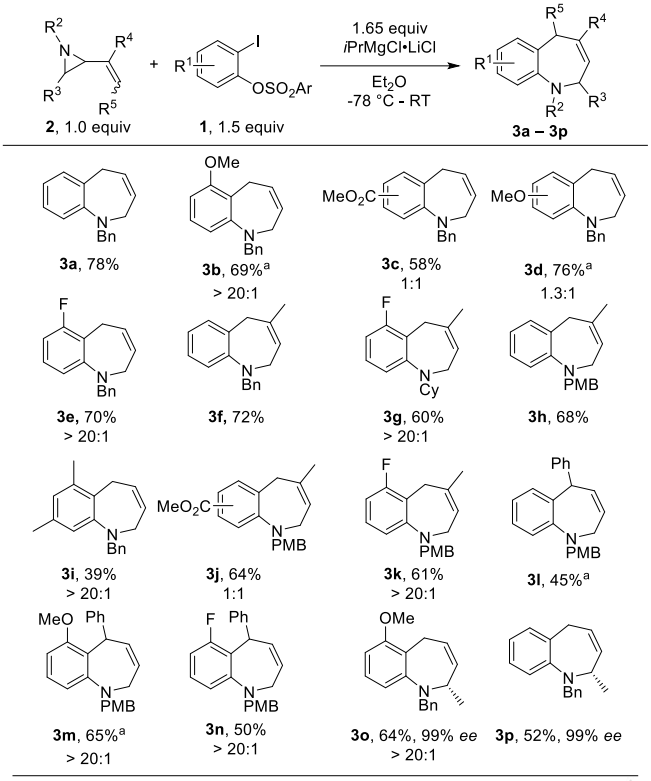
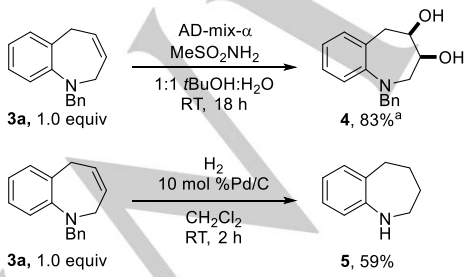


Scheme 2. Preparation of benzazepines **3a** – **3p** (Ar = 4-ClC_6H_4). Yield refers to isolated yield after column chromatography. Reactions were carried out in 0.05 M Et_2O with 1.50 equiv of aryne precursor and 1.65 equiv of *i*PrMgCl•LiCl (1.3 M in THF). [a]Reaction was warmed to 0 °C and stirred until completion. Isolated yield reported. Ratio of regioisomers determined by analysis of crude NMR mixture.

For the development of bioactive molecules, it is important to have substrates that are easily modified as this simplifies the synthesis of analogues and allows one to rapidly probe the outcome of various structural modifications on bioactivity. Along these lines, we were able to derivatize **3a** through a Sharpless dihydroxylation furnishing the diol **4**. Reduction of the double bond and concomitant benzyl deprotection with Pd/C and H_2 furnished the tetrahydrobenzazepine **5** (Scheme 3). Both **4** and **5** are cores of compounds that have been explored as anti-parasitics and 5-HT_2R modulators.[21]



Scheme 3. Derivatization of **3a** through dihydroxylation (**4**) and hydrogenation (**5**). [a]12% *ee*, without chiral ligand the yield dropped to 25%.

DFT calculations were conducted next using **2a** and benzyne as model components to elucidate whether the transformation proceeds as a formal sequential cycloaddition (see Figure 1a) or as a concerted [5+2] cycloaddition (Figure 2).[22] The vinylaziridne **2a** exists as *cis* and *trans*-isomer, with the latter being slightly more stable (2.1 kcal/mol). Both isomers can engage in the reaction with benzyne to form the corresponding zwitterions **A** and **B** which have similar free energies (-10 kcal/mol). We have identified two transition structures of nucleophilic addition of the aryl anion to the terminal carbon atom of the vinyl group. We could not locate a stable secondary alkyl anion as intermediate of the addition, opening of the aziridinium ring proceeds without additional barrier. In the *cis*-**2a** derived intermediate **A**, the aryl anion moiety and the double bond are distal (*trans* with respect to the aziridinium plane) and the barrier for reaction to **3a** is high (**TS-A**, $\Delta G^{\ddagger}$=40.9 kcal/mol). In intermediate **B** the reacting functionalities are close to each other (*cis*) and nucleophilic addition/aziridinium ring opening proceeds with a remarkably low barrier (**TS-B**, $\Delta G^{\ddagger}$=11.7 kcal/mol) to afford **3a**. Therefore, we assume that addition of *cis*-**2a** to benzyne is reversible and product formation proceeds exclusively *via* intermediate **B**. We could not identify a direct reaction pathway of benzyne and **2a** leading to **3a** *via* a concerted [5+2] cycloaddition.

We have also looked at nucleophilic ring opening of intermediate **B** with fluoride anion (see SI). The free energy of this transition structure is below the intermediate by almost 4 kcal/mol, indicating that this process (initiated by formation of a pre-reactive complex) is competitive with the benzazepine formation. Hence, under appropriate conditions the ring-opening leading to valuable allylic fluorides[23-25] might become the dominant process.

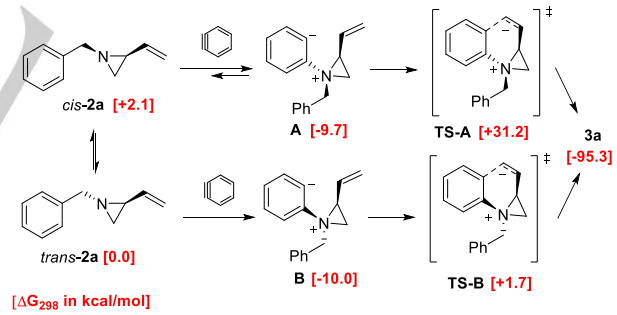


Figure 2. DFT calculated free energies of the reaction of aziridine **2a** with 1,2-benzyne (PW6B95-D3//PBE0-D3/def2-TZVP).

Along these lines, we found after screening conditions that utilizing 3.0 equivalents of TBAF (1.0 M in THF) in combination with 1.0 equivalent of vinylaziridine and 2.0 equivalents of aryne precursor in wet acetonitrile (0.1 M) at -10 °C to be optimal for this transformation. The transformation is rapid, with complete consumption of the vinylaziridine within 60 minutes. The reaction is also completely regioselective for the branched regioisomer.[26]

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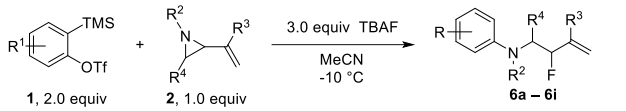
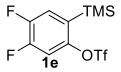
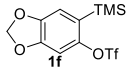
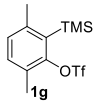
Table 2. Preparation of allyl fluorides **6a** – **6i**.

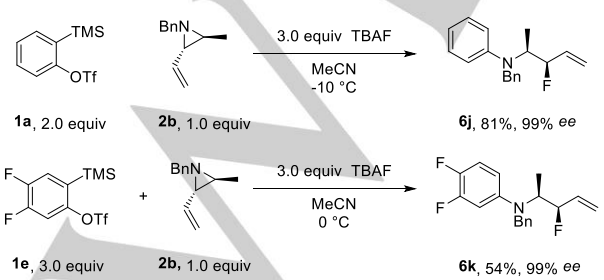


1, 2.0 equiv **2**, 1.0 equiv **6a – 6i**

Aryne Precursor	R^2	R^3	R^4	Yield (%)[a]
 **1a**	Bn	H	H	**6a**, 82%
	Cy	CH_3	H	**6b**, 75%
	PMB	CH_3	H	**6c**, 76%
	Bn	CH_3	CH_3	**6d**, 70%
 **1d**	Bn	H	H	**6e**, 63%
	PMB	CH_3	H	**6f**, 65%
 **1e**	PMB	CH_3	H	**6g**, 67%
 **1f**	Bn	H	H	**6h**, 38%[b]
 **1g**	PMB	H	H	**6i**, 59%

Reaction carried out at -10 °C to minimize amount of cycloaddition product. Reactions were carried out in 0.1 M MeCN with 1.5 equivalents of vinylaziridine and 2.0 equivalents of TBAF (1.0 M in THF) at room temperature overnight. [a]Isolated yield after column chromatography. [b]Reaction ran at -20 °C.

Utilizing the optimized conditions, we were able to synthesize a number of allylic fluorides in good isolated yields (Table 2). The electron-neutral aryne precursor **1a** reacted cleanly with benzyl, cyclohexyl and *p*-methoxybenzyl protected vinylaziridines (**6a** – **6c**). Unlike in the cycloaddition reaction, *cis*-vinylaziridine **2b** reacted smoothly with aryne precursor **1a** to give allyl fluoride **6d** in 70% yield. While electron-rich aryne precursors **1d** and **1f** reacted with slightly diminished yields (**6e**, **6f** and **6h**). In the case of the reaction with aryne **1f**, the major mass balance was found to be cycloaddition product **3l**. Electron-poor aryne precursor **1e** was also tolerated in the reaction to generate **6g** in 67% yield. Furthermore, the more sterically encumbered *o*-disubstituted aryne precursor **1g** furnished the desired allylic fluoride **6i** in 59% yield. Finally, we determined that the ring opening of the aziridinium proceeded stereospecifically by utilizing enantiopure *trans*-vinylaziridine **2b** to furnish enantiopure allylic fluorides **6j** (81%, 99% *ee*) and **6k** (54%, 99% *ee*) (Scheme 4).



Scheme 4. Enantioselective synthesis of allyl fluorides through a stereospecific reaction between arynes and enantiopure vinylaziridine **2b**.

In conclusion, we have demonstrated a highly effective reaction between vinylaziridines and arynes. Depending on the choice of reaction conditions, either benzazepines or allyl fluorides can be obtained with excellent stereoselectivity. Downstream functionalization of the benzazepine scaffold and a DFT investigation of the mechanism were also presented. The present methodology presents advantages over previous work in that it is highly divergent and furnishes enantiopure products. This work also highlights the continuously expanding scope of aryne chemistry and facilitates the exploration of these compounds as biologically active molecules and synthetic intermediates.

Acknowledgements

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Keywords: arynes • vinyl aziridines • aryl anions • strained rings • DFT calculations

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Reaction of Vinylaziridines with Arynes: Synthesis of Benzazepines and Branched Allyl Fluorides.

Chemodivergent and enantiospecific! The addition of vinylaziridines to in situ generated arynes provides depending on the reaction conditions and the choice of aryne precursor multi-substituted benzazepines or allylic fluorides. Both reactions proceed stereospecifically and furnish enantiopure products.