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Intramolecular Cyclizations of Vinyl-Substituted *N*,*N*-Dialkyl Arylamines Enabled by Borane-Assisted Hydride Transfer

Jun-Jie Tian,[#,†] *Ning-Ning Zeng*,[#,†] *Ning Liu*,[†] *Xian-Shuang Tu*,[†] *Xiao-Chen Wang**[,†,‡]

[†]State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China.

[‡]Collaborative Innovation Center of Chemical Science and Engineering, Nankai University, Tianjin 300071, China.

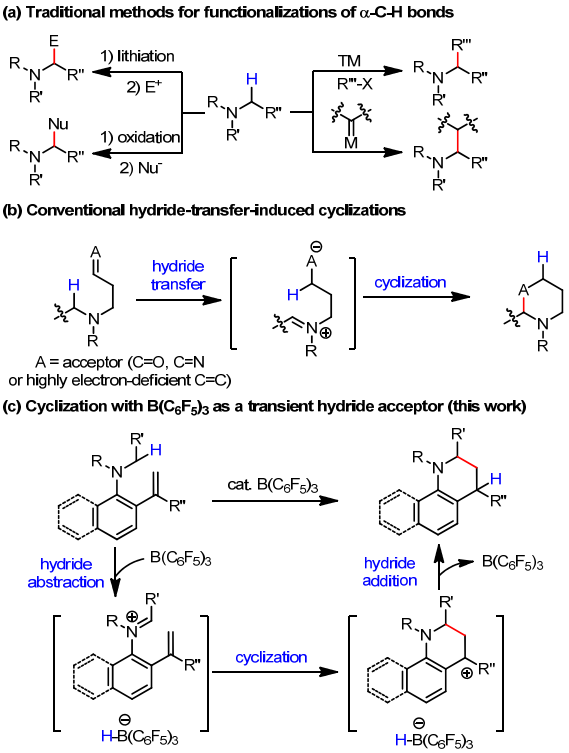
ABSTRACT: Catalytic amounts of $B(C_6F_5)_3$ have been found to be able to promote the intramolecular cyclization of vinyl-substituted *N*,*N*-dialkyl arylamines to afford nitrogen-containing heterocycles. Our mechanistic studies indicate the reaction is initiated by abstraction of an α-hydride from an *N*-alkyl substituent by $B(C_6F_5)_3$, which is followed by cyclization, and is concluded by delivery of the hydride to the cyclic cationic intermediate. The dual roles of $B(C_6F_5)_3$, first as an oxidant and then as a hydride-carrying reductant, have enabled a rare redox-neutral cyclization process between a sp^3 carbon and an electron-rich olefin without using a transition metal or an external oxidant.

KEYWORDS: boron, hydride abstraction, cyclization, heterocycles, homogeneous catalysis

Studies of C–H functionalization reactions have attracted tremendous attention due to their fast and convenient access to new carbon-carbon and carbon-heteroatom bonds with selective disconnection of ubiquitous carbon-hydrogen bonds.[1] To activate the α-C–H bonds adjacent to a nitrogen atom in particular, common methods include 1) lithiation followed by addition with an electrophile,[2] 2) oxidation to generate an iminium ion that is subsequently trapped by nucleophiles,[3] 3) transition metal-catalyzed C–H activation reactions,[4,5] and 4) carbene insertions[6] (Scheme 1a). These methods require the use of either stoichiometric amounts of an organometallic reagent or an oxidant, or catalytic amounts of a transition metal with a tailor-made ligand. Alternatively, the hydride-transfer-induced intramolecular cyclization reactions have been found effective in constructing various cyclic and heterocyclic scaffolds via direct activation of α-C–H bonds (Scheme 1b).[7] These reactions rely on the use of starting materials having both a good hydride donor (e.g. α-C–H bonds) and a good hydride acceptor (e.g. aldehydes, imines, and α,β-unsaturated carbonyls) so that a hydride transfer from the donor to the acceptor will initiate the cyclization process. The high energy barrier for the hydride transfer is the primary challenge for the reactivity. To improve the reactivity, Lewis acids or Brønsted acids were often added to increase the electrophilicity of acceptors by coordination. Despite this, these cyclization reactions are still limited in substrate scope, and starting materials without an acceptor group are normally unreactive.

During the past decade, the versatile reactivities of $B(C_6F_5)_3$ with small molecules have been utilized to develop a myriad of catalytic organic reactions.[8] Among them, hydrogenations,[9] hydrosilylations,[10] transfer hydrogenations,[11] and transfer hydrosilylations[12] have been extensively studied. However, a known reactivity of $B(C_6F_5)_3$, that is its capability to abstract a hydride from α-carbons of an amine to generate an iminium ion and a borohydride,[13] has rarely been studied for a catalytic

Scheme 1. C–H functionalizations of α-C–H bonds adjacent to a nitrogen atom.

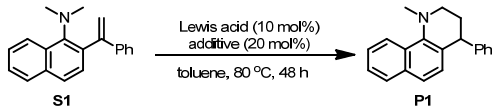


reaction, and the existing examples have been confined to transfer hydrogenation reactions using amines as a hydride donor,[11a] dehydrogenation reactions of heterocycles[14] and intermolecular coupling reactions[15] between tertiary amines and electron-deficient olefins. Recently, we questioned whether this reactivity could be utilized in promoting hydride-transfer-induced cyclization reactions. Specifically, we hypothesized

that $B(C_6F_5)_3$ could function as an transient hydride acceptor so that the requirement of having an acceptor group in a starting material could be obviated. Herein, we report that $B(C_6F_5)_3$ is able to function as a transient acceptor in the cyclization reactions of vinyl-substituted *N*,*N*-dialkyl arylamines (Scheme 1c). Our mechanistic studies indicate the conventional two-step mechanism in a hydride-transfer-induced cyclization reaction has been broken down into three steps: borane-mediated hydride abstraction, cyclization, and rebound of hydride from $B(C_6F_5)_3$. Notably, when our paper was under review, the Paradies group reported a similar cyclization process using another group of vinyl-substituted *N*,*N*-dialkyl arylamines.[16] In their report, the hydride abstraction occurs at a secondary *N*-alkyl group so that the obtained products contain tetrasubstituted stereocenters. And, *N*-methyl was unreactive under their reaction conditions.

We commenced the study by testing styryl-substituted *N*,*N*-dimethyl-1-naphthylamine **S1** as the starting material (Table 1). Conventionally, **S1** is unreactive for cyclization due to the lack of an acceptor group. The absence of any cyclization product after reacting **S1** in toluene at 80 °C for 48 h proved its poor reactivity (entry 1). Encouragingly, in the presence of 10 mol% of $B(C_6F_5)_3$, the desired cyclization occurred, giving product **P1** in 72% yield (entry 2). Less Lewis acidic triarylboranes, including $B(p\text{-}C_6F_4H)_3$, $B(2,6\text{-}F_2C_6H_3)_3$ and BPh_3, were found less active or inactive (entries 3–5). After an extensive optimization, we discovered that the addition of a silyl triflate as an addtive could influence the reactivity. The addition of 20 mol% of TMSOTf improved the yield to 88% (entry 6) while the addition of bulkier Lewis acids, such as TESOTf and TBSOTf, decreased the yields (entries 7 and 8). On the contrary, the addition of TMSCl or TESCl as an additive had no obvious influence on the reactivity (entries 9 and 10). Without $B(C_6F_5)_3$, TMSOTf itself was unable to promote the reaction probably because of its relatively weak Lewis acidity (entry 11). Various solvents were next evaluated (entries 12–16), but toluene still gave the highest yield. We then tested several commonly used Lewis acids as a substitute for $B(C_6F_5)_3$, including $BF_3{\bullet}OEt_2$, $Sc(OTf)_3$, $Zn(OTf)_2$ and $FeCl_3$, but these Lewis acids were found to be inactive (entries 17–20).

Table 1. Optimization of the reaction conditions[a]



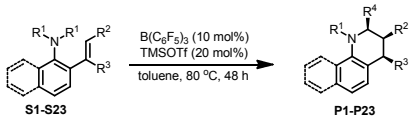
S1 P1

entry	Lewis acid	additive	solvent	yield (%)[b]
1	none	none	toluene	n. d.
2	$B(C_6F_5)_3$	none	toluene	72
3	$B(p\text{-}C_6F_4H)_3$	none	toluene	51
4	$B(2,6\text{-}F_2C_6H_3)_3$	none	toluene	n. d.
5	BPh_3	none	toluene	n. d.
6	$B(C_6F_5)_3$	TMSOTf	toluene	88
7	$B(C_6F_5)_3$	TESOTf	toluene	70
8	$B(C_6F_5)_3$	TBSOTf	toluene	42
9	$B(C_6F_5)_3$	TMSCl	toluene	74
10	$B(C_6F_5)_3$	TESCl	toluene	75
11	none	TMSOTf	toluene	n. d.
12	$B(C_6F_5)_3$	TMSOTf	*p*-xylene	75
13	$B(C_6F_5)_3$	TMSOTf	$PhCF_3$	31
14	$B(C_6F_5)_3$	TMSOTf	DCE	40
15	$B(C_6F_5)_3$	TMSOTf	$1,2\text{-}Cl_2C_6H_4$	34
16	$B(C_6F_5)_3$	TMSOTf	THF	4
17	$BF_3{\bullet}OEt_2$	TMSOTf	toluene	n. d.
18	$Sc(OTf)_3$	TMSOTf	toluene	n. d.
19	$Zn(OTf)_2$	TMSOTf	toluene	n. d.
20	$FeCl_3$	TMSOTf	toluene	n. d.

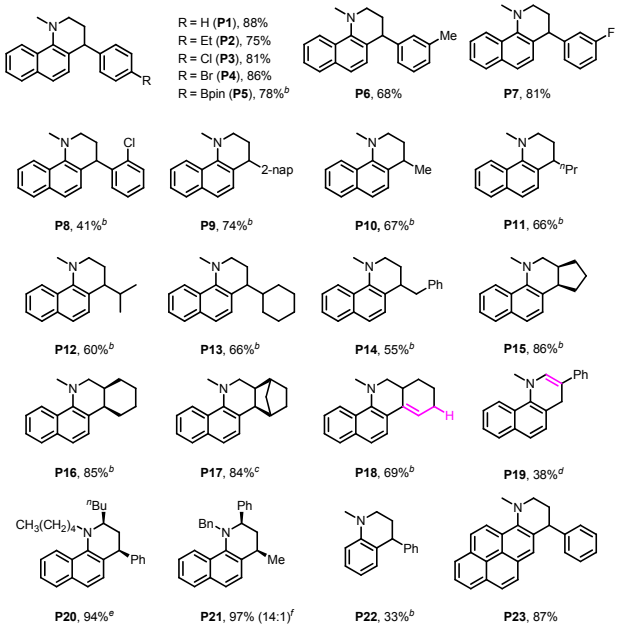
[a] Unless otherwise specified, all reactions were performed in 0.5 mL toluene with 0.2 mmol **S1** under N_2. [b] Isolated yield; n. d. = not detected.

With the optimal conditions in hands, we began to investigate the scope of this cyclization reaction (Table 2). Various aryl groups on the olefin was first examined. Alkyl (**P2**), halo (**P3** and **P4**) and Bpin (**P5**) at the *para* position of a phenyl ring were tolerated, giving the desired products in 75–86% yields. *Meta*-substituted (**P6** and **P7**), *ortho*-substituted (**P8**) phenyls and 2-naphthyl (**P9**) were also compatible. Changing the aryl group to an alkyl group, such as methyl (**P10**), ^{n}propyl (**P11**), isopropyl (**P12**), cyclohexyl (**P13**) and benzyl (**P14**), was feasible; the desired products were obtained in 55–67% yields. We subsequently tested sterically encumbered tri-substituted olefins. Gratifyingly, these substrates underwent cyclization with exclusive formation of the *cis* products (**P15**–**P17**) in 84–86% yields. Interestingly, with a starting material having a conjugated diene (**S18**), double bond migration occurred after cyclization, affording **P18** in 69% yield. Moreover, a starting

Table 2. Investigation of vinyl-substituted *N*,*N*-dialkyl arylamines[a]



S1-S23 P1-P23



[a] Unless otherwise specified, all reactions were performed in 0.5 mL toluene with 0.2 mmol substrate under N_2; Isolated yields were reported. [b] Reaction temperature, 120 °C. [c] Reaction temperature, 100 °C. [d] Reaction temperature, 140 °C; reaction solvent, *p*-xylene. [e] Reaction temperature, 25 °C. [f] Reaction temperature, 40 °C; 14:1 is the ratio of *cis*/*trans*.

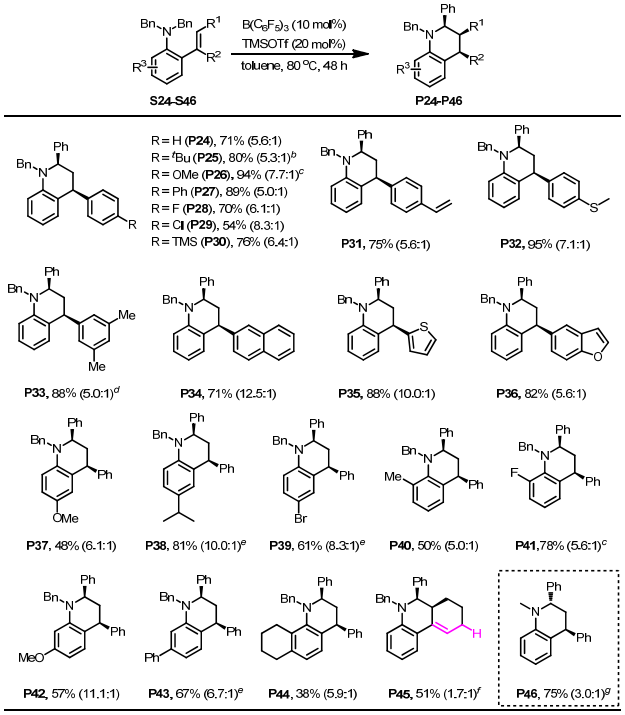
material having a phenyl group at the distal carbon of the olefin underwent a cyclization/dehydrogenation reaction to give **P19** in 38% yield. Changing the *N*-alkyl group from methyl to *n*pentyl (**P20**) and benzyl (**P21**)[17] was feasible. However, changing the naphthylamine to an aniline significantly decreased the reactivity; product **P22** was obtained in only 33% yield. On the contrary, a pyrenamine-derived substrate was highly reactive, giving the corresponding product (**P23**) in 87% yield.

We reasoned that the decreased reactivity of the *N*,*N*-dimethylaniline (**P22**) compared with those *N*,*N*-dimethylnaphthylamines might be due to the diminished steric hindrance around the nitrogen atom, resulting in undesired acid/base coordination. Therefore, in order to improve the reactivity, we changed the *N* alkyl substituent from methyl to benzyl to increase steric bulk around the nitrogen atom and simultaneously to provide more stabilization to the iminium ion by conjugation. To our delight, *N*,*N*-dibenzylanilines were significantly more reactive (Table 3). Anilines with various phenyls at the proximal carbon of the olefin were tolerated, providing products **P24**–**P33** in 54–95% yields with good stereocontrol in favor of the *cis* configuration. Notably, in the reaction of **S31**, a separate olefin group was preserved (**P31**) without undergoing an intermolecular Friedel-Crafts reaction; and in the reaction of **S32**, a coordinative MeS group did not inhibit the reaction. Furthermore, 2-naphthyl (**P34**) and heterocyclic aryls (**P35** and **P36**) were compatible substituents. Various substituents on the aniline ring were also tested. The presence of *para* (**P37**–**P39**), *ortho* (**P40**, **P41**) and *meta* (**P42**, **P43**) substituents was allowed, giving the cyclization products in 48–81% yields. A staring material with a fused carbocyclic structure was reactive, giving **P44** in 38% yield. Moreover, same as the reaction with **P18**, the double bond migration occurred with a substrate having a conjugated diene, generating **P45** in 51% yield and 1.7:1 diastereomeric ratio. An *N*-benzyl-*N*-methylaniline underwent cyclization selectively at the benzyl side, giving **P46** in 75% yield with the *trans* isomer as the major diastereomer.[18]

We then investigated the reaction mechanism by several control experiments (Scheme 2). Firstly, we subjected the deuterium-labelled *N*,*N*-dimethylnaphthylamine **S1-[D6]** to the standard reaction conditions (Scheme 2a), the corresponding product was obtained in 46% yield with deuterium exclusively transferred to the benzylic position, which is consistent with the proposed mechanism shown in Scheme 1c. The significantly diminished yield compared to the reaction of non-deuterated **S1** is indicative of a large kinetic isotope effect, which suggests that either the hydride abstraction from α-carbons or the hydride addition to cyclic benzylic cations is probably the rate-determining step. To look into the details, we performed two crossover experiments. One experiment was done by subjecting a 1:1 mixture of **S10** and **S1-[D6]** to the reaction conditions (Scheme 2b). It was observed that significant exchange of H/D occurred at α-carbons and benzylic carbons in the obtained cyclization products. This result suggests that the hydride abstraction is reversible, and the resulting borohydrides are not confined to their parent ion pairs and would freely react with iminium ions and cyclic benzylic cations produced from other molecules. Moreover, the ratios of H to D at α-carbons of these products were close to 1, but the ratios of H to D at benzylic carbons were relatively large. Therefore, the hydride abstraction and its reverse reaction should be relatively facile while the hydride addition to cyclic benzylic cations is highly possibly the rate-determining step.

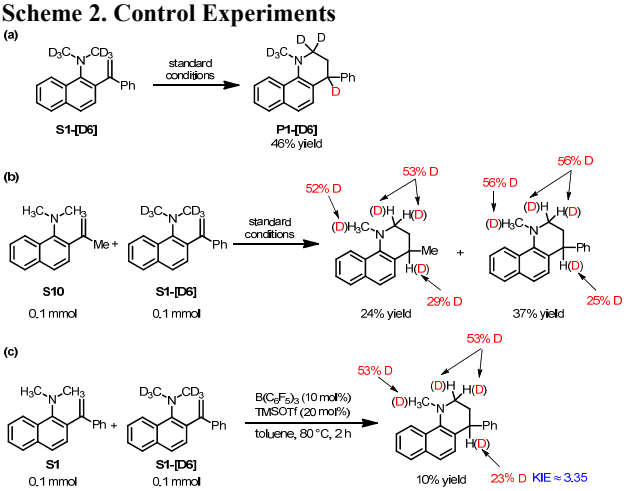
We subsequently performed a similar crossover experiment using **S1** and **S1-[D6]** with a shortened reaction time of 2 h (Scheme 2c). At low conversions, the ratio of H to D at the benzylic carbon was 77:23, giving an approximate KIE value of 3.35, which is in agreement with the hydride addition as the rate-determining step.[19]

Table 3. Investigation of vinyl-substituted *N*,*N*-dibenzylanilines[a]



[a] Unless otherwise specified, all reactions were performed in 1.0 mL toluene with 0.2 mmol substrate under N_2; Isolated yields were reported; *cis*/*trans* ratios were given in parentheses. [b] 2.0 mL toluene was used. [c] Reaction temperature, 60 °C. [d] Reaction time, 24 h. [e] Reaction temperature, 90 °C. [f] Reaction temperature, 40 °C. [g] Solvent, *p*-xylene; reaction temperature, 140 °C; *trans*/*cis* = 3.0:1.

Scheme 2. Control Experiments



The role of TMSOTf was then studied. We monitored both reactions of **S1** with and without the addition of TMSOTf (20 mol%) for the first two hours using ^{1}H NMR, and the yield of **P1** was plotted against the reaction time (Figure 1a). The graph

indicates that the reactivity enhancement by TMSOTf is obvious. We hypothesized that the hydride exchange between the borohydride anion $[B(C_6F_5)_3–H]^–$ and TMSOTf might occur to generate small amounts of a pentacoordinate anion $[Me_3Si(OTf)H]^–$,[20] which is a better hydride donor than $[B(C_6F_5)_3–H]^–$ because of the weaker Lewis acidity of TMSOTf, so that the rate-determining hydride addition to the cyclic benzylic cation would be facilitated.[21] To gain experimental evidence, we firstly prepared $[B(C_6F_5)_3–H]^–$ by reacting Et_2NPh with $B(C_6F_5)_3$,[22] whose ^{11}B NMR spectrum gave a characteristic doublet signal at δ -23.4 (d, J = 77.5 Hz) due to B–H coupling. After the addition of 1 equiv. of TMSOTf, this signal became a broad singlet, indicating the hydride exchange between $[B(C_6F_5)_3-H]^–$ and TMSOTf might have occurred (Figure 1b).

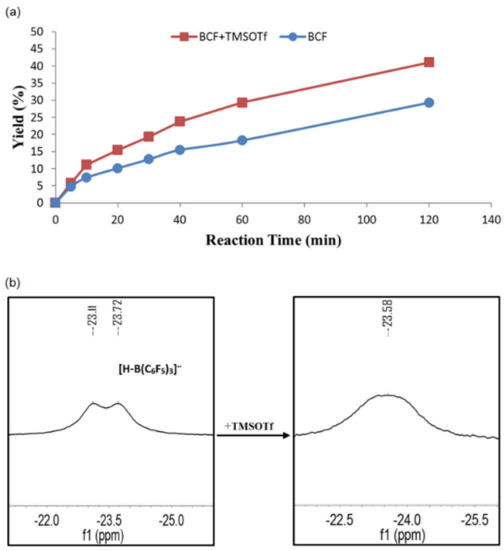


Figure 1. (a) Yield of **P1** versus reaction time for reactions with (red) and without (blue) TMSOTf, (b) ^{11}B NMR spectra (128 MHz, 25 ºC, C_6D_6) of $[B(C_6F_5)_3-H]^–$ before (left) and after (right) the addition of TMSOTf.

In summary, we have developed a $B(C_6F_5)_3$-catalyzed hydride-transfer-induced cyclization reaction of vinyl-substituted *N*,*N*-dialkyl arylamines. The use of $B(C_6F_5)_3$ as a transient hydride acceptor has enabled the cyclization of substrates without an acceptor unit. Moreover, this protocol features broad substrate scope and provides easy acess to various synthetically useful *N*-heterocyles. Further studies aiming at extending the reaction to other hydride donors (e.g. α-C–H bonds adjacent to an oxygen atom) as well as developing enantioselective variant using a chiral borane catalyst are under way in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental Procedures, characterizations of new compounds, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*xcwang@nankai.edu.cn

ORCID

Xiao-Chen Wang: 0000-0001-5863-0804

Author Contributions

#These authors contributed equally.

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(21) The use of a weaker Lewis acid as co-catalyst to facilitate hydride delivery has been described and studied by Paradies, see Ref 14a.

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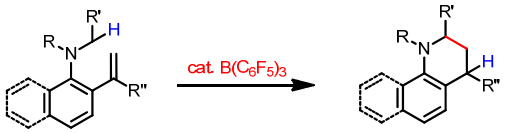
TOC Artwork



- metal and oxidant-free C-H functionalization
- $B(C_6F_5)_3$ as a transient hydride acceptor