Heterocycles

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Intramolecular Polar [4⊕+2] Cycloadditions of Aryl-1-aza-2-azoniaallene Salts: Unprecedented Reactivity Leading to Polycyclic Protonated Azomethine Imines**

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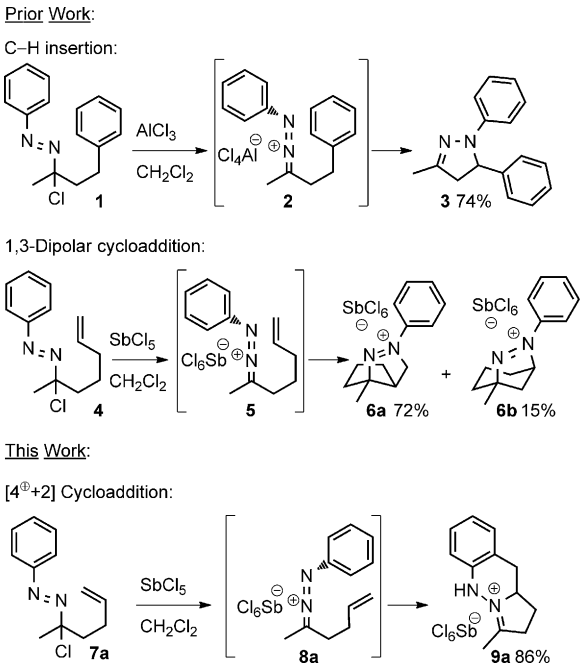
Polar cycloadditions, in which one of the reacting partners is ionic, are less common than cycloadditions involving uncharged or dipolar components, but often occur more readily.[1] For example, whereas [4+2] cycloaddition reactions that involve styrene subunits as the 4π component generally require reactive dienophiles or harsh reaction conditions to proceed,[2] the Povarov reaction, which is the stepwise[3] [4⊕+2] cycloaddition of N-aryliminium ions with electron-rich olefins, occurs readily at or below room temperature.[4,5] The charge that is present in the ionic partner of polar cycloadditions is often due to the presence of a heteroatom and these systems can provide useful routes to heterocyclic products,[1a] which are prevalent scaffolds in biologically active molecules.[6] Although uncharged heteroallenes have been used extensively in the preparation of heterocyclic compounds,[7] cationic heteroallenes have received less attention. To this end, we have been exploring the use of 1-aza-2-azoniaallene cations (e.g. **2**, Scheme 1) in intramolecular reactions as a means of preparing a variety of aza-heterocycles. Herein we report our discovery that aryl-1-aza-2-azoniaallene cations can react by an unprecedented intramolecular [4⊕+2] cycloaddition with pendant alkenes wherein the azo bond and one aromatic π bond make up the 4π component.

1-Aza-2-azoniaallene cations are known to react by several different pathways, thus leading to a variety of products. For example, these species can add nucleophiles at the carbon atom to provide azo products,[8] can undergo 3,3-sigmatropic rearrangements,[9] and can react in stereospecific intramolecular C–H amination reactions to provide pyrazolines by what appears to be a concerted nitrenoid-type insertion (e.g. **2** to **3**, Scheme 1).[10] In addition, these cationic heteroallenes can act as 1,3-dipoles in [3+2] cycloaddition reactions with a variety of π systems to provide five-membered-ring heterocycles.[11] We have taken advantage of this latter reactivity to prepare bicyclic diazenium salts (e.g. **6a** and **6b**, Scheme 1).[12]



Scheme 1. Varied reactivity of aryl-1-aza-2-azoniaallene salts.

While continuing our studies on intramolecular reactions of 1-aza-2-azoniaallene cations we recently prepared the heteroallene **8a** (Scheme 1), which could in principle form a 5,5-bridged bicyclic diazenium salt similar to **6b**. However, orbital alignment in the transition state leading to that product would not be ideal; this asynchronous ring closure would be Baldwin-disfavored in the same way that 5-(enolendo)-*exo*-trig aldol condensations are disfavored.[13] We were interested to observe that **8a** in fact did not undergo intramolecular [3+2] cycloaddition, but instead reacted by an unprecedented intramolecular [4⊕+2] cycloaddition to provide a tricyclic protonated azomethine imine containing a 1,2,3,4-tetrahydrocinnoline scaffold (**9a**, Scheme 1). Cinnoline derivatives, including 1,2,3,4-tetrahydrocinnolines, show diverse biological activity[14] and although tetrahydrocinno-

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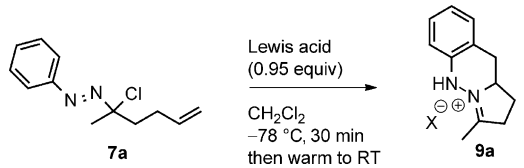
lines can be prepared by several classical methods,[15] the development of new methods to prepare this useful scaffold continues to be an active area of research.[16] The unprecedented nature of this reaction, the uniqueness of the protonated azomethine imine products,[17] and the potential that these products will have diverse reactivity, and thus be useful synthetic intermediates, encouraged us to examine this polar cycloaddition in more detail. Our preliminary results are presented here.

Our first task was to optimize the reaction conditions for the conversion of **7a** into **9a** (Table 1) . Our initial results were obtained by adding 1.2 equivalents of $SbCl_5$ to a solution

Table 1: Assessment of Lewis acids.



Entry	Lewis acid	Yield [%][a]
1	$SbCl_5$	86
2	$AlCl_3$	84
3	AgOTf[b,c]	70
4	TMSOTf[c,d]	84

[a] Yield determined by ^{1}H NMR spectroscopy using an internal standard, and based on the limiting reagent. [b] Reaction conducted at room temperature for 2 h. [c] 1 equiv of Lewis acid was used. [d] Reaction conducted at room temperature for 24 h. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

of **7a** in CH_2Cl_2 at −78 °C, with warming to room temperature. After some experimentation, we discovered that using a slight deficiency of $SbCl_5$ (0.95 equiv) resulted in cleaner crude reaction mixtures. Alternative Lewis acids were screened and while we were pleased to see that $AlCl_3$, AgOTf, and TMSOTf could each mediate the reaction, they did not improve the yield or product purity compared to the use of $SbCl_5$. However, the triflate counter ion did give a product that was more crystalline, and allowed us to confirm the structure of **9a** by X-ray crystallography.[18] Factoring in both cost and the simplicity of using a liquid Lewis acid caused us to select $SbCl_5$ as the Lewis acid of choice for further studies.

With optimized reaction conditions in hand, we next explored the scope of this intramolecular cycloaddition (Table 2).[19] We were pleased to note that increased substitution adjacent to the heteroallene carbon atom was well tolerated. The more sterically hindered isopropyl derivative **7b** (entry 2) provided the desired product in 88% yield, whereas the cyclohexanone-derived α-chloroazo **7c** (entry 3) provided the tetracycle **9c** in 83% yield as a 2:1 mixture of diastereomers.[20] Incorporation of a silyloxy group adjacent to the heteroallene carbon atom was also well tolerated and the silyl ether **7d** provided the more-heteroatom-rich product **9d** in 71% yield (entry 4). In this case, one could envision the cationic heteroallene intermediate undergoing a competitive 1,2-hydride migration to the electrophilic carbon atom facilitated by the adjacent oxygen center, but this product was not observed.

We next examined the scope of this reaction with respect to alkene substitution. We were pleased to observe that the α-chloroazo compounds **7e** and **7f** (Table 2, entries 5 and 6), which contained a di- and trisubstituted olefin respectively, provided excellent yields (97% and 98%, respectively) of the desired product. Importantly, these examples show that this transformation can efficiently form nitrogen-bearing and all-carbon quaternary centers.

In an effort to gain some understanding of the concerted nature of the bond-forming events, we prepared *trans* and *cis* alkenes **7g** and **7h**, respectively (Table 2, entries 7 and 8) and subjected each to the cyclization conditions. The cycloaddition reaction proved to be stereospecific. Each substrate led to a unique diastereomer of the product, thus suggesting that the cycloaddition process is concerted.[21]

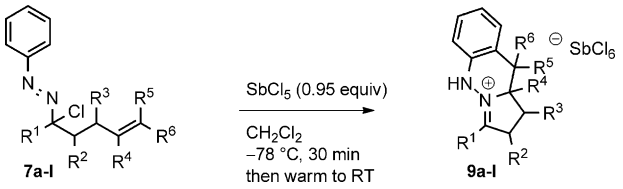
Incorporation of the alkene component into a ring provided the tetracyclic products **9i** and **9j** (Table 2, entries 9 and 10) as single diastereomers in high yield. These results highlight the ability of this transformation to provide structurally complex products from structurally simple starting materials.

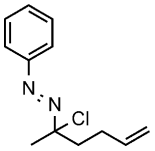
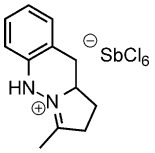
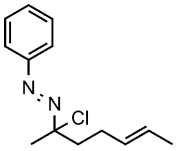
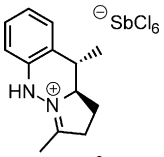
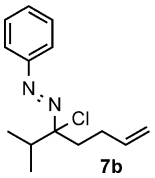
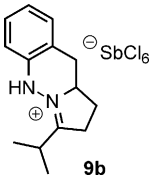
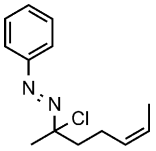
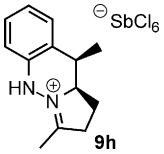
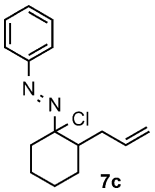
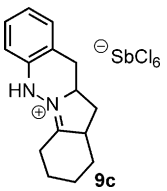
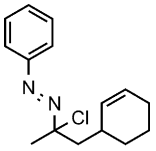
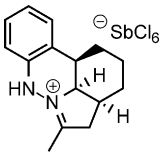
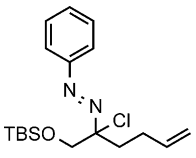
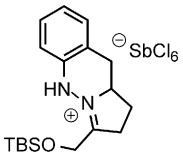
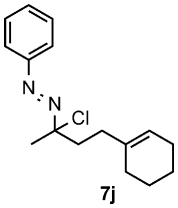
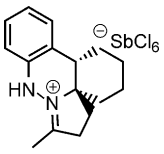
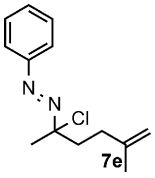
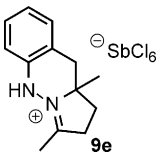
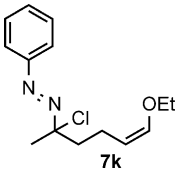
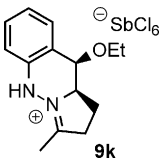
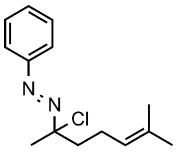
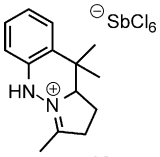
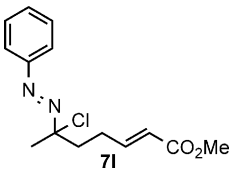
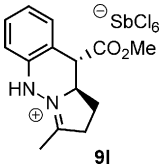
The electronic nature of the dienophile can have a dramatic effect on the efficiency of polar cycloadditions. For example, the Povarov reaction fails when the dienophile is electron deficient.[4d] To test the scope of this reaction with respect to the electronics of the pendant dienophile we prepared the cyclization precursors **7k** and **7l** (Table 2, entries 11 and 12) which contain electron-rich and electron-deficient olefins, respectively. The electron-rich olefin (**7k**) was surprisingly difficult to prepare as both it and the hydrazone precursor decomposed readily. Treating **7k** under the reaction conditions provided the cycloaddition product **9k** in a modest 33% yield. We suspect that this low yield is not due to the cycloaddition step itself, but rather to the instability of **7k** which became noticeably dark in color while setting up the reaction. It is interesting to note that this highly electron-rich olefin reacted to provide a single diastereomer of product. In view of the cationic nature of the heteroallene intermediate, we expected an electron-deficient alkene to be a poor reaction partner. We were surprised to observe that **7l** (entry 12) provided the cycloadduct **9l** in 93% yield. This high yield further demonstrates the broad scope of this reaction.

In view of the similarity between **5** and **8a** (Scheme 1), which are identical except for the length of the tether that separates the heteroallene from the pendent alkene, it is interesting that **5** provides only the diazenium salt product and none of the corresponding protonated azomethine imine. In addition, intermolecular cycloadditions of 1-aza-2-azoniaallene cations proceed by the [3$^{\oplus}$+2] manifold[11a–g] and taken together these facts indicate that the [3$^{\oplus}$+2] pathway is intrinsically more favorable than the alternative [4$^{\oplus}$+2] cycloaddition described here. It seems likely that this latter reaction occurs in the cases described here because of the orbital alignment constraints discussed above, which stem from the intramolecular nature of these reactions.

In conclusion, we have discovered an unprecedented reactivity of aryl-1-aza-2-azoniaallene salts. The [4$^{\oplus}$+2] cyclo-

Table 2: Substrate scope.



Entry	Substrate	Product	Yield [%][a]	Entry	Substrate	Product	Yield [%][a]
1	 **7a**	 **9a**	86	7	 **7g**	 **9g**	81
2	 **7b**	 **9b**	88	8	 **7h**	 **9h**	82
3	 **7c**	 **9c**	83 (2:1 d.r.)	9	 **7i**	 **9i**	89
4	 **7d**	 **9d**	71	10	 **7j**	 **9j**	85
5	 **7e**	 **9e**	97	11	 **7k**	 **9k**	33
6	 **7f**	 **9f**	98	12	 **7l**	 **9l**	93

[a] Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

addition reaction described herein is likely concerted and provides high yields of protonated azomethine imine products which contain a 1,2,3,4-tetrahydrocinnoline core. This reaction occurs at low temperature, is quite general with respect to alkene substitution, and delivers products which contain all-carbon or nitrogen-bearing quaternary centers in high yield. Further studies on the scope and mechanism of this transformation including computational studies and application of this cycloaddition in natural product synthesis are planned.

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[17] Protonated azomethine imines are not common species, but are known to be more stable than their deprotonated dipolar counterparts. For examples of these species, see: a) Y. Tamura, J.-I. Minamikawa, Y. Miki, Y. Okamoto, M. Ikeda, *Yakugaku Zasshi* **1973**, *93*, 648 – 653; b) T. Hashimoto, Y. Maeda, M. Omote, H. Nakatsu, K. Maruoka, *J. Am. Chem. Soc.* **2010**, *132*, 4076 – 4077.

[18] CCDC 952450 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] The crude reaction mixtures were triturated with petroleum ether to provide products with minimal impurities. Attempts to further purify the products by chromatography or crystallization failed. The yields reported in Tables 1 and 2 are based on the limiting reagent (Lewis acid) and were determined by proton NMR spectoscopy using 1,3,5-trimethoxybenzene as an internal standard.

[20] The diastereomers were not separable and the relative configuration of the major and minor component was not determined.

[21] The relative configuration of **9g–l** were determined by evaluation of the coupling constants between the benzylic proton and the proton adjacent to the positively charged amine. This is more fully described in the Supporting Information.

