JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

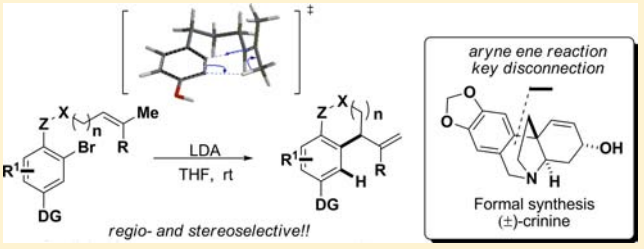
Development of an Intramolecular Aryne Ene Reaction and Application to the Formal Synthesis of (±)-Crinine

David A. Candito, Dennis Dobrovolsky, and Mark Lautens*

Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada

Supporting Information

ABSTRACT: A general and high yielding annulation strategy for the synthesis of various carbo- and heterocycles, based on an intramolecular aryne ene reaction is described. It was found that the geometry of the olefin is crucial to the success of the reaction, with exclusive migration of the *trans*-allylic-H taking place. Furthermore, the electronic nature of the aryne was found to be important to the success of the reaction. Deuterium labeling studies and DFT calculations provided insight into the reaction mechanism. The data suggests a concerted asynchronous transition state, resembling a nucleophilic attack on the aryne. This strategy was successfully applied to the formal synthesis of the ethanophenanthridine alkaloid (±)-crinine.



INTRODUCTION

Arynes are among the first reactive intermediates studied by organic chemists. Since their discovery they have fascinated chemists from both theoretical and synthetic perspectives. Although the field of aryne chemistry is relatively developed and may be considered mature, it has recently undergone a renaissance, as evidenced by the large number of reports in the literature.[1] This resurgence of aryne chemistry is partly due to new and milder methods of aryne generation[2] that permit new reactions to be uncovered.

The aryne ene reaction, although known, has not gained widespread use in synthetic organic chemistry, and only a few limited reports are found in the literature. Often the authors were studying other reactivity and observe an ene reaction as a side pathway.[3] Only recently have a few reports emerged that utilize the aryne ene reaction as a synthetic methodology.[4] Thus, the ene reaction warrants investigation as a methodology in its own right.

We postulated that the lack of literature reports on the subject was related to the difficulty in controlling the chemo- and regioselectivity of the ene reaction, rather than a lack of interest. The intramolecular Diels–Alder reaction of arynes has been used as a successsful strategy in organic synthesis, and drawing inspiration from the work of Martin,[5a] Buszek,[5d] Danhieser,[5e] and Castedo and Guitán,[5b,c] who have demonstrated very elegant examples of these reactions, we wondered whether the outcome of the reaction could be controlled by tethering the olefin to the aryne precursor (Figure 1). Doing so would allow for the use of deprotonation-based methods of aryne generation, thereby simplifying the starting materials employed and providing an interesting annulation strategy.

Herein, we report the development of a general, high yielding, and selective intramolecular aryne ene reaction providing straightforward access to benzofused carbo- and heterocycles and demonstrate its application to the formal synthesis of (±)-crinine.[6]

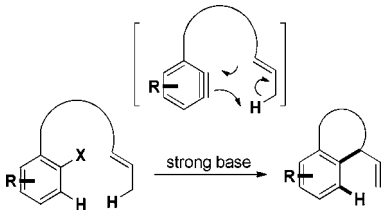


Figure 1. Intramolecular aryne ene reaction.

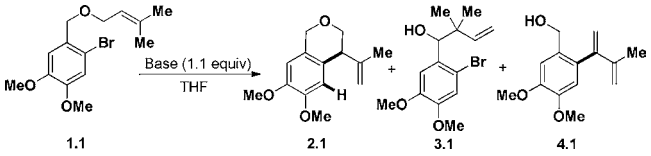
RESULTS AND DISCUSSION

Optimization Studies. Initial experiments began with substrate **1.1** at very high dilution in order to minimize any potential intermolecular reactions with the base or substrate. Deprotonation was carried out at cryogenic temperatures (−78 °C) by slow addition of LDA using a syringe pump. Following complete addition, the reaction was allowed to slowly warm to room temperature. The reaction was found to be very sluggish when carried out in this manner; however, **1.1** had cleanly converted to **2.1**. Increasing the concentration steadily increased the conversion and yield (Table 1, entries 1–3), and adding the base at room temperature at the beginning of the reaction further improved the conversion (Table 1, entry 4). The improved conversion is likely a result of the more rapid rate of LDA addition and the longer time spent at room temperature. When 2 equiv of LDA was added at the beginning of the reaction, **2.1** reacted further to form product **4.1**, which likely arose from deprotonation at the benzylic position of **2.1**

Received: July 20, 2012
Published: August 20, 2012

   dx.doi.org/10.1021/ja306881u | J. Am. Chem. Soc. 2012, 134, 15572–15580

Table 1. Optimization[a]



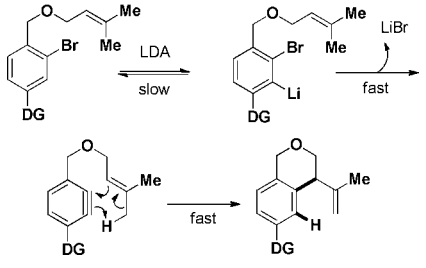
entry	base	conc. (M)	conv.[b] (%)	**2.1**[b] (%)	**3.1** (%)	**4.1** (%)
1[c,e]	LDA	0.003	23	23[d]		
2[c]	LDA	0.012	54	52		
3[c]	LDA	0.024	64	63		
4	LDA	0.024	100	88[d]		<5
5[f]	LDA	0.024	100	54		40[d]
6	LiHMDS	0.024	<5			
7	KHMDS	0.024	80	67		
8	LiTMP	0.024	77	39	38[d]	
9	$Me_2Zn(TMP)Li$	0.024	51	23	28[d]	

[a]Reaction conditions: **1.1** (1 equiv, 1 mmol), base (1.1 equiv), THF (conc. based on substrate), rt, 24 h. [b]Determined by ^1H NMR using mesitylene as an internal standard. [c]Lithium amide added at −78 °C using syringe pump (rate = 6 mL/h, LDA 0.1 M), then rt, 24 h (total time). [d]Isolated yield. [e]48 h. [f]LDA (2 equiv).

and subsequent ring-opening (Table 1, entry 5). Other lithium amide bases were also investigated; LiHMDS did not lead to any conversion, likely due to its decreased basicity, and KHMDS was a competent base but did not prove advantageous (Table 1, entries 6 and 7). Interestingly, LiTMP and $Me_2Zn(TMP)Li$[2b] gave mixtures of **2.1** and **3.1**, which likely arose by deprotonation of **1.1** at the benzylic position and subsequent [2,3]-Wittig rearrangement.[7] The difference in reactivity between LDA, LiTMP, and $Me_2Zn(TMP)Li$ is likely due to the difference in the steric properties of these bases as opposed to the difference in pK_a; the larger LiTMP and $Me_2Zn(TMP)Li$ complexes deprotonate the more accessible benzylic protons as opposed to the aromatic proton. With suitable conditions identified for the intramolecular aryne ene reaction, we went on to investigate both the scope and mechanism.

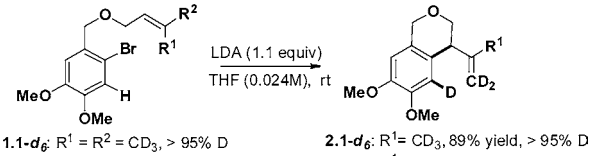
Mechanistic Studies. Early on, we were interested in probing the mechanism of this reaction and determining the critical factors necessary for its success. When the leaving group is a bromide, the deprotonation by LDA is likely to be the rate-determining step of the reaction[1a,8] because elimination is fast and because of the low concentrations employed. The deprotonation is expected to initially generate a lithiated intermediate, which undergoes elimination to generate the aryne intermediate. The aryne then engages the tethered olefin in an ene reaction to give the final product (Scheme 1). The aryne ene reaction is generally believed to proceed in a concerted manner;[9] however, a radical mechanism has also been proposed.[9d] Another possibility would be a polar mechanism where the olefin attacks the aryne and a zwitterionic intermediate is formed. Clearly each of these mechanisms will possess different structural requirements of the starting material. Even a partial understanding of the mechanism would greatly aid the use of this reaction in organic synthesis.

Scheme 1. Proposed Mechanism



We decided to probe the mechanism using deuterium labeling experiments. Reaction of labeled substrate **1.1**-d_6 led to complete transfer of deuterium (Scheme 2), consistent with a unimolecular concerted process. Inspection of hand-held and computer models suggested that the olefin geometry was important for the reaction and there should be a preference for migration of the *trans*-allylic-H. In order to test this hypothesis, substrate **1.1**-d_3 was synthesized with deuteration at the *trans*-methyl group, as a 91:9 mixture of isomers. Reaction of substrate **1.1**-d_3 led to complete deuterium transfer, which confirmed the preference for the *trans*-allylic-H to migrate and further reinforced the notion that no radical or polar intermediates were formed in this reaction, because rotation about the single bond of the intermediate radical or cation would have led to scrambling of the label.

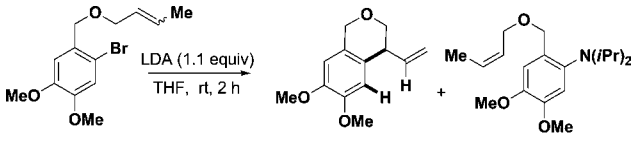
Scheme 2. Reactions of Deuterium Labeled Substrates



1.1-d_6: $R^1 = R^2 = CD_3$, > 95% D
1.1-d_3: $R^1 = CH_3$, $R^2 = CD_3$, 91:9 *E*:*Z*
2.1-d_6: $R^1 = CD_3$, 89% yield, > 95% D
2.1-d_3: R^1 = Me, 89% yield, 93% D

We were intrigued by the complete and selective deuterium transfer from **1.1**-d_3 and wondered whether this was a kinetic effect (i.e., the *trans*-substituent reacts much faster than the *cis*-substituent) or whether *cis*-olefins are incapable of reacting. In order to test this hypothesis, we synthesized substrates *cis*- and *trans*-**1.2** and subjected each to the reaction conditions. The substrates displayed marked differences in reactivity (Table 2).

Table 2. Reactions of *cis*- and *trans*-1.2[a]



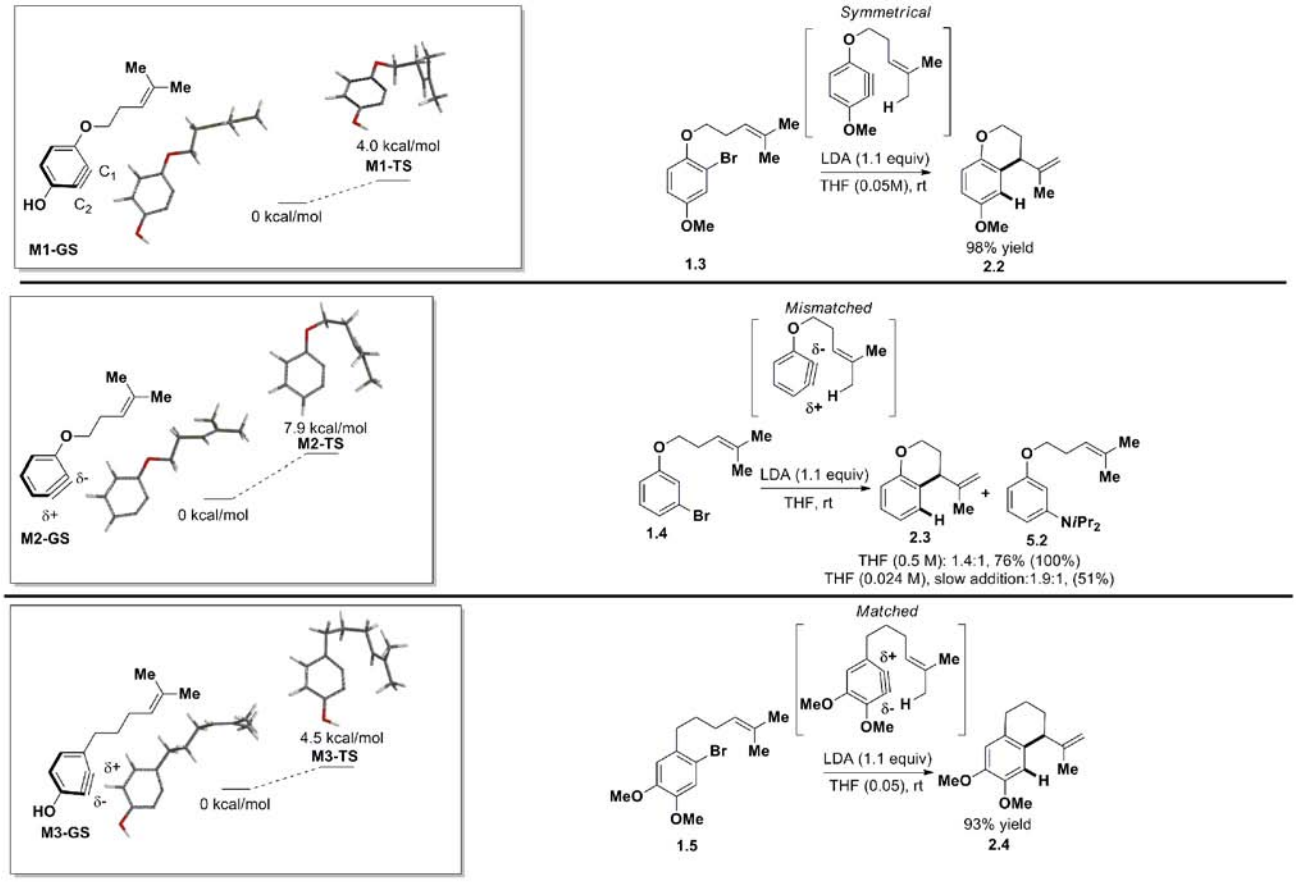
entry	**1.2**	*cis*/*trans*	conv.[b] (%)	ratio[b] (**2.30**/**5.1**)	yield (%)[c]
1	***trans*-1.2**	6:94	79	94:6	69
2	***cis*-1.2**	98:2	84	2:98	73

[a]Reaction conditions: **1.2** (1 equiv, 0.5 mmol), LDA (1.1 equiv), THF (0.024 M, based on substrate), rt, 2 h. [b]Determined by ^1H NMR analysis of the crude reaction mixture. [c]Combined isolated yield.

The compound *trans*-**1.2** reacted to give **2.30** as the major product (entry 1), whereas *cis*-**1.2** reacted to give **5.1** as the major product. The isomeric ratio of the starting material is reflected in the product distribution, revealing that the ene reaction of *cis*-**1.2** is too slow and outcompeted by the intermolecular reaction of the aryne intermediate with an external nucleophile. The transition state for the concerted reaction requires proper alignment of all components, and the

dx.doi.org/10.1021/ja306881u | J. Am. Chem. Soc. 2012, 134, 15572−15580

Scheme 3. Substituent Effects



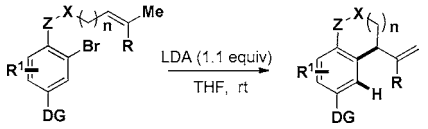
cis-olefin cannot adopt the correct conformation for reaction due to the intramolecular nature of the reaction. Thus, the geometry of the olefin is an important factor in determining the success of this reaction, with *cis*-olefins being unsuitable reaction partners.

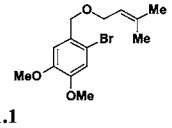
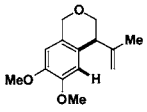
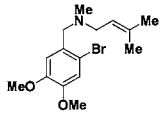
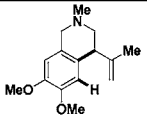
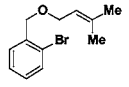
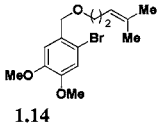
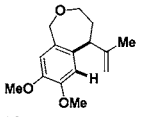
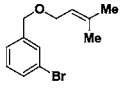
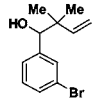
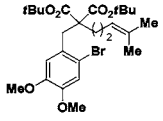
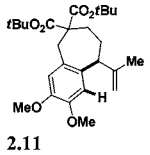
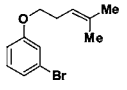
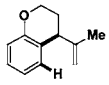
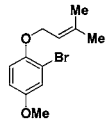
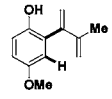
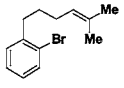
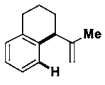
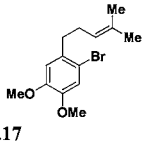
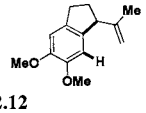
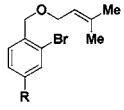
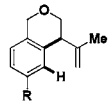
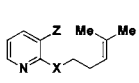
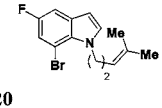
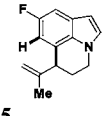
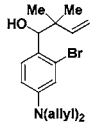
Alongside the experimental work, we also used computational models to investigate the nature and reactivity of the aryne intermediate. The results of DFT calculations performed at the B3LYP/6-31G* level of theory revealed an early pseudo-chairlike transition state that proceeded in a concerted manner; however, bond formation was asynchronous, with C−C bond formation being more advanced (Scheme 3).[10] Recently Houk and Garg have put forth a distortion model to predict the site selectivity of nucleophilic additions to arynes.[11,12] The presence of a σ-electron withdrawing substituent distorts the ground state structure of the aryne, causing nucleophilic attack to occur at the site with a larger internal angle because less energy is needed to distort the ground state into the transition state structure. From the computational and experimental data, it is apparent that the aryne ene reaction resembles a nucleophilic attack on the aryne, because the electronic nature of the aryne has a dramatic effect on the outcome of the reaction. In the case of **M1-GS** the aryne ground state does not suffer much distortion and the activation barrier was computed to be 4.0 kcal/mol (Scheme 3). Experimentally, the reaction of substrate **1.3**, which should yield a relatively symmetrical aryne intermediate, goes on to provide a single product in excellent yield. In the case of **M2-GS**, the aryne is polarized toward the oxygen atom such that nucleophilic attack would be preferred at C2, a so-called "mismatched" case (the site of nucleophilic attack is not the preferred site for nucleophilic attack) (Scheme 3). The activation barrier for this process was computed to be 7.9 kcal/mol. Interestingly, reaction of substrate **1.4**, which should yield an aryne intermediate that is polarized similarly to **M2-GS**, provides a mixture of the desired ene product and a product resulting from attack of the base (Scheme 3). In an attempt to improve the ratio in favor of the ene product the reaction was diluted, and LDA was added via syringe pump; however, this lead to only a modest change in the ratio and the reaction suffered from poor conversion (Scheme 3). This result clearly demonstrates that despite the intramolecular nature of the ene reaction, intermolecular nucleophilic attack can become a competitive pathway. Finally, in the case **M3-GS**, the aryne ground state is similarly polarized to **M2-GS**, but in the opposite direction, a so-called "matched case" (the site of nucleophilic attack coincides with the preferred site for nucleophilic attack). The activation barrier for this process was computed to be 4.5 kcal/mol. Experimentally, substrate **1.5** yields a single product in good yield. Thus, one must consider the electronic influence of substituents on the aryne when designing a reaction; efficient reactions occur with symmetrical/relatively nonpolarized arynes and substrates with "matched" reactivity.

Scope of the Reaction. With this knowledge, we went on to explore the scope of the reaction (Table 3). In order to achieve a selective deprotonation and efficiently generate the aryne, a directing group is necessary that can precomplex the lithium amide base.[13] We were interested in exploring the

dx.doi.org/10.1021/ja306881u | J. Am. Chem. Soc. 2012, 134, 15572−15580

Table 3. Scope of the Intramolecular Aryne Ene Recation[a]



Entry	Substrate	Product	Yield (%)[b]	Entry	Substrate	Product	Yield (%)[b]
1	 **1.1**	 **2.1**	89	10	 **1.13**	 **2.9**	89
2	 **1.6**	 **3.2**	61	11	 **1.14**	 **2.10**	35[d]
3	 **1.7**	 **3.3**	80	12	 **1.15**	 **2.11**	90
4	 **1.4**	 **2.3**	44[c]	13	 **1.16**	 **4.2**	89[e]
5	 **1.8**	 **2.5**	74	14	 **1.17**	 **2.12**	92
6	 **1.9** R=F	 **2.6** R=F	65	15	 **1.18** Z= Cl, X=O	 **2.13** X=O	50[f]
7	**1.10** R=Cl	**2.7** R=Cl	54	16	**1.19** Z= Br, X=S	**2.14** X=S	60
8	**1.11** R=pyrazolyl	**2.8** R=pyrazolyl	80	17	 **1.20**	 **2.15**	100
9	**1.12** R=N(allyl)$_2$	 **3.4**	50				

[a]Reaction conditions: substrate (1 equiv), LDA (1.1 equiv, 0.1 or 0.5 M in THF), THF (0.024 or 0.05 M or 0.10 M, based on substrate), rt (See Supporting Information for specific examples). [b]Isolated yields. [c]Amine addition competes (32% of **5.2**). [d]Amine addition competes (60% of **5.3**). [e]LDA (2.2 equiv). [f]Amine addition competes (13% of **5.4**).

directing effects of substituents on the substrate and probing the limits of the deprotonation based approach of aryne generation. When we remove the directing group, benzylic deptotonation occurs and the product of [2,3]-Wittig rearrangement results (entry 2), demonstrating that the bromine on its own is not a sufficiently strong directing group. In the reaction of substrate **1.7**, the bromine has been moved to the meta-position; two possible regioisomeric arynes could be formed. It was thought that the ether oxygen and bromine would direct in concert to selectively deprotonate the ortho-position; however, benzylic deprotonation occurred to give **3.3** (entry 3). When the position of the oxygen is moved, as in substrate **1.4**, the bromine and oxygen direct in concert to give a selective deprotonation; however, in this case the yield is low due to competing addition of external base (entry 4). In the case of substrate **1.8**, the Wittig rearrangement cannot take place, and the desired ene reaction takes place in good yield (entry 5). In this case, one could imagine a scenario where an equilibrium exists with other lithiated species; however, the elimination of the bromine is irreversible; therefore the desired pathway is traversed. Substrates **1.9** and **1.10** demonstrate the directing effect of two halogens and the selective elimination of the bromine to give predominately one aryne, which undergoes the ene reaction (entries, 6 and 7). In the case of substrate **1.10**,

dx.doi.org/10.1021/ja306881u | J. Am. Chem. Soc. 2012, 134, 15572−15580

the chlorine provides a synthetic handle. The pyrazolyl group proved to be an excellent directing group, whereas the teriary amine was not (entries 8 and 9). Significantly, substrate **1.13**, bearing a basic tertiary amine, reacted smoothly to give the heterocycle **2.9** in excellent yield (entry 10). We then went on to explore the ring sizes that are accessible using this methodology. The reaction of substrate **1.14** proceeded cleanly to give a mixture of the desired cyclized product in 35% and a product resulting from external attack by base in 60%, demonstrating that cyclization to make seven-membered rings is slow and competing nucleophilic attack can compete (entry 11). However, the reaction of substrate **1.15** proceeded smoothly to give the cyclized product **2.11** in 90% yield (entry 12). In the five-membered ring series, the reaction of substrate **1.16** proceeded to give starting material and product **4.2**, which arises from an ene reaction followed by further reaction of the ene product. Under the standard reaction conditions, none of the ene product was observed, likely because of the good leaving group ability of the phenolate anion and the strain released when opening the five-membered ring. A good yield of **4.2** could be obtained by addition of 2.2 equiv of LDA at the outset of the reaction (entry 13). If an all carbon linker is utilized, as in substrate **1.17**, then a good yield of the cyclized product can be obtained (entry 14). We were interested in extending the intramolecular ene cyclization strategy to include the use of hetarynes (entries 15−17). Reaction of substrate **1.18** proceeded in a modest 50% yield with some (13%) competing addition of the external base to the 4-position (entry 15). This competing nucleophilic attack is a result of the polarization of the aryne triple bond toward the ring nitrogen, which makes the carbon at the 4-position more electrophilic. Substrate **1.20** was selected because the fluorine atom adjacent to the newly formed aryne would counteract the effect of the indole nitrogen, thereby making the aryne more symmetrical and allowing for an efficient reaction to take place. A similar strategy was used by Garg in the synthesis of indolactam V, where a bromine substituent was used to improve the site selectivity of nucleophilic attack and could later be removed.[14] Reaction of substrate **1.20** proceeded to give the ene product in quantitative yield (entry 17).

Amides and carbamates are excellent directing groups for directed ortho-lithiation, and we thought to use them to guide selective aryne formation; however, substrates of this type did not provide any desired product and only gave complex mixtures. This is likely due to cyclization of the carbonyl group onto the aryne (Scheme 4). It has been demonstrated that benzoxazole and benzothiazole type products can be formed by intramolecular cyclization of the carbonyl compound onto the aryne followed by quenching with electrophiles.[15]

We also explored alternate methods of aryne generation and found that protocols based on metal−halogen exchange and deprotonation with alkyl lithiums provided the desired products in comparable yields to deprotonation with LDA (Table 4). The absence of nucleophilic species after the deprotonation may prove advantageous in avoiding side reactions.

With prior knowledge that the olefin geometry is important in the ene reaction, we explored the variation of substituents on the olefin (Table 5). An interesting spirocyclic compound bearing an all carbon quaternary center could be formed in good yield (entry 1). A styrenyl olefin was tolerated (entry 2). Substrate **1.23** bearing two similar alkyl substituents reacted regioselectively to give **2.18** in good yield (entry 3). Interestingly, a vinyl silane could also be employed in the

Scheme 4. Cyclization of Amides, Ureas, and Carbamates

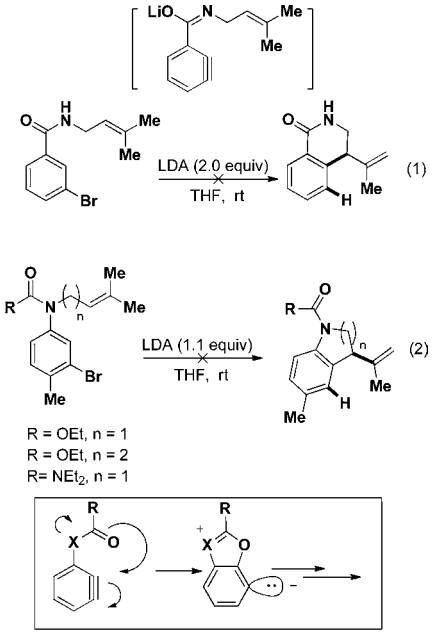
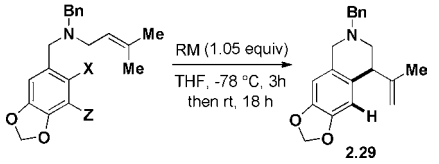


Table 4. Alternate Methods of Aryne Generation[a]



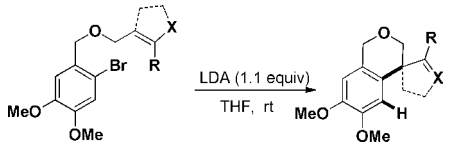
	substrate				
entry	X	Z		RM	yield (%)[b]
1	OSO_2-4-Cl-Ph	Br	**1.41**	*i*PrMgCl·LiCl	84
2	OSO_2-4-Cl-Ph	Br	**1.41**	*n*BuLi	65
3	Cl	H	**1.42**	*n*BuLi	80

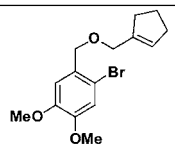
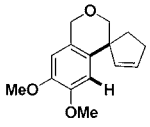
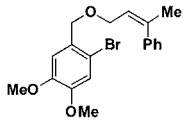
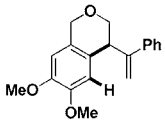
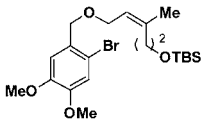
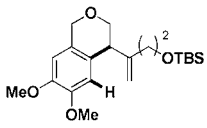
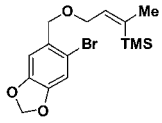
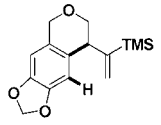
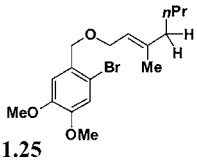
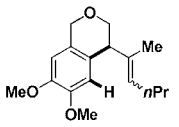
[a]Substrate (1 equiv), RM (1.05 equiv), THF (0.1 M, based on substrate), −78 °C for 3 h then rt for 18 h. [b]Isolated yield.

reaction (entry 3), to give an isomerized vinyl silane, which is poised for further manipulation. In this case, **1.24** was obtained as an inseparable mixture of *E*/*Z* isomers, but we have demonstrated that only the *Z*-isomer will react; we have based the yield of **2.19** on the amount of *Z*-isomer in the mixture. Up to this point, the ene reactions unambiguously gave a single product bearing a terminal olefin. We were interested in the possibility of controlling oelfin geometry. We synthesized substrate **1.25**, which would be expected to give an internal olefin following the ene reaction. Modeling the reaction revealed two transitions states, **TS1** and **TS2**, which were quite close in energy (Figure 2). **TS1** suffers from 1,2-allylic strain between the two eclipsing methyl groups and would lead to the *E*-olefin geometry; on the other hand, in **TS2** the 1,2-allylic strain is minimized, but it suffers from 1,3-allylic strain and would lead to the *Z*-olefin geometry. The energy difference between these competing interactions will dictate the product distribution. Computationally there was found to be an energy difference of 0.53 kcal/mol, corresponding to a product distribution of 1:2.4 (*E*/*Z*). Experimentally, substrate **1.25** gives a 1:2 ratio of *E*/*Z*-isomers in favor of the *Z*-olefin, this ratio could not be improved on conducting the reaction at temperatures as low as −78 °C.

dx.doi.org/10.1021/ja306881u | J. Am. Chem. Soc. 2012, 134, 15572−15580

Table 5. Scope of the Intramolecular Aryne Ene Reaction[a]



Entry	Substrate	Product	Yield (%)[b]
1	 **1.21**	 **2.16**	76
2	 **1.22** (14:1 *Z*:*E*)	 **2.17**	81
3	 **1.23**	 **2.18**	82
4	 **1.24** (6:1) *Z*:*E*	 **2.19**	75[c]
5	 **1.25**	 **2.20**	86[d]

[a]Reaction conditions: substrate (1 equiv), LDA (1.1 equiv, 0.1 or 0.5 M in THF), THF (0.024 or 0.05 M or 0.10 M, based on substrate), rt (See Supporting Information for specific examples). [b]Isolated yields. [c]Yield based on *Z*-isomer. [d]1:2, *E*/*Z* determined by ^{1}H NMR analysis of the crude reaction mixture.

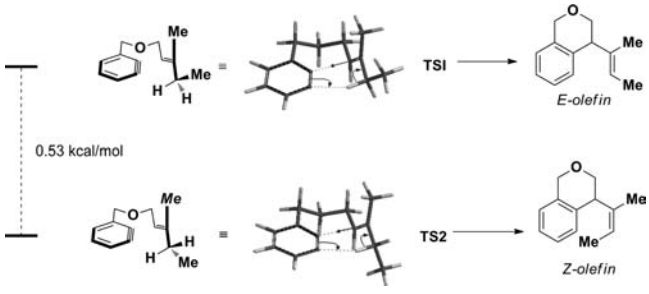


Figure 2. Model reaction to provide an internal olefin.

We were interested in the possibility of a substrate-controlled stereoselective ene reaction. We modeled the reaction of a substrate bearing an allylic stereocenter and DFT calculations revealed two pseudo-chairlike transition states, **TS3** and **TS4**, with significantly different energies (Figure 3). The effect of the

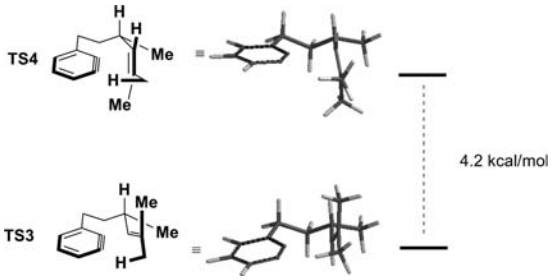
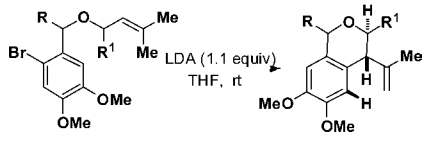


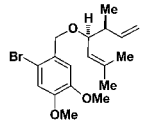
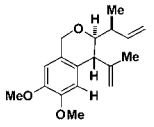
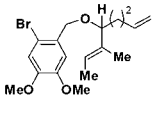
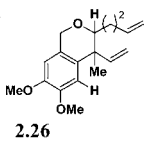
Figure 3. Model of a Stereoselective Aryne Ene Reaction.

stereocenter is to populate a chair conformation in which the allylic substituent (methyl in the model) is placed pseudoequatorially; rotation about the single bond then provides access to either diastereomer. **TS4** suffers from 1,3-allylic strain, raising its energy 4.19 kcal/mol above **TS3**. An energy difference of this magnitude should result in the observation of only one diastereomer and the relative stereochemistry is predicted to be *trans*.

These predictions were confirmed experimentally: when a substituent was present at the allylic position, diastereoselectivities of >20:1 in favor of the *trans*-product were observed (Table 6, entries 1−5). Substrate **1.31** reacted to give product

Table 6. Stereoselective Aryne Ene Reaction[a]



Entry		R	R^1	product	dr[b]	Yield (%)[c]
1	**1.26**	H	Me	**2.21**	>20:1	70
2	**1.27**	H	Bn	**2.22**	>20:1	83
3	**1.28**	H	*i*Pr	**2.23**	>20:1	100
4	**1.29**	H	vinyl	**2.24**	>20:1	84
5	 **1.30**			 **2.25**	>20:1	81
6	 **1.31**			 **2.26**	1.4:1	85
7	**1.32**	Me	H	**2.27**	1.8:1	85
8	**1.33**	*t*Bu	H	**2.28**	1.2:1	91

[a]Reaction conditions: substrate (1 equiv), LDA (1.1 equiv, 0.1 or 0.5 M in THF), THF (0.024 or 0.05 M or 0.10 M, based on substrate), rt (See Supporting Information for specific examples). [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Isolated yields.

2.26 bearing an all carbon quaternary center in good yield as a 1.4:1 mixture of isomers. The presence of the methyl group on the olefin reduces the energy difference between the two diastereomeric transition states, leading to an unselective reaction. When the stereocenter is placed at the benzylic position, poor selectivity is observed (entries 7 and 8), which is not so surprising, given that it is more remote. Stereoselective reactions of arynes are rare in the literature, and this may be

dx.doi.org/10.1021/ja306881u | *J. Am. Chem. Soc.* 2012, 134, 15572−15580

due to the commonly held notion that a highly reactive substrate is not very selective; however, this does not appear to be the case. The origin of the high selectivity is largely a result of the substrate's preference for a single low-energy ground state conformation, explaining why selectivity can be achieved despite an early, reactant-like transition state.

Formal Synthesis of (±)-Crinine. With the knowledge garnered from our mechanistic and substrate studies, we sought to validate the utility of this methodology in the context of the synthesis of a natural product. We identified crinine as a potential target that could be accessed via an intramolecular aryne ene reaction (Figure 4). Crinine is a member of the

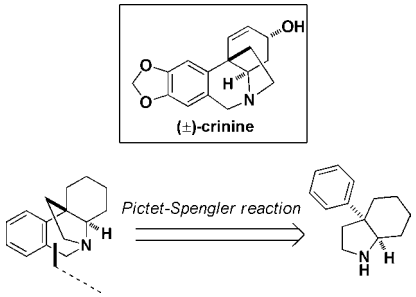


Figure 4. (±)-Crinine and Common Disconnection.

5,10b-ethanophenanthridine class of the *amaryllidaceae* family of alkaloids, characterized by its unique skeleton. Members of the *amaryllidaceae* family of alkaloids have a number of interesting and varied biological activities.[16] The compound was first isolated by Wildman in 1955 from the bulbs of two unidentified crinum species from South Africa. In a remarkable study Wildman demonstrated the skeletal connectivity of this alkaloid by degradation and chemical correlation studies.[17] A number of syntheses have relied on strategic disconnection to the C3-arylpolyhydroindole substructure (Figure 4). The first total synthesis of crinine was reported by Muxfeldt and co-workers in 1966 .[18] In addition to providing support for the assigned structure and defining the relative configuration of crinine, the synthesis demonstrated the strategic disconnection to the C3-arylpolyhydroindole substructure, laying the groundwork for many syntheses that followed. Since this time a number of approaches to (±)-crinine have been described,[19] many of them relying on accessing a C3-arylpolyhydroindole motif. Furthermore, many elegant approaches have been developed to access other members of the ethanophenanthridine class of natural products.[20]

The plan we devised relied on intercepting intermediate **1.38**, which was used in the Whitlock[19a] synthesis of (±)-crinine (Figure 5). This intermediate provided a way in which to build the C-ring onto the B-ring, which would ultimately be created by the ene reaction. In the forward direction, a sequence of intramolecular aldol reaction of **1.37** followed by dehydration could provide **1.38**, which would constitute a formal synthesis of crinine. Ketoaldehyde **1.37** could be traced back to **1.36** by ozonolytic cleavage. Disconnection of the key bond to build the B-ring leads back to compound **1.35**, which is poised for the ene reaction. Inspection of computer and hand-held models revealed that the presence of the pyrrolidine ring in **1.35** would secure the correct relative stereochemistry because the allyl group would prefer to occupy a pseudoequatorial position. We have seen previously that quaternary centers could be easily installed

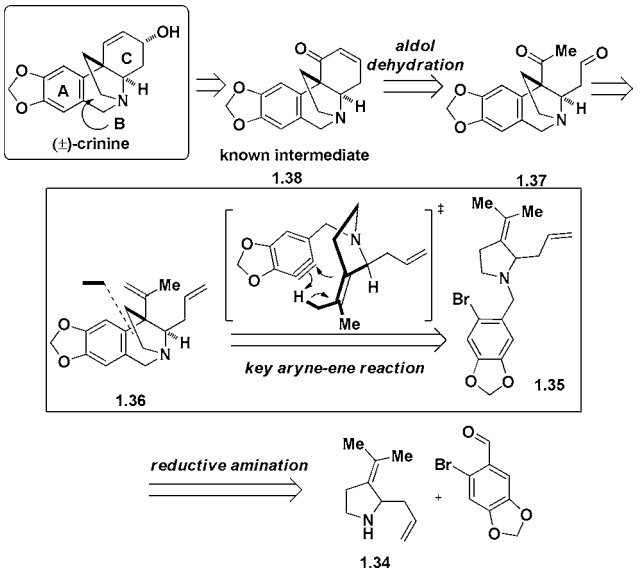
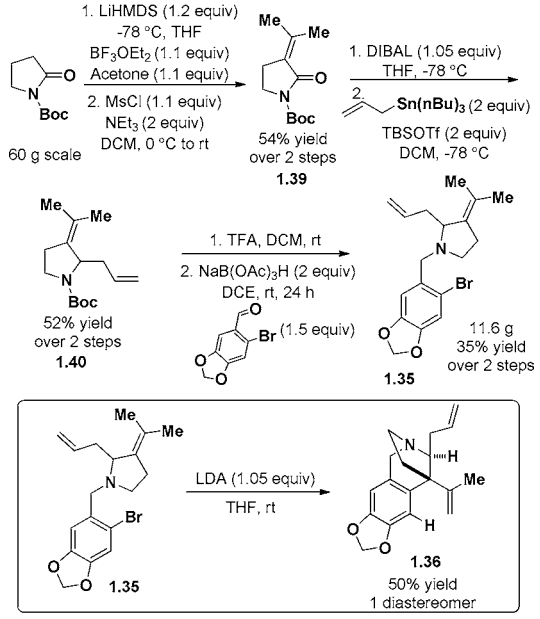


Figure 5. Retrosynthesis.

using the ene reaction, so we had some confidence that this key step would succeed. Key intermediate **1.35** can be disconnected into the pyrrolidine **1.34** and commercially available 6-bromopiperonal.

The first task in the synthesis was to synthesize compound **1.35** succintly, in order to test the key ene reaction (Scheme 5).

Scheme 5. Forward Synthesis



The synthesis began with commercially available N-Boc-pyrrolidinone, which underwent an aldol reaction with acetone to give the adduct, which was used without purification and dehydrated by formation of the mesylate and *in situ* elimination to give pyrrolidinone **1.39** in a moderate, 54%, overall yield. The oxidation state of **1.39** was adjusted by action of DIBAL and the crude reaction mixture was directly allylated to give compound **1.40** in 52% yield over two steps. Pyrrolidinone **1.40** was deprotected under standard conditions, and the amine was used directly without any further purification. Reductive

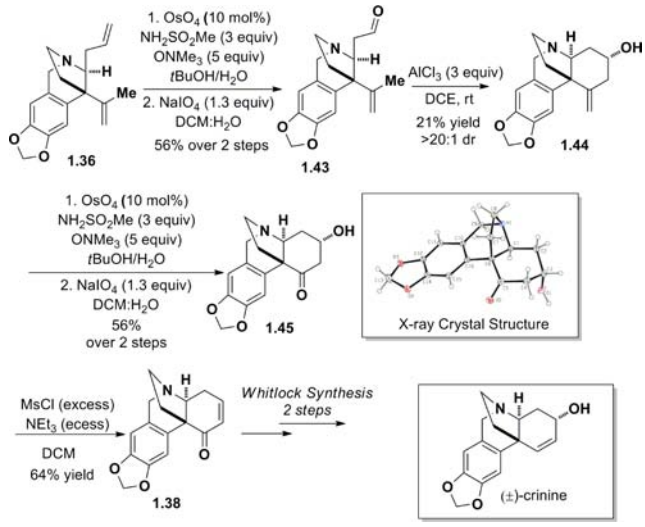
dx.doi.org/10.1021/ja306881u | J. Am. Chem. Soc. 2012, 134, 15572−15580

amination of 6-bromopiperonal in the presence of $NaBH(OAc)_3$ proceeded in moderate yield, likely due to the steric hindrance associated with the secondary amine. Other reduction procedures failed to improve the result. With **1.35** in hand, the key aryne ene reaction could be tested, and we were pleased to see a relatively clean reaction with the formation of the desired product **1.36**, in 50% yield, as a single diastereomer with the correct relative configuration. The moderate yield of product **1.36** relative to some of the acyclic congeners (see previous section) is thought to be a result of increased strain in the transition state associated with the formation of the bicyclic structure.

All that remained in order to finish the formal synthesis of (±)-crinine was the projected ozonolytic cleavage of both olefins, followed by aldol cyclization and dehydration. We found that ozonolysis was complicated by the electron-rich aromatic ring and teriary amine. So we attempted to attenuate the reactivity by using the hydrochloride salt of **1.36** (**1.36·HCl**). Ozonolysis of **1.36·HCl** at −78 °C in DCM followed by reductive work up led to the formation of **1.43** in 23% yield, another compound that possessed a molecular formula corresponding to over-oxidation, in approximately equal amounts (27%), and the rest of the mass balance was mainly decomposition products. An ozonolysis experiment was also attempted by using SudanRed 7B as an indicator to avoid over-oxidation, but this gave identical results to the reaction without any indicator. Switching the solvent to MeOH or EtOAc did not lead to improved results, and there was extensive decomposition of the starting material. Under several conditions for dihydroxylation or oxidation with *m*CPBA, only oxidation of the 1-substituted olefin took place, indicating that the 1,1-disubstituted olefin was more sterically hindered than we anticipated at the outset of the synthesis. In order to circumvent the difficult oxidation, we recognized that cyclization via a carbonyl ene reaction[21] could lead to a change in the conformation of the molecule, providing more accessibility to the olefin. We screened a number of Lewis acids such as Me_2AlCl, $EtAlCl_2$, $SnCl_4$, $TiCl_4$, $Sc(OTf)_3$, MAD, and MADPH; however, only starting material or decomposition was observed. A report from the Overman group demonstrated a difficult type II carbonyl ene reaction of a ketone, using aluminum trichloride as a promoter. It is noteworthy that this is one of the few examples where a carbonyl ene reaction has be carried out with a tertiary amine present in the molecule.[22]

We were pleased to find that using $AlCl_3$ in DCE resulted in cyclization to give **1.44** in 21% yield as a single diastereomer (Scheme 6). During the optimization of this step, high conversions and low yields were always observed. Due to the lack of observable byproducts in the ^1H NMR spectrum, it is likely that polymerization of the substrate takes place or there is extensive decomposition, leading to insoluble byproducts. The poor yields in this reaction are likely due to the basic tertiary amine, which complexes the Lewis acid and leads to side reactions. Although the yield of the carbonyl ene reaction was low, we were interested in determining whether our initial hypothesis was correct. We subjected **1.44** to dihydroxylation conditions and found that this compound smoothly reacted to give one product by ^1H NMR analysis, in essentially quantitative yield. The glycol could then be cleaved with sodium periodate in moderate yield to provide compound **1.45**, whose structure was proven by X-ray crystallography, confirming our previous stereochemical assignments (Scheme 6). Hydroxy ketone **1.45** could be dehydrated in a straightforward manner to give compound **1.38**, which was previously prepared by Whitlock and co-workers in their synthesis of (±)-crinine,[19a] constituting a formal synthesis of the natural product.

Scheme 6. Completion of Synthesis of (±)-Crinine



CONCLUSIONS

The development of a general and high yielding method for the formation of various carbo- and heterocycles based on an intramolecular aryne ene reaction has been disclosed. The intramolecular strategy has allowed for high levels of chemo-, regio-, and stereoselectivity to be achieved. Deuterium labeling experiments, carefully designed substrates, and calculations have provided insight into the reaction mechanism. The knowledge gained in our mechanistic and substrate studies was put to use in a formal synthesis of the alkaloid (±)-crinine. The synthesis showcases the use of the aryne ene reaction in a key step where an all carbon quanternary center is set and the relative configuration of both stereocenters is secured in a single step, vastly increasing the complexity of the precursor. However, the synthesis is later plagued by the unforeseen difficulty of oxidizing the 1,1-disubstituted olefin. Although the synthesis suffers from a low yield following the key step, it successfully shows how the aryne ene reaction can be applied in target oriented synthesis. We are currently trying to expand the repertoire of annulation strategies using aryne intermediates to form C−C bonds and further the use of arynes in stereoselective synthesis.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic and analytical data for all products and starting materials, copies of NMR spectra, and X-ray data for compound **1.45**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

mlautens@chem.utoronto.ca

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Merck Frosst Center for Therapeutic Research, the Natural Science and Engineering Research Council (NSERC), and the University of Toronto for financial support. D.A.C. thanks NSERC for a CGS D fellowship. D.D. thanks NSERC for an undergraduate student research award.

■ REFERENCES

(1) Reviews: (a) Dyke, A. M.; Hester, A. J.; Lloyd-Jones, G. C. *Synthesis* **2006**, 4093. (b) Chen, Y.; Larock, R. C. In *Modern Arylation Methods*; Akermann, L., Ed.; WILEY-VCH: Weinheim, Germany, 2009; pp 401−473. (c) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215. (d) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (e) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. (f) Gilchrist, T. L. In *Science of Synthesis*; Hopf, H., Ed.; Georg Thieme Verlag KG: Stuttgart, Germany, 2011; pp 151−203. (g) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (h) Kitamura, T. *Aust. J. Chem.* **2010**, *63*, 987. (i) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766.

(2) (a) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211. (b) Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otani, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514. (c) Lin, W.; Chen, L.; Knochel, P. *Tetrahedron* **2007**, *63*, 2787. (d) Sapountzis, I.; Lin, W.; Fischer, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4364.

(3) (a) Arnett, E. M. *J. Org. Chem.* **1960**, *25*, 324. (b) Simmons, H. E. *J. Am. Chem. Soc.* **1961**, *83*, 1657. (c) Wittig, G.; Dürr, H. *Justus Liebigs Ann. Chem.* **1964**, *672*, 55. (d) Kampmeier, J. A.; Rubin, A. B. *Tetrahedron Lett.* **1966**, 2853. (e) Nakayama, J.; Yoshimura, K. *Tetrahedron Lett.* **1994**, *35*, 2709. (f) Aly, A. A.; Mohamed, N. K.; Hassan, A. A.; Mourad, A.-F. E. *Tetrahedron* **1999**, *55*, 1111.

(4) (a) Aly, A. A.; Shaker, R. M. *Tetrahedron Lett.* **2005**, *46*, 2679. (b) Jayanth, T.; Jeganmohan, M.; Cheng, M.; Chu, S.; Cheng, C. *J. Am. Chem. Soc.* **2006**, *128*, 2232.

(5) (a) Chen, C.-L.; Sparks, S. M.; Martin, S. F. *J. Am. Chem. Soc.* **2006**, *128*, 13696. (b) Pérez Meirás, D.; Guitián, E.; Castedo, L. *Tetrahedron Lett.* **1990**, *31*, 2331. (c) González, C.; Pérez, D.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1995**, *60*, 6318. (d) Buszek, K. R. *Tetrahedron Lett.* **1995**, *36*, 9125. (e) Hayes, M. E.; Shinokubo, H.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3917.

(6) Our preliminary Communication: Candito, D. A.; Panteleev, J.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 14200.

(7) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.

(8) (a) Huisgen, R.; Sauer, J. *Ber. Dtsch. Chem. Ges.* **1959**, *72*, 192. (b) Zoltewicz, J.; Bunnett, J. *J. Am. Chem. Soc.* **1965**, *87*, 2640. (c) Dunn, G.; Krueger, P.; Rodewald, W. *Can. J. Chem.* **1961**, *39*, 180.

(9) (a) Crews, P.; Beard, J. *J. Org. Chem.* **1973**, *38*, 522. (a) Friedman, L.; Osiewicz, R. J.; Rabideau, P. W. *Tetrahedron Lett.* **1968**, 5735. (b) Wasserman, H. H.; Solodar, A. J.; Keller, L. S. *Tetrahedron Lett.* **1968**, 5597. (c) Wasserman, H. H.; Keller, L. S. *Tetrahedron Lett.* **1974**, 4355. (d) Tabushi, I.; Okazaki, K.; Oda, R. *Tetrahedron* **1969**, *25*, 4401. (e) Ahlgren, G.; Akermark, B. *Tetrahedron Lett.* **1970**, 3047. (f) Garsky, V.; Koster, D. F.; Arnold, R. T. *J. Am. Chem. Soc.* **1974**, *96*, 4207. (g) Jayanth, T.; Jeganmohan, M.; Cheng, M.; Chu, S.; Cheng, C. *J. Am. Chem. Soc.* **2006**, *128*, 2232.

(10) Calculations were performed using Spartan '08 V1.2.0. Geometry optimizations were carried out at B3LYP/6-31G* level of theory. Frequency calculations were used to characterize stationary points as minima or transition states. See Supporting Information.

(11) (a) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G-Y. J.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 1267. (b) Im, G.-Y. J; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933. (c) Goetz, A. E.; Bronner, S. M.; Cisneros, J. D.; Melamed, J. M.; Paton, R. S.; Houk, K. N.; Garg, N. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 2758.

(12) (a) Buszek, K. R.; Luo, D.; Kondrashov, M.; Brown, N.; VanderVelde, D. *Org. Lett.* **2007**, *9*, 4135. (b) Brown, N.; Lou, D.; VanderVelde, D.; Yang, S.; Brassfield, A.; Buszek, K. R. *Tetrahedron Lett.* **2009**, *50*, 63. (c) Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. *Org. Lett.* **2010**, *12*, 96.

(13) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(14) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 3832.

(15) (a) Clark, R. D.; Caroon, J. M. *J. Org. Chem.* **1982**, *47*, 2804. (b) Stanetty, P.; Krurnpak, B. *J. Org. Chem.* **1996**, *61*, 5130. (c) Fairhurst, R. A.; Janus, D.; Lawrence, A. *Org. Lett.* **2005**, *7*, 4697.

(16) (a) Ghosal, S.; Saini, K. S.; Razdan, S. *Phytochemistry* **1985**, *24*, 2141. (b) Kornienko, A.; Evidente, A. *Chem. Rev.* **2008**, *108*, 1982. (c) Banwell, M. G.; Gao, N.; Schwartz, B. D.; White, L. V. *Top. Curr. Chem.* **2012**, *309*, 163.

(17) (a) Mason, L. H.; Puschett, E. R.; Wildman, W. C. *J. Am. Chem. Soc.* **1955**, *77*, 1253. (b) Wildman, W. C. *J. Am. Chem. Soc.* **1958**, *80*, 2567.

(18) Muxfeldt, H.; Schneider, R. S.; Mooberry, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 3670.

(19) (a) Whitlock, H. W.; Smith, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 3600. (b) Overman, L. E.; Jacobsen, E. J. *Tetrahedron Lett.* **1982**, *27*, 2741. (c) Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745. (d) Martin, S. F.; Campbell, C. L. *Tetrahedron Lett.* **1987**, *28*, 503. (e) Martin, S. F.; Campbell, C. L. *J. Org. Chem.* **1988**, *53*, 3184. (f) Pearson, W. H.; Lovering, F. E. *Tetrahedron Lett.* **1994**, *35*, 9173. (g) Pearson, W. H.; Lovering, F. E. *J. Org. Chem.* **1998**, *63*, 3607. (h) Bohno, M.; Imase, H.; Chida, N. *Chem. Commun.* **2004**, 1086. (i) Bohno, M.; Sugie, K.; Imase, H.; Yusof, Y. B.; Oishi, T.; Chida, N. *Tetrahedron* **2007**, *63*, 6977. (j) Tam, N. T.; Chang, J.; Jung, E.-J.; Cho, C.-G. *J. Org. Chem.* **2008**, *73*, 6258. (k) Tam, N. T.; Cho, C.-G. *Org. Lett.* **2008**, *10*, 601. (l) Liu, J.-D.; Wang, S.-H.; Zhang, F.-M.; Tu, Y.-Q.; Zhang, Y.-Q. *Synlett* **2009**, 3040. (m) Guillou, C.; Bru, C. *Tetrahedron* **2006**, *62*, 9043. (n) Pandey, G.; Gupta, N. R.; Gadre, S. R. *Eur. J. Org. Chem.* **2011**, 740.

(20) For recent reports aimed at the synthesis of ethanophenanthridine alkaloids, see: (a) Yang, L.; Chen, W.; Wang, X.; Pan, Z.; Zhou, M.; Yang, X. *Synlett* **2011**, 207. (b) Findlay, A. D.; Banwell, M. G. *Org. Lett.* **2009**, *11*, 3160. (c) Roe, C.; Stephenson, G. R. *Org. Lett.* **2008**, *10*, 189. (d) Gao, S.; Tu, Y. Q.; Song, Z.; Wang, A.; Fan, X.; Jiang, Y. *J. Org. Chem.* **2005**, *70*, 6523. (e) Song, Z. L.; Wang, B. M.; Tu, Y. Q.; Fan, C. A.; Zhang, S. Y. *Org. Lett.* **2003**, *5*, 2319. (f) Banwell, M. G.; Harvey, J. E.; Jolliffe, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2002. (g) Ley, S. V.; Schucht, O.; Thomas, A. W.; Murray, P. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1251. (h) Schkeryantz, J. M.; Pearson, W. H. *Tetrahedron* **1996**, *52*, 3107. (i) Pearson, W. H.; Lovering, F. E. *J. Am. Chem. Soc.* **1995**, *117*, 12336. (j) Grigg, R.; Santhakumar, V.; Sridharan, V.; Thornton-Pett, M.; Bridge, A. W. *Tetrahedron* **1993**, *49*, 5177. (k) Burk, R. M.; Overman, L. E. *Heterocycles* **1993**, *35*, 205.

(21) Clarke, M. L.; France, M. B. *Tetrahedron* **2008**, *64*, 9003.

(22) Overman, L. E.; Lesuisse, D. *Tetrahedron Lett.* **1985**, *26*, 4167.