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Stereospecific Intramolecular C−H Amination of 1-Aza-2-azoniaallene Salts

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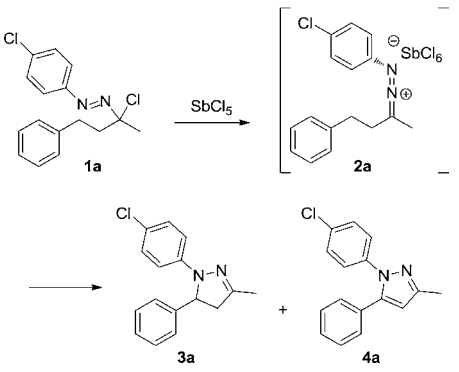
Supporting Information

ABSTRACT: We report that 1-aza-2-azoniaallene salts, generated from α-chloroazo compounds by treatment with halophilic Lewis acids, participate in intramolecular C−H amination reactions to provide pyrazoline products in good to excellent yield. This intramolecular amination occurs readily at both benzylic and tertiary aliphatic positions and proceeds at an enantioenriched chiral center without loss of enantiomeric excess. A competition reaction shows that insertion occurs more readily at an electron-rich benzylic position than an electron-deficient one. These observations are consistent with the 1-aza-2-azoniaallene intermediate reacting as a nitrenium-like ion by a concerted insertion mechanism.

Reactions that result in direct functionalization of unactivated C−H bonds are powerful transformations because they provide new synthetic strategies that can be more efficient and simpler to execute than traditional synthetic sequences.[1] For example, Rh-catalyzed carbene insertion reactions, wherein Rh complexes selectively functionalize C−H bonds, have become an important strategy for C−C bond formation.[2] Similarly, since Breslow and Gellman's[3,4] seminal demonstration that (imidoiodo)benzene derivatives react with alkanes in the presence of a transition metal to provide amine products, transition-metal-catalyzed C−H amination reactions have become important ways to prepare organic amines.[5−9] These techniques are powerful because they allow for the selective installation of N atoms both inter- and intramolecularly at a late stage in a synthetic sequence and provide fundamentally new approaches to the preparation of N heterocycles, which are prevalent in bioactive molecules.[10−12] The significant advances that have been made over the past decade in transition-metal-mediated amination were made possible in part by the discoveries by Che[13] and Du Bois[14] that metal nitrenoid species could be prepared in situ from amine derivatives, iodine(III) reagents, and a transition metal catalyst. Recently, amination reactions have been used elegantly in natural product synthesis[15,16] and have been rendered stereoselective.[17−20] Here we report our discovery that 1-aza-2-azoniaallene salts[21] (e.g., **2a**, Scheme 1) undergo intramolecular C−H insertion reactions to provide pyrazoline products without the formation of a metal nitrenoid intermediate.

Recent work in our group has focused on investigating 1-aza-2-azoniaallene salts as reactive intermediates for the synthesis of N heterocycles.[22,23] We have demonstrated that these heteroallene salts, which can be generated by reaction of α-chloroazo compounds with halophilic Lewis acids,[21] productively react with pendant alkenes to provide bicyclic diazenium salts via intramolecular 1,3-dipolar cycloaddition reactions similar to the intermolecular cycloadditions described by Jochims et al.[24,25] The requisite α-chloroazo compounds are easily prepared by reaction of hydrazones with chlorodimethylsulfonium chloride.[26] We became interested in exploring the reactivity of these cationic heteroallenes in systems that cannot participate in 1,3-dipolar cycloadditions because they lack a pendant alkene.[27] To this end, we prepared heteroallene **2a** (Scheme 1) by treating the α-chloroazo compound **1a** with $SbCl_5$, and upon purifying this reaction we were surprised to isolate pyrazoline **3a** in good yield as well as traces of pyrazole **4a**. This unexpected result is, to our knowledge, the first example of heteroallenes such as **2a** reacting by a nitrene-like manifold to provide the product of an intramolecular C−H amination reaction. Although pyrazolines can be readily prepared by reaction of hydrazines with α,β-unsaturated aldehydes and ketones or by 1,3-dipolar cycloaddition of diazoalkanes with alkenes,[28,29] the development of new methods to prepare these compounds is still of interest[30−36] due to their prevalence in biologically active compounds.[30,37,38] The novelty of this C−H amination reaction encouraged us to examine this new reactivity more thoroughly.

Scheme 1. Preparation of a Pyrazoline from an α-Chloroazo Compound



Upon repeating this transformation several times, we noted that the ratio of pyrazoline **3a** and pyrazole **4a** varied significantly between trials, and we reasoned that the pyrazole likely formed by a precedented $SbCl_6^-$-mediated oxidation of the pyrazoline.[39] This secondary oxidation reaction proved

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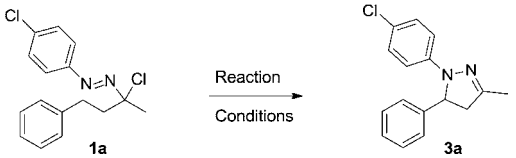
Table 1. Optimization of Reaction Conditions for Pyrazoline Formation



1a 3a

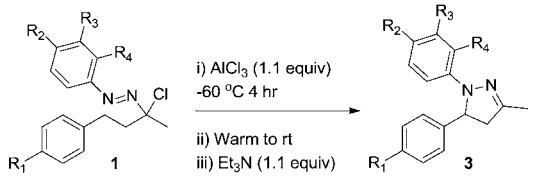
entry	MCl_X	equiv	solvent	time (h)	temp (°C)	yield (%)[a]
1	$SbCl_5$	1.1	CH_2Cl_2	2	−60	53
2	$AlCl_3$	1.1	CH_2Cl_2	2	−60	51
3	$AlCl_3$	1.1	CH_2Cl_2	4	−60	61
4	$AlCl_3$	1.1	CH_2Cl_2	6	−60	62
5	$AlCl_3$	1.1	CH_2Cl_2	32	−60	59
6	$AlCl_3$	1.1	CH_2Cl_2	48	−60	38
7	$AlCl_3$	1.1	CH_2Cl_2	34	−40	56
8	$AlCl_3$	1.1	CH_2Cl_2	24	25	49
9	$AlCl_3$	1.1	THF	24	−60	0
10	$AlCl_3$	2.2	CH_2Cl_2	24	−60	36

[a]Yields determined by ^{1}H NMR integration relative to an internal standard.

difficult to control, but we were pleased to find that changing the Lewis acid from $SbCl_5$ to $AlCl_3$ eliminated formation of pyrazole **4a** while providing comparable yields of the desired pyrazoline (Table 1, entry 2).[21] We next evaluated the effect of reaction time on the reaction outcome. Increasing the reaction time from 2 to 4 h resulted in increased product yield (entries 2 and 3), but further extending the reaction time added no benefit (entries 4−6). We also evaluated the temperature dependence of the reaction and observed the best results at −60 °C; higher temperatures resulted in slightly lower yields (entries 7 and 8). Changing the solvent from CH_2Cl_2 to THF inhibited the reaction altogether (entry 9), and increasing the equivalents of $AlCl_3$ decreased the pyrazoline yield (entry 10).

To gain insight into the role that electronic effects might play in this reaction, we prepared a series of substrates having either electron-donating or -withdrawing groups on the N-aryl or the pendant aryl ring (Table 2). Electron-rich N-aryl rings facilitated the reaction, and changing the N-aryl ring from 4-chlorophenyl to phenyl, 4-methylphenyl, or 4-methoxyphenyl

Table 2. Effect of Aryl Ring Electronics on the Intramolecular Amination



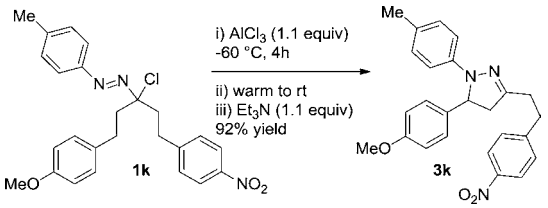
1 3

entry	α-chloroazo	R_1	R_2	R_3	R_4	yield (%)
1	**1a**	H	Cl	H	H	61
2	**1b**	H	H	H	H	74
3	**1c**	H	CH_3	H	H	79
4	**1d**	H	OCH_3	H	H	76
5	**1e**	H	H	NO_2	H	<20
6	**1f**	H	H	H	CH_3	80
7	**1g**	OCH_3	Cl	H	H	79
8	**1h**	CH_3	Cl	H	H	65
9	**1i**	Cl	Cl	H	H	62
10	**1j**	NO_2	Cl	H	H	65

resulted in an increase in yield of ∼15%. The 3-nitrophenyl derivative (entry 5), in contrast, returned product in at most 20% yield.[40] A moderate increase in steric hindrance adjacent to the amine was well tolerated; 2-methylphenyl derivative **1f** provided the expected product in 80% yield (entry 6). Changing the electronics of the pendant aryl ring from marginally electron-rich (entry 8) to electron-neutral (entry 1) to electron-poor (entries 9 and 10) had surprisingly little influence on the reaction outcome; in each case a similar quantity of pyrazoline product was formed (61−65% yield). In contrast, a strong electron-donating group on the pendant aryl ring (entry 7) appeared to activate the benzylic C−H bond toward amination and gave a significantly higher product yield (79%).

To test this finding more directly, we devised a competition experiment in which the heteroallene intermediate has equal opportunity to react at an electron-rich or -deficient benzylic position. For this experiment, we prepared α-chloroazo substrate **1k** (Scheme 2), which contains both electron-poor

Scheme 2. Competition Experiment



and -rich pendant aryl rings. The heteroallene generated from this substrate reacted with complete selectivity at the more electron-rich benzylic C−H bond to provide pyrazoline **3k** as the only product in 92% yield.[41] The high yield obtained for this reaction is likely due to the electron-rich nature of both the N-aryl and pendant aryl ring. It is accepted that, over the course of carbenoid and nitrenoid C−H insertion reactions, positive charge builds at the C undergoing the C−H insertion, and sites adjacent to electron-donating groups react more quickly.[2,42] The result of the competition study supports the notion that heteroallene intermediate **2**, which could exist in nitrenium ion form **5** (Figure 1), may be reacting similarly to a nitrenoid via a

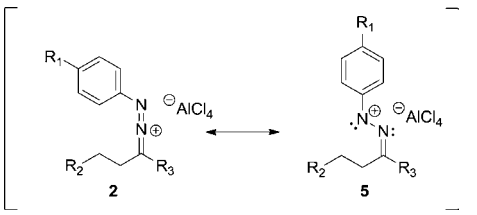


Figure 1. Nitrenium ion resonance form.

C−H amination reaction. Theoretical studies support the ability of 1-aza-2-azoniaallene cations to react by a nitrenium ion manifold.[43] Nitrenium ions are isoelectronic with carbenes, but despite the plethora of research in carbene chemistry, nitrenium ions have been far less studied,[44−46] although recently aryl nitrenium ions[47−49] have received more attention due to their proposed role in mutagenesis and carcinogenesis. Additionally, nitrenium ions are known to undergo concerted addition to alkenes to provide aziridinium products,[50−53] and they can act as hydride acceptors.[54] The increased yields of

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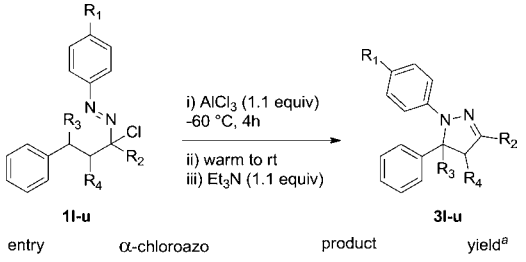
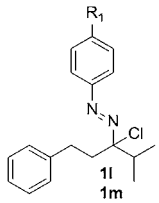
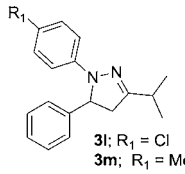
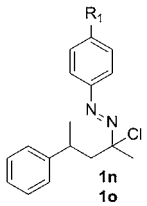
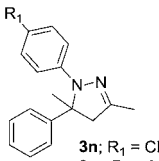
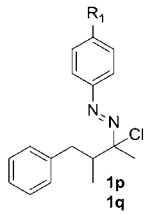
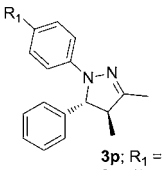
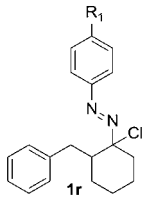
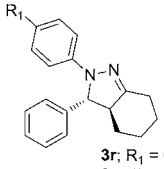
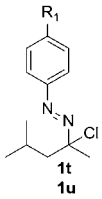
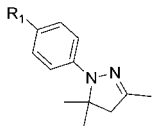
pyrazoline we obtained for electron-rich N-aryl substrates (Table 2, entries 3 and 4, and Table 3, all entries) are also consistent with a nitrenium ion-type reaction intermediate since electron-rich aryl rings and adjacent heteroatoms are known to stabilize the nitrenium ion singlet state,[55] which should undergo insertion reactions more readily than the triplet state.

We next examined the effect of adding substituents on the C chain of the α-chloroazo substrate (Table 3) on the reactions leading to tri- or tetrasubstituted pyrazolines. Adding a substituent adjacent to the chloroazo center and between the reacting centers returned a single diastereomer[56] of product; however, in these cases yields suffered (entries 3 and 4). The reduction in yield is likely due to an increase in steric interactions that make pyrazoline formation less facile, and not a subtle electronic effect imparted by the extra substituent since adding a group adjacent to the chloroazo center on the side opposite the aryl ring provided the expected product in good yield (entry 1). Adding a substituent in the benzylic position was well tolerated when the N-aryl ring was electron-rich to provide 5,5-disubstituted pyrazoline **3o** (entry 2).[57] For reasons that we do not fully understand, this transformation consistently failed when the N-aryl ring was electron-deficient (entry 2, **1n**). In this latter case, substantial quantities of the starting ketone were isolated upon workup.

Table 3. Substrate Scope



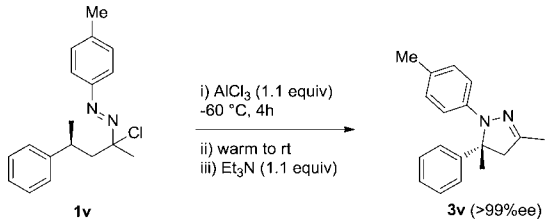
entry	α-chloroazo	product	yield[a]
1	 **1l** **1m**	 **3l**; R_1 = Cl **3m**; R_1 = Me	64% 79%
2	 **1n** **1o**	 **3n**; R_1 = Cl **3o**; R_1 = Me	~6% 66%
3	 **1p** **1q**	 **3p**; R_1 = Cl **3q**; R_1 = Me	12% 35%[b]
4	 **1r** **1s**	 **3r**; R_1 = Cl **3s**; R_1 = Me	44%[c] 67%[d]
5	 **1t** **1u**	 **3t**; R_1 = Cl **3u**; R_1 = Me	59%[e] 62%[f]

[a]Isolated yield. [b]^{1}H NMR yield, 40%. [c]^{1}H NMR yield, 56%. [d]^{1}H NMR yield, 71%. [e]^{1}H NMR yield, 75%. [f]^{1}H NMR yield, 66%.

Successful insertion into a tertiary benzylic center led us to examine the potential of the heteroallene to react at a tertiary non-benzylic site. Importantly, subjecting isopropyl derivative **1t** or **1u** to the reaction conditions returned pyrazoline **3t** or **3u** (Table 3, entry 5) in 59% and 62% isolated yield, respectively. Unfortunately, attempts to insert into a secondary aliphatic position were not fruitful; the heteroallene derived from 2-pentanone returned a complex mixture.

Mechanisms that could account for pyrazoline formation include the concerted C−H insertion of a singlet-state nitrenium ion-type intermediate, a radical abstraction of a benzylic H by a triplet-state nitrenium ion-type intermediate followed by a radical recombination to form the new C−N bond, or a 1,5-hydride shift followed by nucleophilic attack of N onto the newly formed benzylic cation. To give some indication of which of these mechanisms might be operative, we prepared substrate **1v** (Scheme 3) in enantioenriched form.

Scheme 3. Stereospecific C−H Amination



Subjecting this material to the reaction conditions provided pyrazoline **3v** with complete stereochemical fidelity, as determined by HPLC analysis on a chiral stationary phase. This result favors a concerted C−H insertion reaction since the other two mechanistic possibilities would proceed through achiral intermediates. However, these latter two mechanisms cannot be ruled out entirely since the recombination steps could, in principle, occur faster than bond rotation; further studies are planned to more fully probe the operative mechanism.

In summary, 1-aza-2-azoniaallene salts have been observed to participate in unprecedented amination reactions at benzylic and tertiary aliphatic centers to provide pyrazoline products. A substrate that contained an enantioenriched tertiary benzylic center reacted without erosion of stereopurity. The results gathered thus far support the hypothesis that the amination reaction occurs via a concerted C−H insertion of a singlet-state nitrenium ion intermediate. Further studies on the scope and mechanism of this transformation are underway.

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■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, spectral data for all compounds, and HPLC traces for **3o** and **3v**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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