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Acid-Mediated Ring-Expansion Reaction of *N*-Aryl-2-vinylazetidines: Synthesis and Unanticipated Reactivity of Tetrahydrobenzazocines

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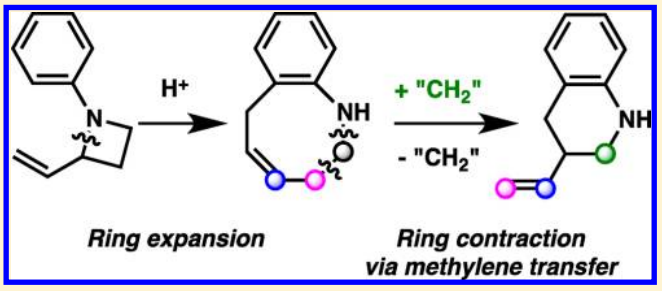
Supporting Information

ABSTRACT: The aza-Clasen rearrangement of *N*-aryl-2-vinylazetidines has been explored. *N*-Aryl-2-vinylazetidines were transformed to corresponding tetrahydrobenzazocines in good yields. Unexpectedly, the tetrahydrobenzazocine was unstable and readily isomerized to vinyltetrahydroquinoline in the presence of acid. The mechanism of this ring contraction was studied in detail.



INTRODUCTION

The aza-Claisen rearrangement is a [3,3]-sigmatropic rearrangement that incorporates a nitrogen atom at the 3-position, and the reactions of various allylenamines or allylanilines have been reported to date (Figure 1a). The ability to construct an elaborate structure from a readily available material with chemo-, regio-, and/or stereoselective manner by this rearrangement has attracted considerable interest of organic chemists. Aza-Claisen rearrangement under thermal conditions classically requires high reaction temperature of 200 °C or above and is plagued with undesired side reactions.[1] Meanwhile, the protonation or quaternization of the amine results in the acceleration of the reaction, and the progress of the rearrangement has been observed at lower temperature.

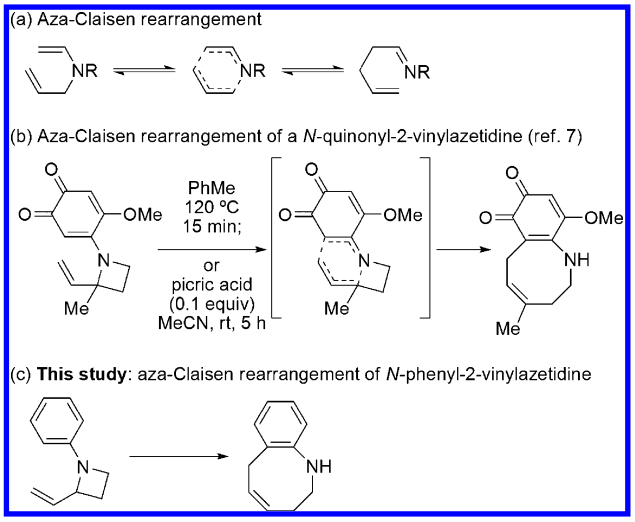


Figure 1. Aza-Claisen rearrangement reaction.

A practical application of this rearrangement in synthetic organic chemistry has been developed by using a strained substrate, which was more reactive, and some aza-Claisen rearrangement reactions of vinylaziridines have been reported to date.[2−6] For example, Gallo and co-workers reported the aza-Claisen rearrangement of *N*-aryl-2-vinylaziridines, which were vulnerable to heat and acids.[4] Gin and co-workers demonstrated an example of strain release aza-Claisen rearrangement/ring-expansion reaction of *N*-alkenyl-2-arylaziridine in the context of the total synthesis of a natural product, (−)-deoxyharringtonine.[5,6]

On the basis of the chemistry of *N*-aryl-2-vinylaziridines, one would expect that the corresponding azetidine analogue, an *N*-aryl-2-vinylazetidine, would be a good substrate for the aza-Claisen rearrangement. Surprisingly, to the best of our knowledge, the aza-Claisen rearrangement of *N*-phenyl-2-vinylazetidine has not been reported, and only the rearrangement of *N*-quinonylazetidine has appeared in the literature (Figure 1b).[7]

Recently, we studied a series of the ring-expansion reactions of vinylaziridines as well as vinylazetidines and developed new methods for the synthesis of medium-sized heterocyclic compounds.[8] Herein we report the acid-catalyzed aza-Claisen rearrangement of *N*-aryl-2-vinylazetidine to yield tetrahydrobenzazocine (Figure 1c). The unanticipated instability of the benzazocine derivatives is also disclosed.

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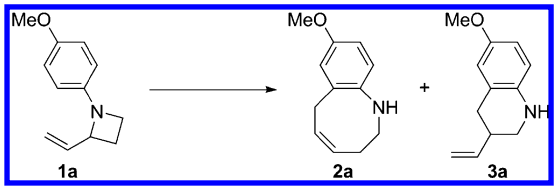
RESULTS AND DISCUSSION

Acid-Mediated Ring-Expansion Reaction of *N*-Aryl-2-vinylazetidine. The ring-expansion reaction of *N*-(4-methoxyphenyl)-2-vinylazetidine (**1a**) was investigated under various reaction conditions to selectively obtain tetrahydrobenzazocine **2a**. Due to the instability of **2a** (*vide infra*), the ratio of products was analyzed by NMR spectroscopy. The results are summarized in Table 1.

Table 1. Screening of Reaction Conditions[a]

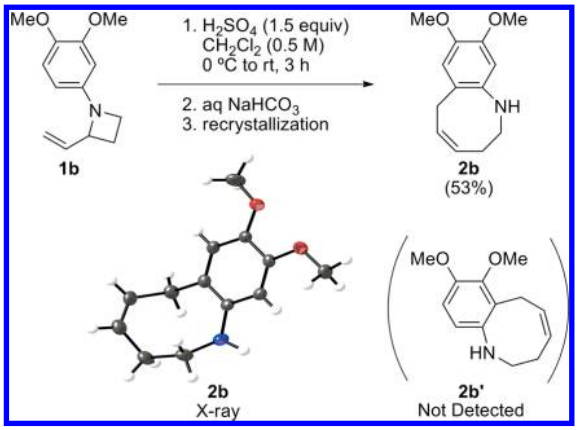


entry	acid (equiv)	solvent (M)	temp[b]	time (h)	1a/2a/3a[c]
1		$ClCH_2CH_2Cl$ (0.05)	83 °C (reflux)	24	100/0/0
2		PhMe (0.05)	120 °C	24	100/0/0
3	H_2SO_4 (0.2)	$ClCH_2CH_2Cl$ (0.05)	rt	101	41/10/49
4	H_2SO_4 (0.2)	$ClCH_2CH_2Cl$ (0.05)	50 °C	28	17/33/50
5	TfOH (0.3)	$ClCH_2CH_2Cl$ (0.05)	rt	20	0/7/93
6	CF_3CO_2H (0.8)	$ClCH_2CH_2Cl$ (0.05)	rt	27	0/9/91
7	H_2SO_4 (1.5)	$ClCH_2CH_2Cl$ (0.05)	rt	1.5	0/87/13
8	H_2SO_4 (2.0)	$ClCH_2CH_2Cl$ (0.05)	rt	2	5/60/35
9	H_2SO_4 (1.5)	CH_2Cl_2 (0.5)	0 °C	24	0/90/10
10	H_2SO_4 (1.5)	CH_2Cl_2 (0.5)	0 °C to rt[d]	3	0/>95/<5

[a]Reaction procedure: compound **1a** (0.5 mmol) was dissolved in solvent, and the mixture was stirred at the indicated temperature under argon atmosphere for the indicated period. At the completion of the reaction, the mixture was treated with aqueous sodium bicarbonate, separated, and concentrated. The products were analyzed by ^{1}H NMR spectroscopy. [b]External temperature, unless otherwise noted. [c]Determined by ^{1}H NMR integration of the crude product. [d]The reaction mixture was stirred at 0 °C for 2 h and then allowed to warm to room temperature.

Compound **1a** was stable at high temperature, and the expected rearrangement did not take place at 83 °C in 1,2-dichloroethane or 120 °C in toluene (entries 1 and 2). The observed stability of **1a** is in contrast to the reported high reactivity[7] of a vinylazetidine derivative. Interestingly, the reaction of **1a** proceeded sluggishly in the presence of H_2SO_4 to give a mixture of the desired tetrahydrobenzazocine **2a** and 3-vinyl-1,2,3,4-tetrahydroquinoline **3a** (entry 3). An attempt to accelerate the reaction by heating the reaction mixture to 50 °C failed, and the formation of a large amount of **3a** was observed (entry 4). Employing TfOH or CF_3CO_2H as the catalyst resulted in the formation of a mixture predominantly containing **3a** (entries 5 and 6). Increasing the amount of H_2SO_4 was beneficial, and the reaction proceeded at a reasonable rate with 1.5 equiv of H_2SO_4 (entry 7). Using a larger amount of H_2SO_4 was detrimental, and the proportion of vinyltetrahydroquinoline byproduct increased with 2.0 equiv of H_2SO_4 (entry 8). The ratio of tetrahydrobenzazocine to vinyltetrahydroquinoline improved when the reaction was carried out at low temperature (0 °C) and with a higher concentration of **1a** (0.5 M, entry 9). The best result was achieved when the reaction was initially carried out at 0 °C and then allowed to warm to room temperature: the reaction completed in 3 h, and the selective formation of **2a** was observed (entry 10). The structure of a tetrahydrobenzazocine was confirmed by carrying out the reaction of *N*-(3,4-dimethoxyphenyl)-2-vinylazetidine (**1b**, Scheme 1). Thus, the

Scheme 1. Isolation of Tetrahydrobenzazocine



ring-expansion reaction of **1b** was carried out under optimized reaction conditions, and 8,9-dimethoxy-1,2,3,6-tetrahydrobenzazocine (**2b**) was isolated by recrystallization, which also allowed for the elucidation of its structure by an X-ray crystallographic analysis (Scheme 1). The structure of a vinyltetrahydroquinoline was also confirmed by an X-ray analysis (*vide infra*). It is noteworthy that the reaction proceeded regioselectively, and a possible regioisomer **2b′** was not isolated.

To our surprise, the isolation of benzazocine derivatives proved challenging due to their instability. The attempted purification of **2a** (or **2b**) by column chromatography under typical conditions (e.g., silica gel or alumina, hexane/EtOAc, with or without Et_3N) induced the ring-contraction reaction of **2a** and a vinyltetrahydroquinoline **3a** was isolated. We were thus focused on the derivatization of the initially formed tetrahydrobenzazocine **2a** to isolate the product in a stable form. Catalytic hydrogenation of the crude product (**2a**·H_2SO_4) afforded hexahydrobenzazocine **4a** in 91% yield (Scheme 2a). This compound was stable and the ring-contraction reaction of the product was not observed. Alternatively, the protection of the amino group by acylation resulted in the increased stability of the tetrahydrobenzazocine (Scheme 2b). Several different acyl groups were surveyed, and all of the acylated benzazocine derivatives were isolated as stable compounds (Table 2). Protection with a benzyloxycarbonyl (Cbz), benzoyl (Bz), *tert*-butoxycarbonyl (Boc), or acetyl (Ac) group efficiently provided the products in high yields. Among them, the *N*-acetyl derivative was easier to handle, and the acetylation was harnessed for further studies.[9] These results indicated that the presence of the C=C double bond and the free secondary amino group of the benzazocine derivatives were responsible for the instability of **2a**. The instability of **2a** could be a reason for the presence of few reports concerning the aza-Claisen rearrangement reactions of *N*-aryl-2-vinylazetidines.

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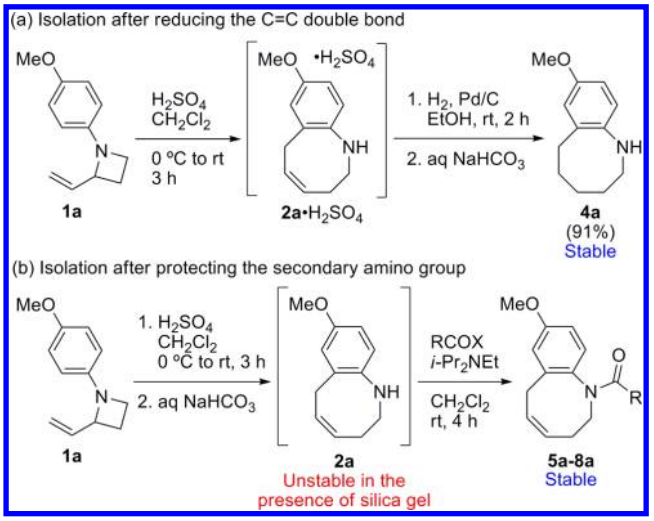
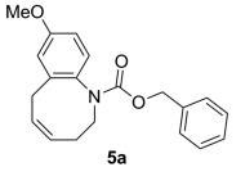
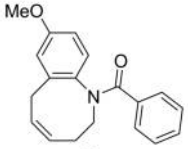
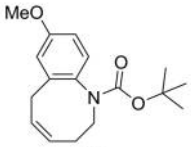
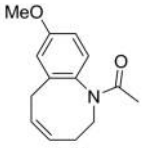
Scheme 2. Isolation of Stable Benzazocine Derivatives[a]



[a]Reagents and conditions: (a) H_2SO_4 (1.5 equiv), CH_2Cl_2 (0.5 M), 0 °C to rt, 3 h; H_2, Pd/C, EtOH, rt, 2 h; aq $NaHCO_3$. (b) H_2SO_4 (1.5 equiv), CH_2Cl_2 (0.5 M), 0 °C to rt, 3 h; aq $NaHCO_3$; RCOX (1.2 equiv), *i*-Pr_2NEt (1.3 equiv), CH_2Cl_2, rt, 4 h. R = Cbz, Bz, Boc, or Ac.

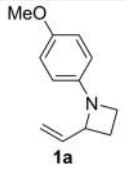
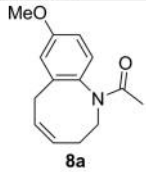
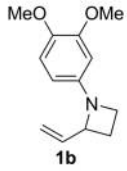
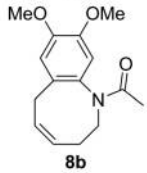
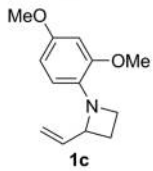
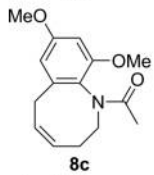
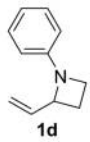
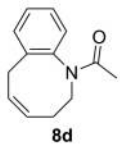
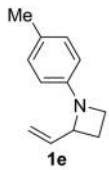
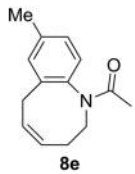
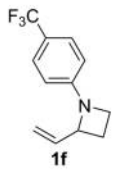
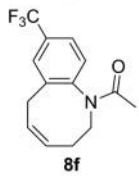
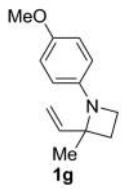
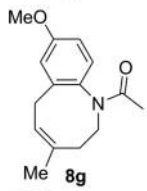
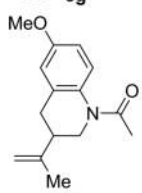
Table 2. Isolation of *N*-Acyl Derivatives[a]

entry	RCOX	product	yield (%)[b]
1	CbzCl	 5a	83
2	BzCl	 6a	88
3	Boc_2O	 7a	89
4	AcCl	 8a	91

[a]Reaction conditions: **1a** (0.5 mmol), H_2SO_4 (1.5 equiv), CH_2Cl_2 (0.5 M), 0 °C to rt, 3 h; aq $NaHCO_3$; RCOX (1.2 equiv), *i*-Pr_2NEt (1.3 equiv), CH_2Cl_2, rt, 4 h. [b]Isolated yield by column chromatography.

Using the established protocol for the formation and isolation of the tetrahydrobenzazocine, the substrate scope of the reaction was explored (Table 3). The ring-expansion reaction and subsequent acetylation of *N*-(3,4-dimethoxyphenyl)-2-vinylazetidine (**1b**) proceeded efficiently, and the corresponding product was isolated in excellent yield (entry 2). The reaction proceeded smoothly even when two methoxy groups were introduced to the *ortho* and *para* positions of the aromatic ring (entry 3). The parent *N*-phenyl derivative **1d** was

Table 3. Substrate Scope[a]

entry	azetidine	product	yield (%)[b]
1	 1a	 8a	91
2	 1b	 8b	93
3	 1c	 8c	80
4	 1d	 8d	84
5	 1e	 8e	92
6	 1f	 8f	80
7	 1g	 8g	59
		 9	26

[a]Reaction conditions: **1a** (0.5 mmol), H_2SO_4 (1.5 equiv), CH_2Cl_2 (0.5 M), 0 °C to rt, 3 h; aq $NaHCO_3$; AcCl (1.2 equiv), *i*-Pr_2NEt (1.3 equiv), CH_2Cl_2, rt, 4 h. [b]Isolated yield.

a good substrate for the reaction, and the product was obtained in 84% yield (entry 4). The use of *N*-tolyl derivative **1e** resulted in efficient transformation (entry 5). Vinylazetidine bearing a 4-(trifluoromethyl)phenyl group (**1f**) was a viable substrate, although the corresponding product was isolated in a decreased yield (entry 6). It is noteworthy that the electronic nature of the aryl group bound to the nitrogen atom of vinylazetidine did not have strong effect on the rearrangement reaction, though

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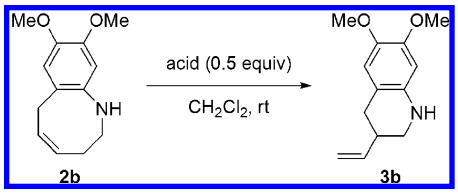
the products bearing electron-rich aromatic groups were obtained in slightly better yields. The ring-expansion reaction of a vinylazetidine bearing 2-methyl group (**1g**) gave two products: 4-methylbenzazocine derivative **8g** was isolated in 59%, and 3-(1-methylvinyl)tetrahydroquinoline **9** was isolated in 26% yield (entry 7).

Ring-Contraction Reaction of Tetrahydrobenzazocine to Vinyltetrahydroquinoline. We were interested in the instability of **2a,2b**, since the cleavage of the C−C bond proceeded under mild conditions and the selective formation of **3a,3b** was observed. To understand the mechanism of this transformation, we studied the acid-catalyzed ring-contraction reaction of **2b** under various reaction conditions. The results are summarized in Table 4. As expected, the treatment of **2b** with silica gel gave 6,7-dimethoxy-3-vinyl-1,2,3,4-tetrahydroquinoline (**3b**) in 81% yield, reproducing the phenomenon observed upon the attempted chromatographic isolation of **2a** (entry 1). We confirmed the structure of **3b** by an X-ray crystallographic analysis (see Supporting Information). Assuming that the reaction would be accelerated in the presence of acid, we treated **2b** with a series of acids. The treatment of **2b** with 0.5 equiv[10] of TfOH in CH_2Cl_2 induced the slow ring-contraction reaction, and **3b** was obtained in 91% yield (entry 2). The ring-contraction reaction of **2b** proceeded less effectively in the presence of weaker acids such as CF_3CO_2H, H_2SO_4, HCl, and AcOH (entries 3−6). It is noteworthy that this ring-contraction reaction was dramatically accelerated in the presence of formaldehyde (Scheme 3a). Thus, the reaction of **2b** and formaldehyde proceeded rapidly (rt, 2 min) to provide **3b** in 76% yield. This result is in marked contrast to the result of the reaction in the absence of formaldehyde, which did not complete after 24 h (Table 4, entry 3). Exposure of **2b** to formaldehyde-d_2 gave rise to a mixture of the vinylquinoline derivatives in 74% yield, in which **3b** and vinylquinoline-d_2 (**3b**-d_2) were present in a ratio of 83:17 (Scheme 3b). When the same experiment was performed using acetaldehyde instead of formaldehyde-d_2, a diastereomeric mixture of 2-methyl vinylquinoline derivative (**3b**-Me) was obtained in 35% yield together with **3b** in 7% yield (Scheme 3c).[11] The incorporation of the exogenous carbon atom to the final product is a characteristic feature of these reactions.

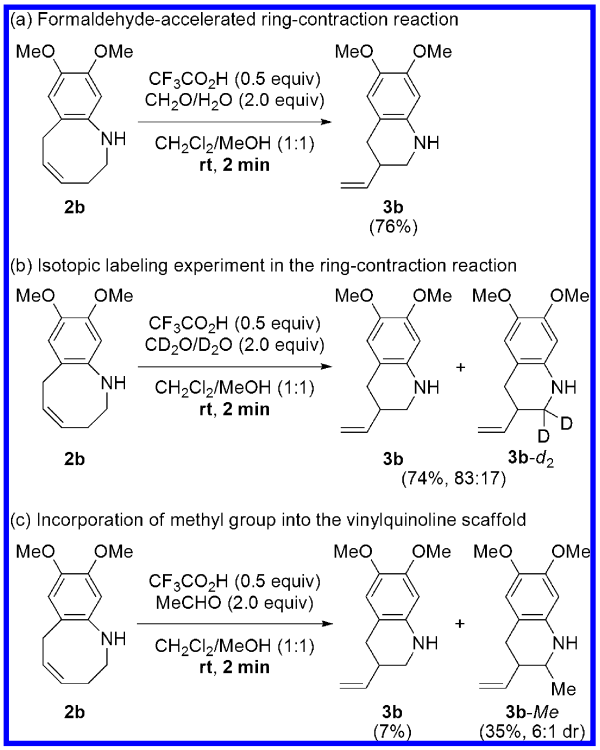
Table 4. Acid-Catalyzed Ring-Contraction Reaction of Tetrahydrobenzazocine[a]



entry	acid	time (h)	convn (%)[b]	yield (%)[c]
1	silica gel[d]	9	100	81
2	TfOH	16	100	91
3	CF_3CO_2H	24	20	*e*
4	H_2SO_4	24	12	*e*
5	12 M HCl	28	18	*e*
6	AcOH	24	13	*e*

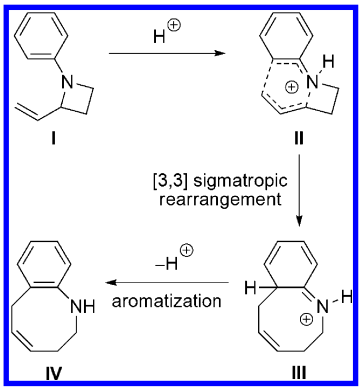
[a]Reaction conditions: **2b** (0.2 mmol), acid (0.5 equiv), CH_2Cl_2, rt. [b]Determined by ^{1}H NMR integration of the crude product. [c]Isolated yield. [d]Silica gel (300 mg, Kanto Chemical silica gel 60N, spherical, neutral, 63-210 μm) was added. [e]No attempt was made to determine the yield.

Scheme 3. Ring-Contraction Reaction of Tetrahydrobenzazocines in the Presence of Aldehydes



Mechanistic Considerations of the Ring-Expansion Reaction of *N*-Aryl-2-vinylazetidine. The ring-expansion reaction of *N*-aryl-2-vinylazetidine to tetrahydrobenzazocine failed to proceed under thermal conditions, whereas the addition of an acid successfully promoted the reaction. We postulate that this transformation proceeds through the charge-accelerated [3,3]-sigmatropic rearrangement (Scheme 4).[1]

Scheme 4. Proposed Mechanism for the Ring-Expansion Reaction of *N*-Aryl-2-vinylazetidine to Tetrahydrobenzazocine



Vinylazetidine **I** is first protonated to form an azetidinium ion intermediate **II**, followed by the [3,3]-sigmatropic rearrangement to give a protonated arene **III**. Deprotonation of this intermediate and restoration of aromaticity leads to the formation of tetrahydrobenzazocine **IV**.

It is interesting to note that the *N*-aryl-2-vinylezetidine studied in this work was stable under thermal reaction

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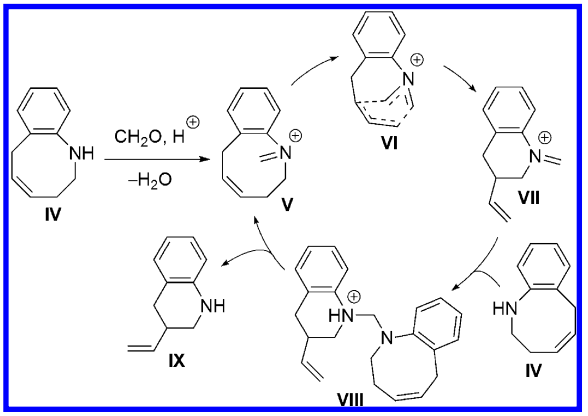
conditions, contrary to the *N*-arylaziridine or *N*-quinonylazetidine analogues reported in the literature.[3,4,7] The reduced ring strain of the four-membered ring can be invoked to explain the increased thermal stability of *N*-aryl-2-vinylazetidine over the aziridine analogue. The ring strain in the starting molecule is also considered to have profound effect on the reaction profile. In contrast to the aza-Claisen rearrangement of *N*-aryl-2-vinylazirdines,[4] in which there are several byproducts arising from other bond breaking pathways, no byproduct generated from processes other than aza-Claisen rearrangement was observed (the generation of the vinyltetrahydroquinoline byproduct such as **1b** will be discussed below in detail). This dissimilar byproduct distribution could be explained by the increased stability of azetidine over aziridine. The aza-Claisen rearrangement of allylanilines is reported to proceed much faster if the aromatic ring is substituted with an electron withdrawing group.[12] The increased reactivity of *N*-quinonyl-2-vinylazetidine[7] can be ascribed to the electron deficiency of the quinone ring. In our experiments under the optimized conditions, however, such dependence of the rate of the aza-Claisen rearrangement on the electronic nature of the benzene ring was not observed, and *N*-aryl-2-vinylazetidines bearing both electron withdrawing and donating substituents provided products in comparable reaction time.

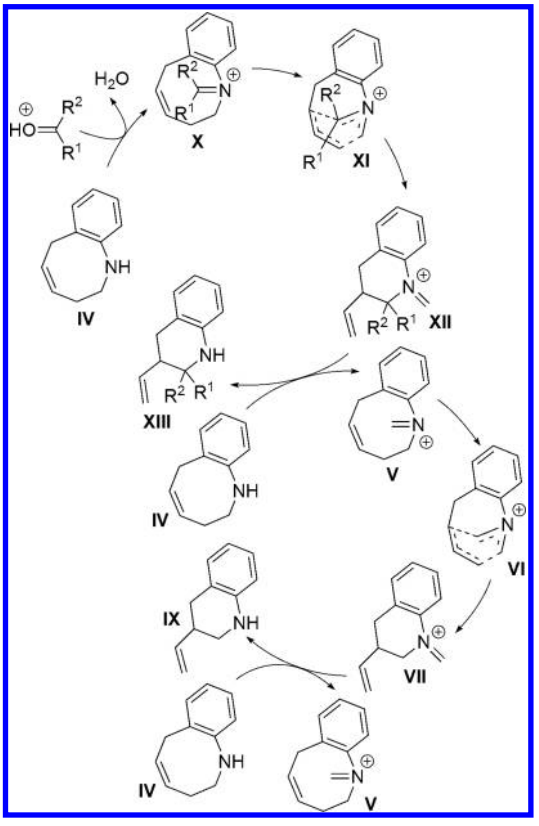
Mechanistic Considerations of the Ring-Contraction Reaction of Tetrahydrobenzazocine to Vinyltetrahydroquinoline. The observed ring-contraction reaction of **2b** to **3b** in the presence of a small amount of acid (Table 4) provided strong supporting evidence that the vinyltetrahydroquinoline byproduct **3a** was generated by the ring-contraction reaction of the initially formed **2a** in the reaction mixture (Table 1). As shown in Table 1, this process proceeded when the amount of acid was small: at higher acid loadings, the acceleration of the rate of the ring-expansion reaction was observed and the formation of **3a** was suppressed. This result could be explained by postulating that the ammonium salt of **2a** was more stable compared to **2a**. The observed stability of *N*-acylated benzazocine derivatives also supports the idea that the presence of a nucleophilic nitrogen atom would destabilize the benzazocine framework. As discussed earlier, formaldehyde proved to be a viable reagent for the ring-contraction reaction of tetrahydrobenzazocine to vinyltetrahydroquinoline (Scheme 3a). We hypothesized that the ring-contraction reaction could involve the formation of iminium ion of tetrahydrobenzazocine (Scheme 5). Tetrahydrobenzazocine **IV** would condense with formaldehyde under acidic condition to afford iminium ion **V**. This intermediate then undergoes aza-Cope rearrangement to form iminium ion **VII**.[13,14] The methylene group of **VII** is expected to transfer to another molecule of tetrahydrobenzazocine through the formation and subsequent decomposition of aminal **VIII**. The generation of vinyltetrahydroquinoline **IX** is accompanied by the liberation of *N*-methylidenetetrahydrobenzazocine **V**, which could recommence the new cycle. Overall, the formation of six-membered ring compound is presumed to be thermodynamically favorable. The protection of the secondary amino group of tetrahydrobenzazocine turned out to be an effective strategy to circumvent the ring-contraction reaction to vinyltetrahydroquinoline during chromatographic purification (Scheme 2b). The observed stability of *N*-acylated benzazocine derivatives could be explained, again, by the reduced nucleophilicity of the nitrogen atom. If the proposed mechanism is indeed operable, a desired alkyl group could be incorporated to the vinylquinoline scaffold by adding

Scheme 5. Proposed Mechanism for the Ring-Contraction Reaction of Tetrahydrobenzazocine to Vinyltetrahydroquinoline



an aldehyde to tetrahydrobenzazocine. The results given in Scheme 3 provided supporting evidence that the iminium ion was formed by the reaction of tetrahydrobenzazocine with an exogenous methylene source. As illustrated in Scheme 6, these

Scheme 6. Proposed Mechanism for the Incorporation of the Exogenous Methylene Group into the Vinylquinoline Scaffold



products, **3b**-d_2 and **3b**-Me, presumably arise from aza-Cope rearrangement of incipient iminium ion intermediate **X**, which was formed by the condensation of tetrahydrobenzazocine with the corresponding aldehyde. In the above-mentioned process, methylene group of the iminium ion **XII** is transferred to another molecule of **IV**, which then undergoes aza-Cope rearrangement to form vinyltetrahydroquinoline, devoid of

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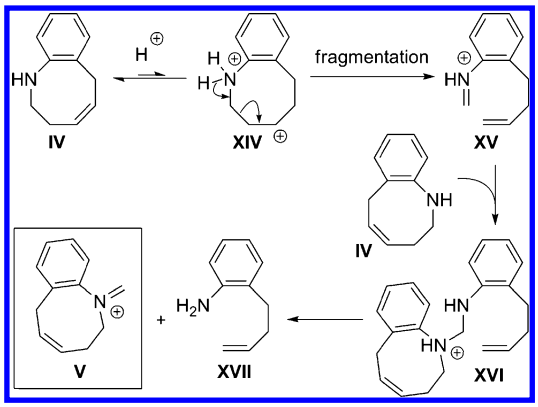
deuterium atoms or methyl group at its 2-position. While a decent amount of acetaldehyde was incorporated to the vinylquinoline structure, a smaller amount of formaldehyde-d_2 was incorporated (Scheme 3b and c). The difference of the degree of the incorporation might be explained by considering the structure of the aldehyde in water. Formaldehyde exists predominantly as methanediol (hydrated form of formaldehyde),[15] which would be less reactive compared to the iminium ion (i.e., **XII** in Scheme 6) or nonhydrated formaldehyde. On the other hand, the concentration of the reactive nonhydrated acetaldehyde would be much higher, and the rate of the reaction of tetrahydrobenzazocine with acetaldehyde would be faster. These findings support the iminium ion-initiated aza-Cope rearrangement and "methylene-catalyzed" ring-contraction mechanism.

Nevertheless, the ring-contraction reaction did occur without exogenous aldehyde (Table 4). The formation of vinyltetrahydroquinoline was also observed in the ring-expansion reaction of vinylazetidine, suggesting that an iminium ion should be generated in the reaction mixture (Table 1). Scheme 7 depicts a plausible mechanism for the generation of an iminium ion from tetrahydrobenzazocine. Tetrahydrobenzazocine is protonated to form a dicationic species **XIV** in the presence of acid, which then undergoes Grob-type fragmentation[13a,16] to give an iminium ion **XV**. A molecule of tetrahydrobenzazocine attacks the iminium ion to form aminal **XVI**. The aminal decomposes to release an aniline **XVII**[17] and iminium ion **V**, which can now commence the ring-contraction reaction. It is possible to explain the formation of **9** in the ring-expansion reaction of **1g** (Table 3, entry 7). The 4-methyl group of tetrahydrobenzazocine may stabilize the positive charge accumulating in the Grob-type elimination process, and the iminium ion **XV** could be readily formed. Thus, the presence of the methyl group in tetrahydrobenzazocine facilitated the formation of the vinyltetrahydroquinoline.

Scheme 7. Possible Pathway for the Generation of the Methylene Source



CONCLUSION

In conclusion, we developed the acid-mediated ring-expansion reaction of *N*-aryl-2-vinylazetidines. The benzazocine derivatives thus generated exhibited intriguing and unprecedented reactivity. The ring-contraction reaction of tetrahydrobenzazocines to vinyltetrahydroquinolines proceeded under weakly acidic conditions, and very selective C−C bond formation/cleavage was observed. Detailed analysis of the ring-contraction reaction indicated that the methylene transfer between tetrahydrobenzazocine and the iminium ion was incorporated as the key step. These results provided a basis for the understanding of the synthesis and reactivity of medium-sized nitrogen heterocycles.

EXPERIMENTAL SECTION

General Experimental. Reagents were obtained from commercial supplies and used without further purification unless otherwise stated. NMR spectra were recorded on 500 or 300 MHz instruments. ^{1}H chemical shifts were referenced to the nondeuterated solvent signals in $CDCl_3$ (δ 7.26). ^{13}C chemical shifts were referenced to the solvent signals in $CDCl_3$ (δ 77.00). Multiplicity is indicated by the following abbreviations (or combinations thereof): s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Coupling constants, *J*, are reported in hertz. IR spectra were recorded on an FTIR spectrometer. Column chromatography was performed using silica gel 60N (spherical, neutral, 63-210 μm) or aluminum oxide 90 (active neutral, 70−230 mesh). Melting points were uncorrected. Ethyl 2,4-dibromobutyrate was prepared according to literature procedure.[18]

Synthesis of *N*-Aryl-2-vinylazetdines. Representative Procedure for the Preparation of *N*-Aryl-2-ethoxycarbonylazetidines.[19,20] A solution of ethyl 2,4-dibromobutyrate (13.7 g, 50 mmol, 1.0 equiv), *p*-anisidine (6.16 g, 50 mmol, 1.0 equiv), and $NaHCO_3$ (16.8 g, 200 mmol, 4.0 equiv) in DMF/H_2O/HMPA (16:5:1, 110 mL, 0.45 M) was heated to 100 °C for 4 h under air. The reaction mixture was cooled to room temperature, partitioned between hexane and brine, and separated. The aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed on alumina (hexane/EtOAc, 25:1) to afford *N*-(4-methoxyphenyl)-2-ethoxycarbonylazetidine (**S1**, 6.0 g, 51%) as an orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, J = 9.3 Hz, 2H), 6.52 (d, J = 9.0 Hz, 2H), 4.39 (dd, J = 8.4, 8.1 Hz, 1H), 4.35−4.19 (m, 2H), 3.97 (ddd, J = 8.7, 6.6, 3.6 Hz, 1H), 3.75 (s, 3H), 3.63 (td, J = 8.1, 6.9 Hz, 1H), 2.68−2.45 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 152.9, 145.4, 114.6, 113.4, 64.1, 61.1, 55.7, 50.3, 21.5, 14.2; IR (neat) 2978, 1743, 1512, 1466, 1335, 1288, 1242, 1188, 1049, 825.4 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.11; H, 7.15; N, 6.16.

***N*-(3,4-Dimethoxyphenyl)-2-ethoxycarbonylazetidine (S2).** 40% yield (5.3 g) from 3,4-dimethoxyaniline (alumina, hexane/EtOAc, 8:1), yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, J = 8.7 Hz, 1H), 6.22 (d, J = 2.4 Hz, 1H), 6.07 (d, J = 8.7, 2.4 Hz, 1H), 4.41 (t, J = 8.1 Hz, 1H), 4.35−4.19 (m, 2H), 3.97 (ddd, J = 10.2, 6.6, 3.9 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.66 (td, J = 8.1, 7.2 Hz, 1H), 2.68−2.45 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 149.8, 146.0, 142.4, 112.8, 103.4, 97.8, 64.1, 61.1, 56.6, 55.7, 50.2, 21.2, 14.2; IR (neat) 2939, 2862, 1736, 1512, 1458, 1242, 1188, 1026 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.28; H, 7.44; N, 5.40.

***N*-(2,4-Dimethoxyphenyl)-2-ethoxycarbonylazetidine (S3).** 38% yield (5.0 g) from 2,4-dimethoxyaniline (alumina, hexane/EtOAc, 15:1), yellow solid; mp 74−75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44−6.37 (m, 3H), 4.50 (t, J = 7.8 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 4.01 (td, J = 7.2, 4.5 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.64 (td, J = 8.1, 7.2 Hz, 1H), 2.54−2.38 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 154.0, 150.0, 134.1, 113.4, 103.7, 99.8, 64.9, 60.6, 55.6, 55.1, 51.1, 22.2, 14.3; IR (KBr) 2962, 2939, 2908, 1751, 1512, 1450, 1288, 1250, 1173, 1157, 1057 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.33; H, 7.33; N, 5.24.

***N*-Phenyl-2-ethoxycarbonylazetidine (S4).** 44% yield (4.5 g) from aniline (alumina, hexane/EtOAc, 30:1), pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (dd, J = 8.4, 7.5 Hz, 2H), 6.80 (t, J = 7.5 Hz, 1H), 6.54 (d, J = 8.7 Hz, 2H), 4.47 (dd, J = 8.4, 7.5 Hz, 1H), 4.35−4.20 (m, 2H), 4.02 (ddd, J = 8.4, 6.9, 4.2 Hz, 1H), 3.75−3.67 (m, 1H), 2.68−2.49 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 150.8, 128.9, 118.6, 112.1, 63.7, 61.2, 50.0, 21.6, 14.2; IR (neat) 2978, 2862, 1743, 1597, 1504, 1335, 1188, 756.0,

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694.2 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.18; H, 7.46; N, 6.77.

***N*-(4-Methylphenyl)-2-ethoxycarbonylazetidine (S5).** 47% yield (4.2 g) from *p*-toluidine (alumina, hexane/EtOAc, 30:1), yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 7.8 Hz, 2H), 6.48 (d, J = 8.4 Hz, 2H), 4.42 (dd, J = 8.7, 7.5 Hz, 1H), 4.35−4.20 (m, 2H), 3.99 (ddd, J = 8.4, 6.6, 3.9 Hz, 1H), 3.66 (td, J = 8.1, 6.9 Hz, 1H), 2.68−2.46 (m, 2H), 2.26 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 148.8, 129.4, 127.9, 112.2, 63.9, 61.1, 50.1, 21.6, 20.4, 14.2; IR (neat) 2978, 2924, 2862, 1743, 1520, 1335, 1273, 1234, 1188, 1065, 810.0 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.08; H, 7.86; N, 6.35.

Preparation of *N*-(4-Trifluoromethylphenyl)-2-ethoxycarbonylazetidine (S6). A solution of ethyl 2,4-dibromobutyrate (5.48 g, 20 mmol, 2.0 equiv), aminobenzotrifluoride (1.61 g, 10 mmol, 1.0 equiv), NaI (8.99 g, 60 mmol, 6.0 equiv), and $NaHCO_3$ (3.36 g, 40 mmol, 4.0 equiv) in DMF/H_2O/HMPA (16:3.2:1, 20.2 mL, 0.5 M) was heated to 100 °C for 5 h under air. The reaction mixture was cooled to room temperature, partitioned between hexane and brine, and separated. The aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed on alumina (hexane/EtOAc, 30:1) to afford the title compound (**S6**, 0.98 g, 36%) as a yellow oil that solidified upon standing at 4 °C for several days: mp 32−33 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 2H), 6.53 (d, J = 8.4 Hz, 2H), 4.56 (t, J = 7.8 Hz, 1H), 4.32−4.22 (m, 2H), 4.08 (q, J = 6.6 Hz, 1H), 3.79 (q, J = 7.5 Hz, 1H), 2.66−2.58 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 152.5, 126.1 (q, J = 4.0 Hz), 124.9 (q, J = 269.8 Hz), 119.9 (q, J = 33.0 Hz), 111.2, 63.3, 61.3, 49.7, 21.3, 14.1; IR (KBr) 2978, 2877, 1736, 1620, 1527, 1327, 1119, 1065, 833.1 cm^{-1}. Anal. Calcd for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13. Found: C, 57.09; H, 5.24; N, 4.96.

Preparation of *N*-(4-Methoxyphenyl)-2-ethoxycarbonyl-2-methylazetidine (S7).[21] A solution of *N*-(4-methoxyphenyl)-2-ethoxycarbonylazetidine (4.35 g, 18.5 mmol, 1.0 equiv) in THF (10.3 mL, 1.8 M) was added via a cannula to a solution of lithium diisopropylamide in THF, prepared by the treatment of *i*-Pr_2NH (2.93 mL, 20.9 mmol, 1.13 equiv) with *n*-BuLi in hexane (1.65 M, 12.7 mL, 20.9 mmol, 1.13 equiv) at −78 °C under argon atmosphere. Stirring was continued for 15 min, whereupon methyl iodide (2.45 mL, 39.4 mmol, 2.13 equiv) was added. The mixture was gradually allowed to warm to room temperature and after further 30 min was poured onto water. The mixture was extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/EtOAc, 12:1) to yield the title compound (**S7**, 3.37 g, 73%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, J = 9.0 Hz, 2H), 6.51 (d, J = 9.3 Hz, 2H), 4.26−4.10 (m, 2H), 3.79 (ddd, J = 8.7, 6.3, 5.1 Hz, 1H), 3.74 (s, 3H), 3.74−3.66 (m, 1H), 2.66 (ddd, J = 10.5, 8.7, 6.3 Hz, 1H), 2.15 (ddd, J = 10.8, 8.1, 5.1 Hz, 1H), 1.57 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 152.6, 142.3, 114.5, 114.1, 69.5, 60.9, 55.7, 46.6, 28.9, 20.7, 14.2; IR (neat) 2977, 2962, 2931, 1728, 1511, 1300, 1283, 1242, 1175, 1154, 1130, 1038, 821.5 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.66; H, 7.74; N, 5.73.

Representative Procedure for the Preparation of *N*-Aryl-2-vinylazetidines.[22] A solution of *N*-(4-methoxyphenyl)-2-ethoxycarbonylazetidine (4.71 g, 20 mmol, 1.0 equiv) in THF (80 mL, 0.25 M) was cooled to −78 °C under argon atmosphere, followed by dropwise addition of DIBAL in PhMe (1.0 M, 24 mL, 24 mmol, 1.2 equiv) over 1 h. After the reaction mixture was stirred at −78 °C for 1 h, several small portions of $Na_2SO_4{\cdot}10H_2O$ were added carefully and gradually allowed to warm to room temperature. The mixture was then diluted with EtOAc and filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to afford *N*-(4-methoxyphenyl)-2-formylazetidine. This material was used in the following step without further purification.

Crude *N*-(4-methoxyphenyl)-2-formylazetidine in THF (20 mL, 1 M) was added via a cannula to a solution of methylenetriphenylphosphorane, prepared by the treatment of methyltriphenylphosphonium bromide (14.3 g, 40 mmol, 2.0 equiv) in THF (133 mL, 0.3 M) with *n*-BuLi in hexane (1.65 M, 22 mL, 36.8 mmol, 1.84 equiv) at 0 °C for 1.5 h under argon atmosphere. The mixture was then stirred at room temperature for 20 h. The mixture was poured into water and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/EtOAc, 10:1) to furnish compound **1a** (1.63 g, 43%) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.89−6.76 (d, J = 8.9 Hz, 2H), 6.51−6.48 (d, J = 9.0 Hz, 2H), 6.14−6.02 (ddd, J = 17.0, 10.4, 6.6 Hz, 1H), 5.36−5.29 (dt, J = 17.3, 1.3 Hz, 1H), 5.17−5.13 (d, J = 10.4 Hz, 1H), 4.31−4.24 (q, J = 7.4 Hz, 1H), 3.87−3.81 (td, J = 7.6, 3.2 Hz, 1H), 3.72 (s, 3H), 3.55−3.47 (td, J = 8.4, 6.7 Hz, 1H), 2.40−2.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 147.1, 140.8, 115.2, 114.5, 113.2, 67.0, 55.8, 49.9, 25.0; IR (neat) 2956, 2833, 1510, 1466, 1323, 1242, 1179, 1116, 1038, 992.2, 923.7, 821.5, 798.4, 606.5, 529.4 cm^{-1}; HR-MS (EI) calcd for $C_{12}H_{15}NO$: 189.1154. Found: 189.1153.

***N*-(3,4-Dimethoxyphenyl)-2-vinylazetidine (1b).** 55% yield (2.41 g) from compound **S2** (silica gel, hexane/EtOAc, 8:1), pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (d, J = 8.7 Hz, 1H), 6.19 (d, J = 2.4 Hz, 1H), 6.11 (ddd, J = 17.1, 10.5, 6.9 Hz, 1H), 6.07 (dd, J = 8.7, 2.7 Hz, 1H), 5.36 (ddd, J = 17.1, 1.5, 1.2 Hz, 1H), 5.18 (ddd, J = 10.2, 1.5, 0.9 Hz, 1H), 4.32 (td, J = 7.8, 6.9 Hz, 1H), 3.86 (ddd, J = 8.7, 6.6, 3.3 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.56 (td, J = 8.3, 6.9 Hz, 1H), 2.43−2.33 (m, 1H), 2.31−2.17 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 147.7, 141.8, 140.9, 115.2, 112.9, 103.2, 97.6, 67.0, 56.7, 55.6, 49.8, 24.8; IR (neat) 2955, 2831, 1515, 1465, 1452, 1239, 1218, 1139, 1027 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.13; H, 8.04; N, 6.25.

***N*-(2,4-Dimethoxyphenyl)-2-vinylazetidine (1c).** 42% yield (1.84 g) from compound **S3** (silica gel, hexane/EtOAc, 10:1), pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (d, J = 8.4 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 8.4, 2.4 Hz, 1H), 6.04 (ddd, J = 17.1, 10.2, 6.6 Hz, 1H), 5.27 (ddd, J = 17.1, 1.5, 0.9 Hz, 1H), 5.11 (d, J = 10.2 Hz, 1H), 4.37 (q, J = 7.5 Hz, 1H), 4.06 (td, J = 7.5, 3.0 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.46 (td, J = 8.1, 7.8 Hz, 1H), 2.35−2.16 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0 150.5, 139.9, 135.4, 115.1, 113.6, 103.3, 99.8, 65.8, 55.6, 55.2, 52.6, 25.6; IR (neat) 2954, 2831, 1512, 1458, 1288, 1250, 1203, 1157, 1034 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.13; H, 7.97; N, 6.45.

***N*-Phenyl-2-vinylazetidine (1d).** 53% yield (1.69 g) from compound **S4** (silica gel, hexane/EtOAc, 100:1), colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23−7.17 (m, 2H), 6.75 (t, J = 7.2 Hz, 1H), 6.56 (d, J = 7.5 Hz, 2H), 6.12 (ddd, J = 16.8, 10.2, 6.6 Hz, 1H), 5.36 (ddd, J = 17.1, 1.5, 0.9 Hz, 1H), 5.19 (ddd, J = 10.2, 1.5, 0.9 Hz, 1H), 4.41 (q, J = 7.2 Hz, 1H), 3.92 (ddd, J = 8.7, 6.9, 3.6 Hz, 1H), 3.63 (td, J = 8.4, 6.9 Hz, 1H), 2.47−2.37 (m, 1H), 2.32−2.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 140.5, 128.7, 117.8, 115.2, 112.0, 66.5, 49.4, 25.0; IR (neat) 3001, 2962, 2854, 1597, 1496, 1335, 925.7, 756.0, 694.2 cm^{-1}. Anal. Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.80; H, 8.36; N, 9.02.

***N*-(4-Methylphenyl)-2-vinylazetidine (1e).** 65% yield (2.25 g) from compound **S5** (silica gel, hexane/EtOAc, 50:1), pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, J = 8.1 Hz, 2H), 6.50 (d, J = 8.7 Hz, 2H), 6.13 (ddd, J = 17.1, 10.5, 6.3 Hz, 1H), 5.38 (ddd, J = 17.1, 1.5, 1.2 Hz, 1H), 5.20 (ddd, J = 10.2, 1.5, 0.9 Hz, 1H), 4.37 (q, J = 7.5 Hz, 1H), 3.91 (ddd, J = 8.7, 6.9, 3.3 Hz, 1H), 3.58 (td, J = 8.4, 6.9 Hz, 1H), 2.48−2.21 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 140.7, 129.3, 127.1, 115.1, 112.2, 66.7, 49.6, 25.0, 20.4; IR (neat) 3004, 2959, 2921, 2851, 1613, 1515, 1323, 920.8, 810.9 cm^{-1}. Anal. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.08. Found: C, 83.08; H, 8.87; N, 8.12.

***N*-(4-Trifluoromethylphenyl)-2-vinylazetidine (1f).** 24% yield (196 mg) from compound **S6** (silica gel, hexane/EtOAc, 200:1), colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 8.4 Hz, 2H), 6.08 (ddd, J = 16.8, 10.2, 6.6 Hz, 1H), 5.35

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(ddd, J = 16.8, 1.5, 1.2 Hz, 1H), 5.22 (ddd, J = 10.2, 1.5, 1.2 Hz, 1H), 4.50 (q, J = 7.2 Hz, 1H), 3.97 (ddd, J = 9.0, 7.2, 3.9 Hz, 1H), 3.70 (td, J = 8.1, 7.5 Hz, 1H), 2.55−2.45 (m, 1H), 2.32−2.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 139.5, 126.0 (q, J = 4.1 Hz), 125.1 (q, J = 269.8 Hz), 119.0 (q, J = 33.0 Hz), 115.7, 111.0, 66.3, 49.0, 24.8; IR (neat) 2970, 2862, 1612, 1527, 1327, 1157, 1111, 933.4, 825.4 cm^{-1}. Anal. Calcd for $C_{12}H_{12}F_3N$: C, 63.43; H, 5.32; N, 6.16. Found: C, 63.31; H, 5.32; N, 6.13.

***N*-(4-Methoxyphenyl)-2-methyl-2-vinylazetidine (1g).** 12% yield (329 mg) from compound **S7** (silica gel, hexane/EtOAc, 50:1), pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, J = 9.0 Hz, 2H), 6.44 (d, J = 9.0 Hz, 2H), 6.13 (dd, J = 17.1, 10.5 Hz, 1H), 5.27 (dd, J = 17.4, 1.2 Hz, 1H), 5.14 (dd, J = 10.5, 1.2 Hz, 1H), 3.74 (s, 3H), 3.74−3.61 (m, 2H), 2.34−2.25 (m, 1H), 2.07 (ddd, J = 10.2, 8.1, 4.5 Hz, 1H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 144.1, 143.3, 114.4, 113.9, 113.2, 68.6, 55.7, 45.7, 31.7, 20.6; IR (neat) 2962, 2924, 2831, 1512, 1327, 1304, 1242, 1041, 825.4 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.77; H, 8.50; N, 6.99.

Screening of the Reaction Conditions (Table 1). Compound **1a** (94.6 mg, 0.5 mmol, 1.0 equiv) was dissolved in solvent (CH_2Cl_2, $ClCH_2CH_2Cl$, or PhMe, 1 or 10 mL, 0.5 or 0.05 M), followed by addition of acid (H_2SO_4, TfOH, or CF_3CO_2H, 0.1−1.0 mmol, 0.2−2.0 equiv) at 0 °C or room temperature. The reaction mixture was stirred at the indicated temperature for the indicated time period under argon atmosphere, before the reaction mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was analyzed by ^{1}H NMR spectroscopy to evaluate the ratio of the starting material to the products. The results are summarized in Table 1.

2a. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, J = 8.1 Hz, 1H), 6.70 (d, J = 3.0 Hz, 1H), 6.68 (dd, J = 8.1, 3.0 Hz, 1H), 5.86 (dt, J = 11.1, 6.3 Hz, 1H), 5.62 (dtt, J = 11.1, 7.5, 1.2 Hz, 1H), 3.76 (s, 3H), 3.45 (d, J = 6.3 Hz, 2H), 3.32 (br s, 1H), 3.08−3.05 (m, 2H), 2.23−2.17 (m, 2H).

3a. Orange solid; mp 44−45 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64−6.58 (m, 2H), 6.48 (d, J = 8.4 Hz, 1H), 5.87 (ddd, J = 17.1, 10.5, 6.6 Hz, 1H), 5.14 (d, J = 17.4 Hz, 1H), 5.09 (d, J = 10.5 Hz, 1H), 3.74 (s, 3H), 3.64 (br s, 1H), 3.35- 3.29 (m, 1H), 3.06−2.99 (m, 1H), 2.86−2.78 (m, 1H), 2.73−2.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 140.1, 138.1, 121.8, 115.3, 114.8, 114.5, 113.0, 55.7, 47.2, 36.4, 33.0; IR (KBr) 3240, 2939, 2831, 1504, 1466, 1427, 1250, 1227, 1149, 802.4, 702.0 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.03; H, 8.19; N, 7.28.

Ring Expansion of Vinylazetidine 1b to Tetrahydrobenzazocine 2b (Scheme 1). A solution of compound **1b** (109.6 mg, 0.5 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL, 0.5 M) was cooled to 0 °C, followed by addition of H_2SO_4 (40 μL, 0.75 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 2 h under argon atmosphere and then allowed to warm to room temperature. After stirring for another 1 h, the reaction mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by recrystallization from hexane/EtOAc to afford compound **2b** (58.1 mg, 53%) as a yellow crystal: mp 73−74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (s, 1H), 6.48 (s, 1H), 5.84 (dt, J = 11.4, 6.0 Hz), 5.64−5.56 (m, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.49 (br s, 1H), 3.42 (d, J = 6.0 Hz, 2H), 3.10 (t, J = 5.4 Hz, 2H), 2.16 (td, J = 6.6, 4.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 144.5, 140.1, 130.9, 127.2, 125.1, 113.4, 107.7, 56.2, 55.9, 48.8, 34.1, 27.5; IR (KBr) 3356, 2931, 2908, 2839, 1520, 1489, 1442, 1211, 1165, 1126, 1072, 1011, 856.2, 763.7 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.36; H, 7.96; N, 6.50.

Catalytic Hydrogenation of Tetrahydrobenzazocine (Scheme 2a).[23] A solution of compound **1a** (94.6 mg, 0.5 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL, 0.5 M) was cooled to 0 °C, followed by addition of H_2SO_4 (40 μL, 0.75 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 2 h under argon atmosphere and then allowed to warm to room temperature. After stirring for another 1 h, EtOH (4.2 mL) and 10% palladium on carbon (42 mg) were introduced, and the mixture was stirred at room temperature under hydrogen atmosphere for 2 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/EtOAc, 4:1) to yield compound **4a** (87.1 mg, 91%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92−6.87 (m, 1H), 6.69−6.65 (m, 2H), 3.75 (s, 3H), 3.05−3.02 (m, 2H), 2.76−2.72 (m, 2H), 2.46 (br s, 1H), 1.71−1.63 (m, 2H), 1.51−1.39 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 140.4, 139.2, 125.4, 115.0, 112.1, 55.3, 53.3, 31.8, 31.5, 27.8, 26.0; IR (neat) 3340, 2924, 2846, 1496, 1450, 1265, 1211, 1119, 1041, 810.0 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.33; H, 9.03; N, 7.09.

Representative Procedure for the Acylation of Tetrahydrobenzazocines (Scheme 2b, Tables 2 and 3).[24,25] A solution of compound **1a** (94.6 mg, 0.5 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL, 0.5 M) was cooled to 0 °C, followed by addition of H_2SO_4 (40 μL, 0.75 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 2 h under argon atmosphere and then allowed to warm to room temperature. After stirring for another 1 h, the reaction mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford compound **2a**. This material was used without purification in the following reaction.

To a solution of crude compound **2a** in CH_2Cl_2 (2 mL, 0.25 M) was added *i*-Pr_2NEt (113 μL, 0.65 mmol, 1.3 equiv). After the mixture was stirred at room temperature for 10 min under argon atmosphere, AcCl (43 μL, 0.6 mmol, 1.2 equiv) was added and stirred for another 4 h. The reaction mixture was partitioned between Et_2O and brine. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Chromatography on silica gel (hexane/EtOAc, 3:1) provided compound **8a** (105.2 mg, 91%) as a pale yellow solid: mp 113−114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 3.0 Hz, 1H), 6.75 (dd, J = 8.4, 3.0 Hz, 1H), 5.90−5.81 (m, 1H), 5.72−5.63 (m, 1H), 4.66−4.59 (m, 1H), 3.82 (s, 3H), 3.41 (dd, J = 14.7, 8.1 Hz, 1H), 2.96 (dd, J = 13.5, 6.9 Hz, 1H), 2.65−2.47 (m, 2H), 2.25−2.14 (m, 1H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 159.2, 142.8, 134.9, 131.3, 129.6, 129.1, 114.9, 112.5, 55.4, 48.0, 32.7, 26.8, 22.6; IR (KBr) 2947, 2924, 1643, 1504, 1442, 1404, 1304, 1234, 1211, 1026 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.49; H, 7.34; N, 6.03.

5a. 83% yield (134.2 mg) from compound **1a** (silica gel, hexane/EtOAc, 6:1), viscous colorless oil; the presence of a rotamer was detected on the ^{1}H and ^{13}C NMR at room temperature; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.16 (m, 5H), 7.02 (d, J = 8.1, 1H), 6.78−6.72 (m, 2H), 5.88−5.77 (m, 1H), 5.69−5.57 (m, 1H), 5.11 (s, 2H), 4.35 (ddd, J = 13.2, 7.5, 1.8 Hz, 1H), 3.81 (s, 3H), 3.40 (dd, J = 14.1, 7.8 Hz, 1H), 2.92 (dd, J = 14.1, 6.6 Hz, 1H), 2.67 (ddd, J = 13.5, 9.0, 1.5 Hz, 1H), 2.56−2.46 (m, 1H), 2.21−2.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 155.7, 142.4, 137.0, 133.0, 131.6, 129.7, 128.2, 128.0, 127.6, 127.2, 114.4, 112.0, 66.7, 55.3, 49.5, 33.0, 26.5; IR (neat) 1712, 1709, 1703, 1698, 1694, 1505, 1499, 1404, 1305, 1303 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.32; H, 6.74; N, 4.29.

6a. 88% yield (129.1 mg) from compound **1a** (silica gel, hexane/EtOAc, 5:1), viscous colorless oil; the presence of a rotamer was detected on the ^{1}H NMR at room temperature; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.12 (m, 5H), 6.87 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 3.0

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Hz, 1H), 6.56 (dd, J = 8.4, 3.0 Hz, 1H), 5.94−5.85 (m, 1H), 5.80−5.72 (m, 1H), 4.93−4.86 (m, 1H), 3.73 (s, 3H), 3.58 (dd, J = 14.4, 7.2 Hz, 1H), 3.04 (dd, J = 14.1, 6.6 Hz, 1H), 2.78−2.61 (m, 2H), 2.37−2.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 158.6, 141.6, 136.7, 134.7, 130.7, 130.6, 129.0, 128.8, 127.6, 127.5, 114.6, 112.1, 55.2, 48.7, 33.4, 26.4; IR (neat) 2939, 1643, 1504, 1442, 1396, 1311, 1273, 1242, 725.1, 702.0 cm^{-1}. Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.63; H, 6.78; N, 4.70.

7a. 89% yield (128.8 mg) from compound **1a** (silica gel, hexane/EtOAc, 12:1), viscous colorless oil; the presence of a rotamer[26] was detected on the ^{1}H and ^{13}C NMR at room temperature; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (d, J = 8.4 Hz, 1H), 6.78−6.67 (m, 2H), 5.90−5.79 (m, 1H), 5.68−5.59 (m, 1H), 4.29 (ddd, J = 12.9, 7.5, 1.8 Hz, 1H), 3.79 (s, 3H), 3.46 (dd, J = 13.8, 7.5 Hz, 1H), 2.94 (dd, J = 14.1, 6.6 Hz, 1H), 2.63 (dd, J = 12.9, 8.7 Hz, 1H), 2.56−2.46 (m, 1H), 2.17−2.08 (m, 1H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 155.2, 142.3, 134.1, 131.5, 129.7, 128.2, 114.1, 111.8, 79.4, 55.3, 48.7, 33.1, 28.3, 26.6; IR (neat) 1709, 1703, 1698, 1692, 1686, 1683, 1508, 1500, 1390, 1365, 1313 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.37; H, 8.08; N, 4.74.

8b. 93% yield (121.5 mg) from compound **1b** (silica gel, hexane/EtOAc, 1:1), colorless solid; mp 106−107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (s, 1H), 6.63 (s, 1H), 5.91−5.82 (m, 1H), 5.70−5.62 (m, 1H), 4.67−4.58 (m, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.39 (ddd, J = 14.1, 8.1, 1.2 Hz, 1H), 2.93 (dd, J = 14.1, 6.9 Hz, 1H), 2.62−2.50 (m, 2H), 2.25−2.13 (m, 1H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 148.6, 148.1, 134.0, 133.7, 131.6, 128.6, 111.8, 111.7, 56.1, 56.0, 47.6, 32.1, 26.6, 22.5; IR (KBr) 2939, 1651, 1512, 1450, 1412, 1265, 1227, 1196, 1142 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.98; H, 7.19; N, 5.39.

8c. 80% yield (104.5 mg) from compound **1c** (silica gel, hexane/EtOAc, 7:3), viscous pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (d, J = 2.7 Hz, 1H), 6.34 (d, J = 2.7 Hz, 1H), 5.87−5.78 (m, 1H), 5.69−5.60 (m, 1H), 4.56 (ddd, J = 12.9, 7.2, 1.8 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.46- 3.39 (m, 1H), 2.90 (dd, J = 13.5, 7.2 Hz, 1H), 2.58−2.47 (m, 1H), 2.40 (dd, J = 12.6, 10.5 Hz, 1H), 2.23−2.10 (m, 1H), 1.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 159.8, 156.3, 143.4, 131.3, 129.1, 123.6, 104.7, 97.0, 55.5, 55.3, 46.9, 32.7, 26.8, 21.6; IR (neat) 2939, 1658, 1597, 1496, 1442, 1396, 1327, 1211, 1157, 1088 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.77; H, 7.47; N, 5.27.

8d. 84% yield (84.5 mg) from compound **1d** (silica gel, hexane/EtOAc, 3:1), colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.22 (m, 3H), 7.15−7.09 (m, 1H), 5.90−5.81 (m, 1H), 5.71−5.62 (m, 1H), 4.68−4.62 (m, 1H), 3.45 (ddd, J = 13.5, 8.1, 1.5 Hz, 1H), 3.02 (dd, J = 13.5, 7.2 Hz, 1H), 2.66−2.50 (m, 2H), 2.26−2.14 (m, 1H), 1.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 141.9, 141.4, 131.4, 129.6, 128.8, 128.7, 128.5, 127.8, 47.7, 32.4, 26.6, 22.6; IR (neat) 2937, 1666, 1650, 1490, 1446, 1438, 1395, 1361, 1320, 1304, 769.5, 722.2 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.42; H, 7.72; N, 6.84.

8e. 92% yield (99.0 mg) from compound **1e** (silica gel, hexane/EtOAc, 4:1), colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (s, 1H), 7.04 (dd, J = 8.1, 1.5 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 5.89−5.80 (m, 1H), 5.70−5.61 (m, 1H), 4.66−4.59 (m, 1H), 3.40 (dd, J = 13.5, 8.1 Hz, 1H), 2.96 (dd, J = 13.8, 6.9 Hz, 1H), 2.64−2.47 (m, 2H), 2.34 (s, 3H), 2.25−2.13 (m, 1H), 1.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 141.1, 139.4, 138.5, 131.6, 130.3, 128.8, 128.5, 128.4, 47.8, 32.4, 26.7, 22.6, 21.0; IR (neat) 3016, 2931, 1736, 1658, 1504, 1442, 1396, 1304, 1242, 1049 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.04; H, 8.20; N, 6.43.

8f. 80% yield (107.7 mg) from compound **1f** (silica gel, hexane/EtOAc, 3:1), pale yellow solid; the presence of a rotamer was detected on the ^{13}C NMR at room temperature; mp 69−70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 5.92−5.83 (m, 1H), 5.76−5.67 (m, 1H), 4.69 (dd, J = 13.2, 6.9 Hz, 1H), 3.50 (dd, J = 13.5, 8.1 Hz, 1H), 3.11 (dd, J = 13.5, 6.9 Hz, 1H), 2.69−2.59 (m, 1H), 2.53 (dd, J = 12.9, 9.6 Hz, 1H), 2.28−2.17 (m, 1H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 144.9, 142.4, 130.5, 130.3 (q, J = 32.0 Hz), 129.3, 129.3, 126.3 (q, J = 4.1 Hz), 125.0, 124.5 (q, J = 4.1 Hz), 123.4 (q, J = 271.8 Hz), 47.3, 32.0, 26.4, 22.3; IR (neat) 3024, 2939, 2862, 1666, 1396, 1327, 1304, 1165, 1126 cm^{-1}. Anal. Calcd for $C_{14}H_{14}F_3NO$: C, 62.45; H, 5.24; N, 5.20. Found: C, 62.55; H, 5.30; N, 5.18.

8g. 59% yield (72.4 mg) from compound **1g** (silica gel, hexane/EtOAc, 4:1), pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 2.7 Hz, 1H), 6.71 (dd, J = 8.7, 3.0 Hz, 1H), 5.66 (dd, J = 8.4, 7.2 Hz, 1H), 4.64 (ddd, J = 13.5, 6.9, 1.5 Hz, 1H), 3.80 (s, 3H), 3.32 (dd, J = 13.2, 9.0 Hz, 1H), 2.87 (dd, J = 13.2, 7.2 Hz, 1H), 2.75 (dd, J = 15.0, 9.9 Hz, 1H), 2.44 (dd, J = 12.6, 9.3, Hz, 1H), 2.03 (dd, J = 15.0, 6.9 Hz, 1H), 1.77 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 159.1, 143.4, 137.4, 134.9, 129.6, 124.5, 114.6, 112.1, 55.4, 47.1, 32.9, 32.8, 26.3, 22.7; IR (neat) 2931, 1643, 1504, 1435, 1396, 1311, 1273, 1234, 1041 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.42; H, 7.98; N, 5.63.

9. 26% yield (31.9 mg) from compound **1g** (silica gel, hexane/EtOAc, 4:1), viscous yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−6.96 (m, 1H), 6.71−6.67 (m, 2H), 4.79 (br s, 1H), 4.72 (br s, 1H), 3.99−3.89 (m, 1H), 3.75 (s, 3H), 3.58 (br s, 1H), 2.83−2.78 (m, 1H), 2.67−2.59 (m, 1H), 2.56−2.46 (m, 1H), 2.15 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 156.9, 145.6, 133.8, 132.2, 125.1, 113.3, 111.4, 110.9, 55.2, 46.4, 42.5, 32.6, 22.6, 20.7; IR (neat) 2935, 1655, 1500, 1450, 1377, 1308, 1273, 1234, 1188, 1038 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.19; H, 7.87; N, 5.67.

Ring-Contraction Reaction of Tetrahydrobenzazocine to Vinyltetrahydroquinoline (Table 4). To a solution of compound **2b** (43.8 mg, 0.2 mmol, 1.0 equiv) in CH_2Cl_2 (0.4 mL, 0.5 M) was added silica gel 60N (spherical, neutral, 63-210 μm, 0.1 g), and the reaction mixture was stirred at room temperature for 5 h under argon atmosphere. The resulting mixture was filtered, and concentrated under reduced pressure. The residue was then dissolved in CH_2Cl_2 (2.0 mL, 0.1 M) and treated with silica gel 60N (spherical, neutral, 63−210 μm, 0.2 g). The resulting mixture was stirred at room temperature for 4 h, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/EtOAc, 2:1) to afford compound **3b** (35.5 mg, 81%) as a yellow solid: mp 73−74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (s, 1H), 6.12 (s, 1H), 5.85 (ddd, J = 17.1, 10.5, 3.3 Hz, 1H), 5.14 (ddd, J = 17.1, 1.5, 1.2 Hz, 1H), 5.07 (ddd, J = 10.8, 1.5, 1.2 Hz, 1H), 3.78 (s, 6H), 3.31−3.27 (m, 1H), 3.05−2.96 (m, 1H), 2.81−2.70 (m, 1H), 2.65−2.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 141.5, 140.3, 138.0, 114.5, 113.8, 111.9, 99.5, 56.7, 55.8, 47.1, 36.6, 32.3; IR (KBr) 3371, 2924, 2839, 1520, 1496, 1466, 1227, 1211, 1134, 910.2, 825.4 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.24; H, 7.96; N, 6.31.

To a solution of compound **2b** (43.8 mg, 0.2 mmol, 1.0 equiv) in CH_2Cl_2 (0.4 mL, 0.5 M) was added TfOH (8.8 μL, 0.1 mmol, 0.5 equiv), and the reaction mixture was stirred at room temperature for 16 h under argon atmosphere. The resulting mixture was then partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel to afford compound **3b** (40.1 mg, 91%).

Formaldehyde-Accelerated Ring-Contraction Reaction of Tetrahydrobenzazocine (Scheme 3a). To a solution of compound **2b** (65.8 mg, 0.3 mmol, 1.0 equiv) in CH_2Cl_2/MeOH (1:1, 3 mL, 0.1 M) were added CF_3CO_2H (11.5 μL, 0.15 mmol, 0.5 equiv) and formaldehyde (37% aqueous solution, 83 μL, 0.6 mmol, 2.0 equiv), and the reaction was stirred at room temperature for 2 min under argon atmosphere. The resulting mixture was then partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford compound **3b** (49.8 mg, 76%).

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Isotopic Labeling Experiment (Scheme 3b). To a solution of compound **2b** (65.8 mg, 0.3 mmol, 1.0 equiv) in CH_2Cl_2/MeOH (1:1, 3 mL, 0.1 M) were added CF_3CO_2H (11.5 μL, 0.15 mmol, 0.5 equiv) and formaldehyde-d_2 (20% D_2O solution, 87 μL, 0.6 mmol, 2.0 equiv), and the reaction was stirred at room temperature for 2 min under argon atmosphere. The resulting mixture was then partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford an inseparable mixture of compound **3b** and compound **3b**-d_2 (48.7 mg, 74%, 83:17 by ^{1}H NMR integration in DMSO-d_6).

Incorporation of a Methyl Group into the Vinyltetrahydroquinoline Scaffold (Scheme 3c). To a solution of compound **2b** (65.8 mg, 0.3 mmol, 1.0 equiv) in CH_2Cl_2/MeOH (1:1, 3 mL, 0.1 M) were added CF_3CO_2H (11.5 μL, 0.15 mmol, 0.5 equiv) and acetaldehyde (34 μL, 0.6 mmol, 2.0 equiv), and the reaction was stirred at room temperature for 2 min under argon atmosphere. The resulting mixture was then partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc, 4:1) to afford compound **3b** (4.6 mg, 7%) and compound **3b**-Me (25.1 mg, 35%, 6:1 diastereomeric ratio by ^{1}H NMR integration) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 6.53 (s, 1H), 6.13 (s, 1H), 5.70 (ddd, J = 17.1, 10.2, 8.7 Hz, 1H), 5.17−5.07 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.47 (br s, 1H), 3.11 (dq, J = 9.0, 6.3 Hz, 1H), 2.66 (d, J = 8.1 Hz, 2H), 2.22−2.11 (m, 1H), 1.17 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, major isomer) δ 148.3, 141.3, 140.2, 138.0, 115.6, 113.5, 111.9, 99.1, 56.7, 55.8, 51.2, 44.5, 32.9, 21.0; IR (neat) 3379, 2962, 2839, 1620, 1520, 1458, 1257, 1234, 1211, 1134 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.16; H, 8.33; N, 5.99.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectroscopic data for new compounds and crystallographic data for **2b** and **3b**. 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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■ REFERENCES

(1) For reviews on aza-Claisen rearrangement, see: (a) Majumdar, K. C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B. *Synthesis* **2009**, *13*, 2117−2142. (b) Nubbemeyer, U. *Top. Curr. Chem.* **2005**, *244*, 149−213.

(2) Ohno, H. Vinylaziridines in Organic Synthesis. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; pp 37−71.

(3) Scheiner, P. *J. Org. Chem.* **1967**, *32*, 2628−2630.

(4) (a) Piangiolino, C.; Gallo, E.; Caselli, A.; Fantauzzi, S.; Ragaini, F.; Cenini, S. *Eur. J. Org. Chem.* **2007**, 743−750. (b) Fantauzzi, S.; Gallo, E.; Caselli, A.; Piangiolino, C.; Ragaini, F.; Re, N.; Cenini, S. *Chem.—Eur. J.* **2009**, *15*, 1241−1251.

(5) Eckelbarger, J. D.; Wilmot, J. T.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 10370−10371.

(6) For other examples, see: (a) Calcagno, M. A.; Schweizer, E. E. *J. Org. Chem.* **1978**, *43*, 4207−4215. (b) Figeys, H. P.; Jammar, R. *Tetrahedron Lett.* **1980**, *21*, 2995−2998. (c) Figeys, H. P.; Jammar, R. *Tetrahedron Lett.* **1981**, *22*, 637−640. (d) Hassner, A.; Wiegand, N. *J. Org. Chem.* **1986**, *51*, 3652−3656. (e) Lindstrom, U. M.; Somfai, P. *J. Am. Chem. Soc.* **1997**, *119*, 8385−8386. (f) Lindström, U. M.; Somfai, P. *Chem.—Eur. J.* **2001**, *7*, 94−98.

(7) Viallon, L.; Reinaud, O.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1995**, *36*, 4787−4790.

(8) (a) Koya, S.; Yamanoi, K.; Yamasaki, R.; Azumaya, I.; Masu, H.; Saito, S. *Org. Lett.* **2009**, *11*, 5438−5441. (b) Kanno, E.; Yamanoi, K.; Koya, S.; Azumaya, I.; Masu, H.; Yamasaki, R.; Saito, S. *J. Org. Chem.* **2012**, *77*, 2142−2148. (c) Aoki, T.; Koya, S.; Yamasaki, R.; Saito, S. *Org. Lett.* **2012**, *14*, 4506−4509.

(9) Attempts to transform *N*-aryl-2-vinylazetidines to *N*-acylated benzazocine derivatives in one step by treating vinylazetidines with acylating agents instead of acid were unsuccessful. Vinylazetidine **1a** did not react with, for example, Ac_2O/DMAP or Boc_2O/DMAP.

(10) Although we have not studied the effect of acid concentration on the ring-contraction reaction in detail, the results in Table 1 suggest that the reaction rate would be decreased both at lower acid loadings and with over 1.0 equiv of the acid.

(11) The declined yield of **3b** relative to the reaction with formaldehyde may be due to possible side reactions of iminium ion and enol form of acetaldehyde. This presumed decomposition of iminium ion may also account for the increased incorporation of 2-methyl group through suppression of the methylene transfer pathway.

(12) Cooper, M. A.; Lucas, M. A.; Taylor, J. M.; Ward, A. D.; Williamson, N. M. *Synthesis* **2001**, 621−625.

(13) For related examples of the isomerization of a cyclic iminium ion to 3-vinylpiperidine, see: (a) Grob, C. A.; Kunz, W.; Marbet, P. R. *Tetrahedron Lett.* **1975**, *16*, 2613−2616. (b) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 4894−4906.

(14) For the examples of reactions involving aldehydes as the catalyst operating via iminium ion intermediate, see: MacDonald, M. J.; Schipper, D. J.; Ng, P. J.; Moran, J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 20100−20103.

(15) Guthrie, J. P. *Can. J. Chem.* **1975**, *53*, 898−906.

(16) Iorio, M. A.; Ciuffa, P.; Damia, G. *Tetrahedron* **1970**, *26*, 5519−5527.

(17) The attempted isolation of the intermediate **XVII** was unsuccessful. The yield of **XVII** is presumed to be very low.

(18) Wasserman, H. H.; Lipshutz, B. H.; Tremper, A. W.; Wu, J. S. *J. Org. Chem.* **1981**, *46*, 2991−2999.

(19) Takashima, Y.; Kudo, J.; Hazama, M.; Inoue, A. Process for producing optically active N-substituted azetidine-2-carboxylic acid compound. Eur. Pat. Appl. EP0974670 (A2), 2000.

(20) Juaristi, E.; Madrigal, D. *Tetrahedron* **1989**, *45*, 629−634.

(21) (a) Walker, J. R.; Rothman, S. C.; Poulter, C. D. *J. Org. Chem.* **2008**, *73*, 726−729. (b) Anderson, A.; Belelli, D.; Bennett, D. J.; Buchanan, K. I.; Casula, A.; Cooke, A.; Feilden, H.; Gemmell, D. K.; Hamilton, N. M.; Hutchinson, E. J.; Lambert, J. J.; Maidment, M. S.; McGuire, R.; McPhail, P.; Miller, S.; Huntoni, A.; Peters, J. A.; Sansbury, F. H.; Stevenson, D.; Sundaram, H. *J. Med. Chem.* **2001**, *44*, 3582−3591.

(22) Burnett, D. A.; Caplen, M. A.; Czarniecki, M. F.; Domalski, M. S.; Ho, G. D.; Tulshian, D.; Wu, W. L. Azetidinyl diamines useful as ligands of the nociceptin receptor ORL-1. PCT Int. WO 03043980 (A1), 2003.

(23) Kamei, K.; Maeda, N.; Nomura, K.; Shibata, M.; Katsuragi-Ogino, R.; Koyama, M.; Nakajima, M.; Inoue, T.; Ohno, T.; Tatsuoka, T. *Bioorg. Med. Chem.* **2006**, *14*, 1978−1992.
(24) Rivas, F. M.; Riaz, U.; Giessert, A.; Smulik, J. A.; Diver, S. T. *Org. Lett.* **2001**, *3*, 2673−2676.
(25) Cordeiro, A.; Shaw, J.; O'Brien, J.; Blanco, F.; Rozas, I. *Eur. J. Org. Chem.* **2011**, 1504−1513.
(26) Qadir, M.; Cobb, J.; Sheldrake, P. W.; Whittall, N.; White, A. J. P.; Hii, K. K. M.; Horton, P. N.; Hursthouse, M. B. *J. Org. Chem.* **2005**, *70*, 1552−1557.