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ARTICLE

Organoborohydride-Catalyzed Chichibabin-Type C4-Position Alkylation of Pyridines with Alkenes Assisted by Organoborane

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The first $NaBEt_3H$-catalyzed intermolecular Chichibabin-type alkylation of pyridine and its derivatives with alkenes as the latent nucleophiles is presented with the assistance of BEt_3, and a series of branched C4-alkylation pyridines, even highly congested all-carbon quaternary center-containing triarylmethanes can be obtainned in a regiospecific manner. Therefore, the conventional reliance on high cost and low availability transition metal catalysts, prior formation of *N*-activated pyridines, organometallic reagents, and extra oxidation operation for the construction of C–C bond at the C4-position of the pyridines in previous methods are not required. The corresponding mechanism and the key roles of organoborane were elaborated by the combination of H/D scrambling experiments, ^{11}B NMR studies, intermediate trapping experiments and computational studies. This straightforward and mechanistically distinct organocatalytic technology not only opens a new door for the classical but still far less well-developed Chichibabin-type reaction, but also sets up a new platform for the development of novel C–C bond-forming methods.

Introduction

The development of direct C–C bond-forming reactions of pyridine and its derivatives is of paramount importance, because these motifs are among the most important heterocyclic structural skeletons and exist diffusely in a large number of natural products, agrochemicals, FDA approved drugs and functional materials.[1] Therefore, numerous of methods,[2] including traditional electrophilic aromatic substitution (S_EAr), nucleophilic aromatic substitution of organometallic reagents (S_NAr),[3] metalation-trapping strategy with the strong base,[2a,d,f] radical-based Minisci-type reactions,[4] and transition-metal-catalyzed C–H bond activation reactions,[5,6] have been well established to predominantly access to a wide range of C2- and C3-positions functionalized pyridine-containing molecules. By comparison, the direct C–C bond-forming at the C4-position of pyridines is far less developed.

Until recently, several highly atom-economical and cost-effective protocols, including the pioneering bimetallic Ni/Al catalysis[7] and subsequent mono-transition-metal catalysis (e.g., Co, Cr, and Y),[8] enabled C4-position selective alkylation and alkenylation of pyridines have been achieved in recent years (Scheme 1 A). More recently, Buchwald and co-workers have pioneeringly disclosed a Cu-catalyzed asymmetric C4-position reductive coupling reaction of pyridines and pyridazines with aryl alkenes through a successive dearomatization/reoxidation process.[9a] In addition, Shi et. al. also reported an unprecedented Ni-catalyzed intramolecular asymmetric C–H cyclization of pyridines with alkenes.[10] In spite of these significant advances, some limitations, such as no method enabling to generate all-carbon quaternary centers so far, relying on the non-environmentally benign and undesirable in pharmaceutical industry transition metal catalysts and frequently accompanying some undesired side reactions such as *β*-hydride elimination, indicated that the development of transition metal free C4-position C–C bond-forming reaction of pyridines is in high demand.

The Chichibabin amination reaction,[11a] which undergoes a C2-position addition of the amine anion to pyridine with the aid of the coordination of pyridine to the sodium cation, followed by an elimination of NaH to form 2-aminopyridine, provided a straightforward and alternative strategy for the synthesis of functionalized pyridines under transition metal free conditions. Although this approach has been established more than one hundred years, the analogous examples have rarely been reported to date, and moreover, the strongly basic organolithium reagents as nucleophiles are indispensable in these conversions (Scheme 1 B).[11b,c] Further, the more challenging direct construction of C–C bond at the C4-position by this method is still unexplored to date. The major issues for the sluggish progress in this field might ascribe to: 1) the inherently low electrophilicity of pyridines; 2) the requirement of strongly basic organometallics as nucleophiles that could result in competitive deprotonation/metalation; 3) and the reluctant elimination of hydride from the resulting $σ^H$ adducts to provide pyridine cores in these processes. Indeed, almost all of these nucleophilic aromatic substitution of hydrogen (S_N^H)

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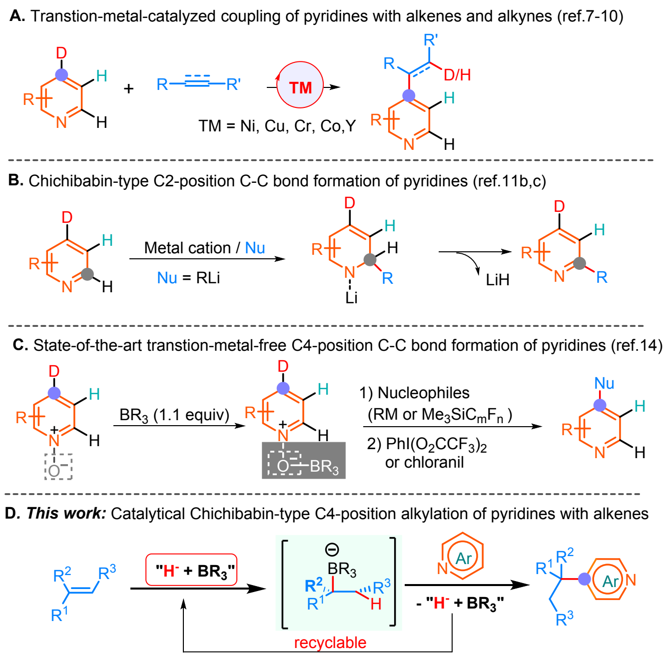

Scheme 1 Direct C4-position C–C bond-forming of pyridines and Chichibabin-type transformations

proceeded through departure of a proton via oxidative or eliminative pathway rather than departure of a hydride anion so far.[12] To surmount these challenges, oxidative Chichibabin-type two-step strategies (nucleophilic addition followed by oxidative aromatization) for mainly access to C2-position functionalized pyridine derivatives have been developed in recent years.[13] Recently, by introduction of the sterically bulky Lewis acid to precisely control the regioselectivity, two examples for direct C4-position C–C bond construction with perfluoroalkylsilanes, Grignard, and organozinc reagents as nucleophiles have also been successfully disclosed by Kanai, and Knochel, respectively (Scheme 1 C).[14] Despite these advances, the presynthesis of activated pyridine salts, organometallics and extra oxidation process are generally necessary. Furthermore, the transition metal free catalytic version of Chichibabin-type reaction has hitherto never been demonstrated but is highly desirable, especially for directly employing pyridines and readily available and bench-stable alkenes as feedstocks.

As a result of our continued interested in hydrofunctionalization of alkenes and alkynes,[15] herein, we report an unprecedented $NaBEt_3H$-catalyzed Chichibabin-type C4-position alkylation of pyridines with alkenes as the latent nucleophiles under the assistance of BEt_3, wherein the conventional transition metal catalyst,[4-10] prior formation of *N*-activated pyridines,[2e,h,13,14] organometallic regents,[2a-d,h,3,11a-d,14] and the extra oxidation operation[9,14] were not required. Therefore, this method provides a convenient and straightforward strategy to access an array of synthetic important diarylmethanes and more challenging all-carbon quaternary carbon center-containing triarylmethanes in a perfect atom-economy manner (Scheme 1 D).

Results and discussion

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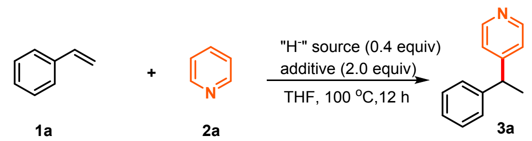
Optimization of reaction conditions

We initially selected styrene **1a** and pyridine **2a** as the pilot substrates. After some trials, we delightedly found that the reductive cross-coupling reaction in the presence of $NaBEt_3H$ as hydride source with BEt_3 as an additive indeed occurred, and provided the C4-position selective branched product **3a** in 90% yield (Table 1, entry 1). Other hydride sources, such as $KBEt_3H$, $LiBEt_3H$, LiB^sBu_3H, NaH and $LiAlH_4$, were also effective "H^-" suppliers, providing **3a** in the range of 34 to 90% yields (Table 1, entries 2-6). Considering the reported significant effect of Lewis acid in the reactivity profile and regioselectivity control of six-membered heteroaromatic compounds,[7,10,14] we subsequently evaluated various Lewis acids. Experimental results showed that B(*n*-Bu)$_3$ exhibited comparable reactivity to BEt_3, while other Lewis acids including $B(O^iPr)_3$, $Al(O^iPr)_3$ and $AlMe_3$ led to the substantial decrease the yields (Table 1, entries 7-10). Likewise, lowering the loading of either "H^-" supplier or BEt_3 also resulted in markedly decreased the yield (Table 1, entries 11-12). In addition, control experiments revealed that both $NaBEt_3H$ and BEt_3 were necessary for this transformation to occur (Table 1, entries 13-14). Remarkably, combination of catalytical amount of LiB^sBu_3H and B^sBu_3 instead of $NaBEt_3H$ and BEt_3 also showed excellent reactivity profile and the branched coupling product **3a** was afforded in excellent yield (Table 1, entry 15). Unfortunately, we found that this reaction condition

Table 1 Optimization of reaction conditions[a]



1a **2a** **3a**

entry	"H^-" source	additive	Yield (%)[b]
1	$NaBEt_3H$	BEt_3	90
2	$KBEt_3H$	BEt_3	79
3	$LiBEt_3H$	BEt_3	80
4	LiB^sBu_3H	BEt_3	64
5	NaH	BEt_3	90
6	$LiAlH_4$	BEt_3	34
7	$NaBEt_3H$	B(*n*-Bu)$_3$	89
8	$NaBEt_3H$	$B(O^iPr)_3$	20
9	$NaBEt_3H$	$Al(O^iPr)_3$	15
10	$NaBEt_3H$	$AlMe_3$	35
11[c]	$NaBEt_3H$	BEt_3	73
12[d]	$NaBEt_3H$	BEt_3	15
13	-	BEt_3	0
14	$NaBEt_3H$	-	0
15[e]	LiB^sBu_3H	B^sBu_3	95

[a]Reaction conditions: **1a** (0.75 mmol, 1.5 equiv), **2a** (0.5 mmol), $NaBEt_3H$ (0.2 mmol), BEt_3 (1.0 mmol) in dry THF (1 mL) at 100 °C under N_2 atmosphere. [b]Yields were determined by ^1H NMR spectroscopy of the crude mixture, using CH_2Br_2 as internal standard. [c]30 mol% $NaBEt_3H$ was used. [d]1.0 equiv BEt_3 was used. [e]20 mol% LiB^sBu_3H and 10 mol % B^sBu_3 were used.

exhibited narrow substrate scope. It is worth noting that all the reactions occurred at the 4-position of pyridine and 2-position alkylated pyridine was not observed.

Substrate scope

With these optimized reaction conditions in hand, we then examined the substrate scope of this $NaBEt_3H$-catalyzed Chichibabin-type alkylation of pyridines. As illustrated in Scheme 2A, an array of styrenes bearing a variety of functional groups, including -alkyl, -aryl, $-OCH_3$, $-OSiR_3$, $-SCH_3$, -F, -Cl, -Br, -OCF_3, and -CF_3, could be effectively cross-coupled with pyridine and delivered corresponding products **3a**-**3v** in generally good to excellent yields with exclusive regioselectivities. The styrenes **1l** and **1m** containing silyl ether functional group and a relatively strong acidic benzylic C–H bond, were well- tolerated under this reaction conditions, providing corresponding products **3l** and **3m** in good yields. The accommodation of silyl ether and aryl halides provided more opportunities for further elaborations. In addition, lower reactivities of electron-donating functional group, such as *para*-OMe and -Me substituted styrenes than styrenes bearing electron-withdrawing functional groups (e. g. -F, -Cl, -Br, and -OCF_3,) was also observed, as demonstrated by **3f**, **3i** versus **3p**-**3t, 3v**. Heteroaromatic substituted alkene, a common scaffold in bioactivate relevant targets, was also coupled with pyridine efficiently, furnishing expected product **3w** in 75% yield. 1,4-Divinylbenzene and (-)-menthol-derived styrene could also be converted into corresponding mono-pyridation product **3x** and **3y** in moderate yields. The more steric hindrance α-methyl styrene, which can't be used as the intermolecular coupling partner under the metal catalysis conditions,[7-10] to our delight, was found to be suitable substrate to afford a quaternary carbon center-containing product **3z**. In addition to terminal alkenes, aryl substituted internal alkenes were also compatible and the respective products **3aa** and **3ab** were obtained in good yields. Subsequently, a further study was initiated to explore the substrate scope regarding the pyridines. Various alkyl-, aryl substituted pyridine derivatives could also be effectively alkylated with styrene, giving desired products **3ac-3ah** in the range of 50%-89% yields. Thienyl, methoxyl and synthetically versatile -B(pin) (pin = pinacolate) substituted pyridines, as well as fused pyridine derivatives found also valid substrates for this transformation, delivering the corresponding products **3ai**-**3am**. For *ortho*-substituted pyridines, we noticed that these reactions became sluggish and required increased reaction temperature, which might be attributed to the steric hindrance.

The success with sterically hindered α-methyl styrene as substrate encourages us to examine whether 1,1-diaryl alkenes could be used as the valid coupling components to synthesize structurally more intriguing all-carbon quaternary carbon center-containing triarylmethanes. These compounds are well-known substructures in photochromic agents,[16] leuco dye precursors,[17] materials and medicinal chemistry,[18] whereas that could otherwise be difficult to access.[19] After briefly screening the reaction conditions, to our delight, the alkylation reaction of 1,1-dibenzylethene with pyridine could proceed with relatively lower loading of organoborohydride and milder conditions (30 mol% $NaBEt_3H$, 70 ^oC). The corresponding coupling product **4a** was afforded in 93% yield in a regiospecific manner. Additionally, this reaction could be also performed at room temperature, despite in relatively low yield and requirement of prolonged reaction time (80% yield, 48 h). As illustrated in Scheme 2B, various diversely functionalized 1,1-diarylethylenes, including these aryl groups having alkyl, methoxyl, methylthio, siloxy, silyl, alkenyl, phenyl, boronate, fluoro-, chloro-, naphthyl- and heteroaryl, were found to be valid substrates to furnish the corresponding products **4b**-**4o** in moderate to excellent yields. In addition, some representative examples using NaH as the hydride supplier were also carried out and corresponding expected products were indeed obtained with similar reactivities compared with that of $NaBEt_3H$, as demonstrated by **3a-3d**, **4a-4c**. Additionally, to demonstrate the practicality of this approach, we carried out gram-scale synthesis of products **3a** and **4a** under the optimal reaction conditions (See supporting information for details). There were negligible changes in the chemical yields (88%, 79% yields for **3a** and **4a**, respectively), suggesting that large-scale chemical production might be possible.

Mechanistic investigation

To gain preliminary insight into the mechanism, a series of control experiments were performed. As illustrated in Scheme 3, a series of isotope labeling experiments were carried out firstly. The use of **2a**-d_5 (> 99% D) instead of **2a** reacting with styrene under standard reaction conditions, 0.66 D incorporation at the β-position methyl of the product **5** was observed, which means the C4-pisition D atom of the pyridine indeed participated in the catalytic cycle (eq. 1). In addition, when commercially available $LiAlD_4$ was used as hydride supplier instead of $NaBEt_3H$, the coupling product **6** with 0.48 D at the β-position was obtained and this result suggests the addition of deuterium anion to alkene occurred (eq. 2). Simultaneously, 0.36 D at the *ortho*-position of pyridine core in **6** was observed. To explain this phenomenon, control experiment with 4-phenylpyridine as substrate in the presence of $LiAlD_4$ was performed, and 0.32 D incorporation at the *ortho*-position of 4-phenylpyridine was also observed (See supporting information for details), indicating that a hydrogen/deuterium exchange could be proceeded directly between pyridines and $LiAlD_4$. Moreover, we also conducted the reaction under optimal conditions with both $LiAlD_4$ as hydride source and **2a**-d_5 as substrates, the corresponding deuterated product **7** containing 1.0 D in the methyl group was observed, which clearly reveals again that the newly introduced D atom in methyl group of the product entirely comes from the hydride

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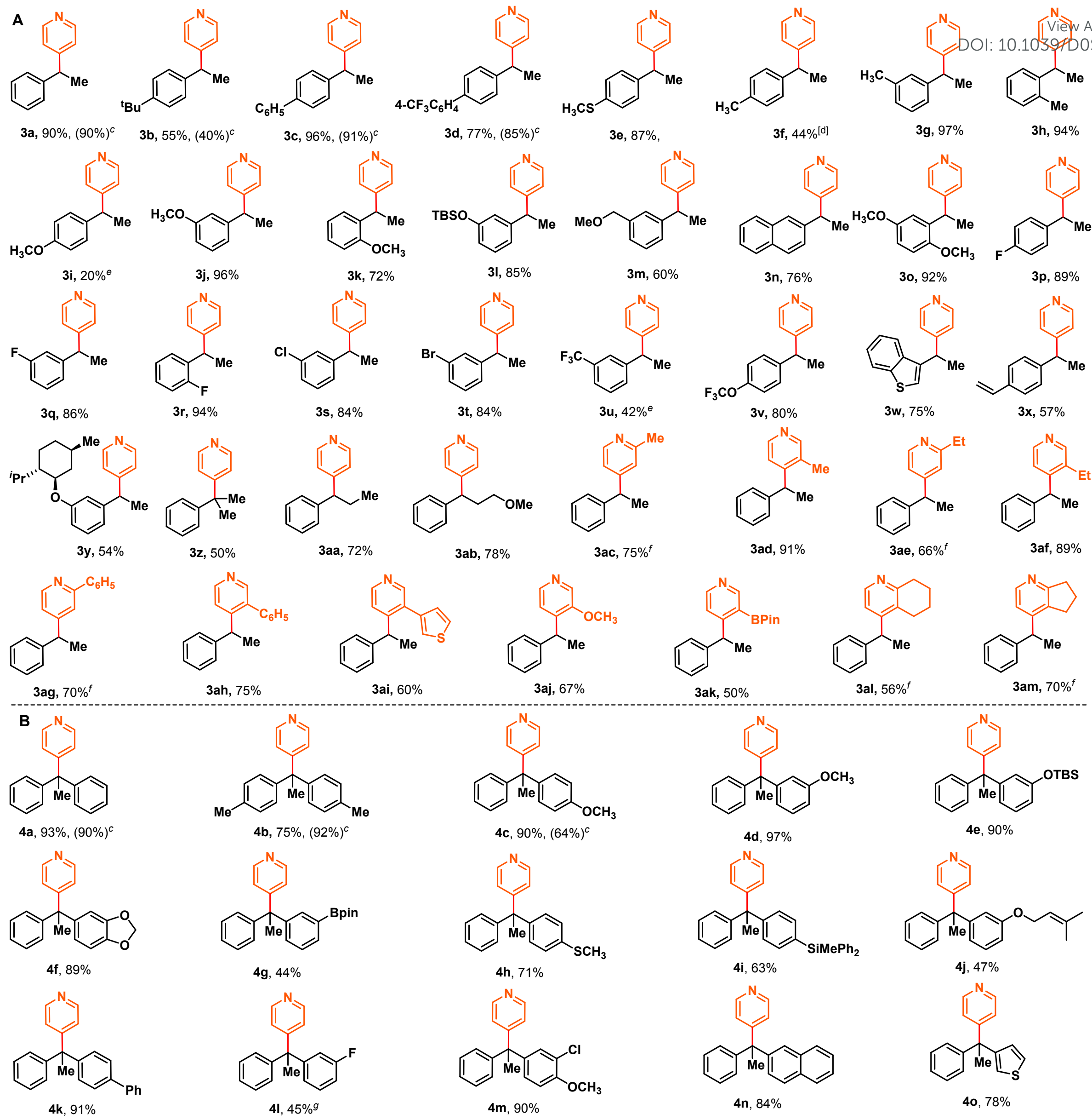
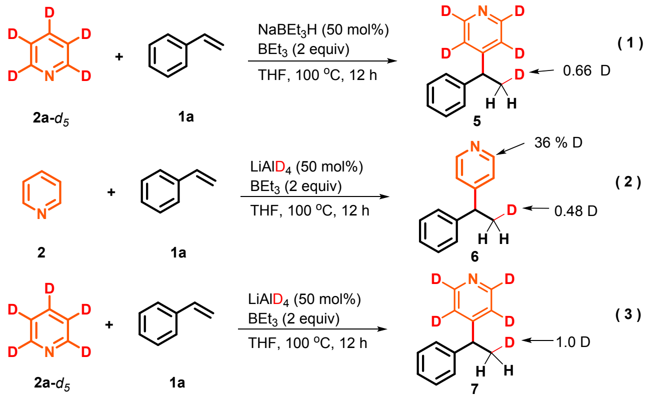


Scheme 2 Substrate scope of alkenes and pyridines.[a,b] [a]Reaction conditions for A: styrenes (0.75 mmol, 1.5 equiv), pyridines (0.5 mmol), $NaBEt_3H$ (0.2 mmol), BEt_3 (1.0 mmol) in dry THF (1.0 mL) at 100 °C for 12 hours under N_2 atmosphere; yield was determined by ^1H NMR spectroscopy of the crude mixture, using CH_2Br_2 as internal standard. [b]Reaction conditions for B: 1,1-diaryl alkenes (0.75 mmol, 1.5 equiv), pyridine (0.5 mmol), $NaBEt_3H$ (0.15 mmol), BEt_3 (1.0 mmol) in dry THF (1.0 mL) at 70 °C for 12 hours under N_2 atmosphere; isolated yields. [c]Using NaH instead of $NaBEt_3H$. [d]24% Alkene was recovered. [e]57% Alkene was recovered. [f]These reactions were carried out at 140 °C. [g]50% Alkene was recovered.

supplier and the *para*-position H atom of pyridine (eq. 3). Collectively, these isotopic labeling experimental results indicate the C4-pisition D atom of the pyridine departed as hydride anion and could then participate in the catalytic cycle. Moreover, several ^{11}B NMR experiments were also conducted to elucidate the possible intermediates in this transformation. As shown in Figure 1A, two peaks were observed from the commercially available $NaBEt_3H$ solution (1.0 M in THF) and confirmed as BEt_3 (δ = 86.5 ppm) and tetraorganoborate anion $[BEt_3H]^-$ (δ = -16.8 ppm), respectively. This experiment indicates that a dissociation equilibrium existed in the $NaBEt_3H$ solution. In addition, the 1 : 1 ratio of pyridine and BEt_3 in THF showed a new peak at 2.8 ppm, assigned as their complex,[20] which means BEt_3-activated pyridine could readily generate and might be involved in this reaction. Moreover, the peak of BEt_3 was completely disappeared that suggests their strong interaction, which might provide the potential clue of using stoichiometric BEt_3 in this Chichibabin-type alkylation reaction. Pleasing, either the mixture of $NaBEt_3H$ and 4-fluorostyrene (1 : 1) or the reaction of pyridine with 4-fluorostyrene under the standard conditions, the same new signal was formed at -15.0 ppm, and was confirmed as tetradentate benzylorganoborate anion species,[21] which means the tetradentate benzylorganoborate anion intermediate is likely involved in this catalytic reaction. Besides, other signals, including tetradentate $[BEt_3H]^-$ and the



Scheme 3 H/D Scrambling experiments.

complex of BEt_3 with pyridine were also observed in the last ^{11}B NMR experiment. In addition, the peaks at 55 and 53.5 in these ^{11}B NMR spectra were likely to be Et_2BOR analogues,[21a] which indicates the decomposition of BEt_3 might occur. To further confirm the intermediate of this transformation, we proposed that the tetraorganoborate anion intermediate might be trapped by an oxidation step to form corresponding alcohol (Figure 1B, top). Indeed, the reaction of 4-phenylstyrene with a stoichiometric quantity of $LiBEt_3H$ in THF at 70 °C, followed by the treatment with an equimolar amount of methanesulfonic acid and oxidation with $NaOH/H_2O_2$, 56% 1-phenylethanol **8** was isolated. This experimental result also provided positive evidence that the tetradentate benzylorganoborate anion species is generated in this $NaBEt_3H$-catalyzed Chichibabin-type alkylation reaction. Moreover, we also investigated the possible

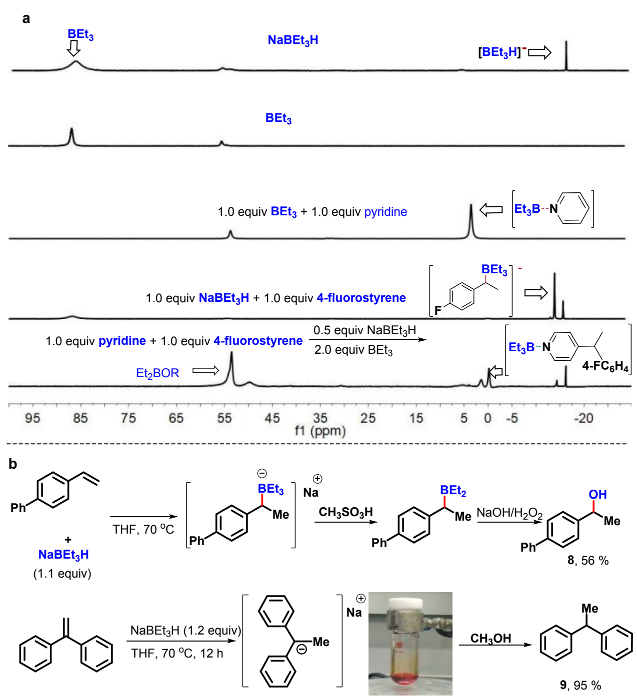


Figure 1. Intermediate investigation experiments

intermediate of the coupling between 1,1-dibenzylethene and pyridine, but the signal of the analogous tetradentate benzylorganoborate anion species was not detected by ^{11}B NMR experiment. Instead, a deep red color was formed immediately when 1.1 equiv. $NaBEt_3H$ was added to the solution of 1,1-dibenzylethene, which suggested 1-sodium-1,1-diphenylethane was likely generated rather than its corresponding organoborate.[22] This probable intermediate was further supported by trapping experiment with MeOH, providing 1,1-diphenylethane **9** in 95% yield (Figure. 1B, bottom).

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To further shed light on the details of this transformation, we conducted density functional theory (DFT) calculations. The calculated free energy profile showed that the lone pair of N atom in pyridine interacts with the empty orbital of B atom of BEt_3 to produce a relatively stable complex **Sub2** with Gibbs free energy change ($\Delta G°$) of –4.1 kcal/mol (Figure 2A). Thus, the **Sub2** directly participates in the reaction. As shown in Figure 2B (yellow line), $NaBEt_3H$ is initially combined with styrene through the electrostatic interaction to form intermediate **1'** (5.1 kcal/mol exergonic), followed by an insertion of hydride ion into C–C double bond process assisted by BEt_3 to generate intermediate **2'** and release the BEt_3 (5.3 kcal/mol, via **TS-1**). Then, **2'** could isomerize to a more stable intermediate **3'** (4.3 kcal/mol exergonic). The following nucleophilic addition of **3'** to **Sub2** occurs via **TS2** to afford intermediate **4'** (20.0 kcal/mol). By contrast, the nucleophilic addition to C2-position of **Sub2** is less favorable with a higher energy barrier of 22.3 kcal/mol (Figure S18). Finally, as Lewis acid the BEt_3 is again involved in the hydride ion transfer to provide the target product **5' (**via **TS-3)** and simultaneously regenerate the $NaBEt_3H$. The hydride ion transfer is the rate-determining step of the whole reaction, which requires a moderate Gibbs activation energy ($\Delta G°^{‡}$) value of 25.0 kcal/mol relative to **3'**. The present calculations are consistent with the experimental results. This reaction can be achieved at a temperature of 373 K. Moreover, we also investigated the hydride ion insertion process without the extra BEt_3 (Figure 2B, black line). Obviously, these results clearly show that the participation of the BEt_3 dramatically accelerates the insertion process and following reaction steps. Actually, the one of key roles of BEt_3 is generation of the stable intermediates **3'** and **4'**, which are more stable than corresponding intermediates **7'** and **8'** and then lead to significantly stabilize the potential energy surface and lower the energy barrier of the rate-determining step. In addition, we have also presented the molecular orbital distributions and energy levels of **3'**, **4'**, **7'** and **8'** in Figures 2b, respectively. The BEt_3 coordination stabilizes the HOMO levels of **3'** and **4'**, respectively, leading the increases in their HOMO-LUMO energy gaps, which makes the intermediate **3'** and **4'** more stable (Figure S17). On the other hand, the experimental phenomenon with 1,1-diaryl alkenes as the alkylating reagents suggested that the tetradentate benzylorganoborate anion species might be not involved in this transformation (Figure 1B, bottom). This observation is further

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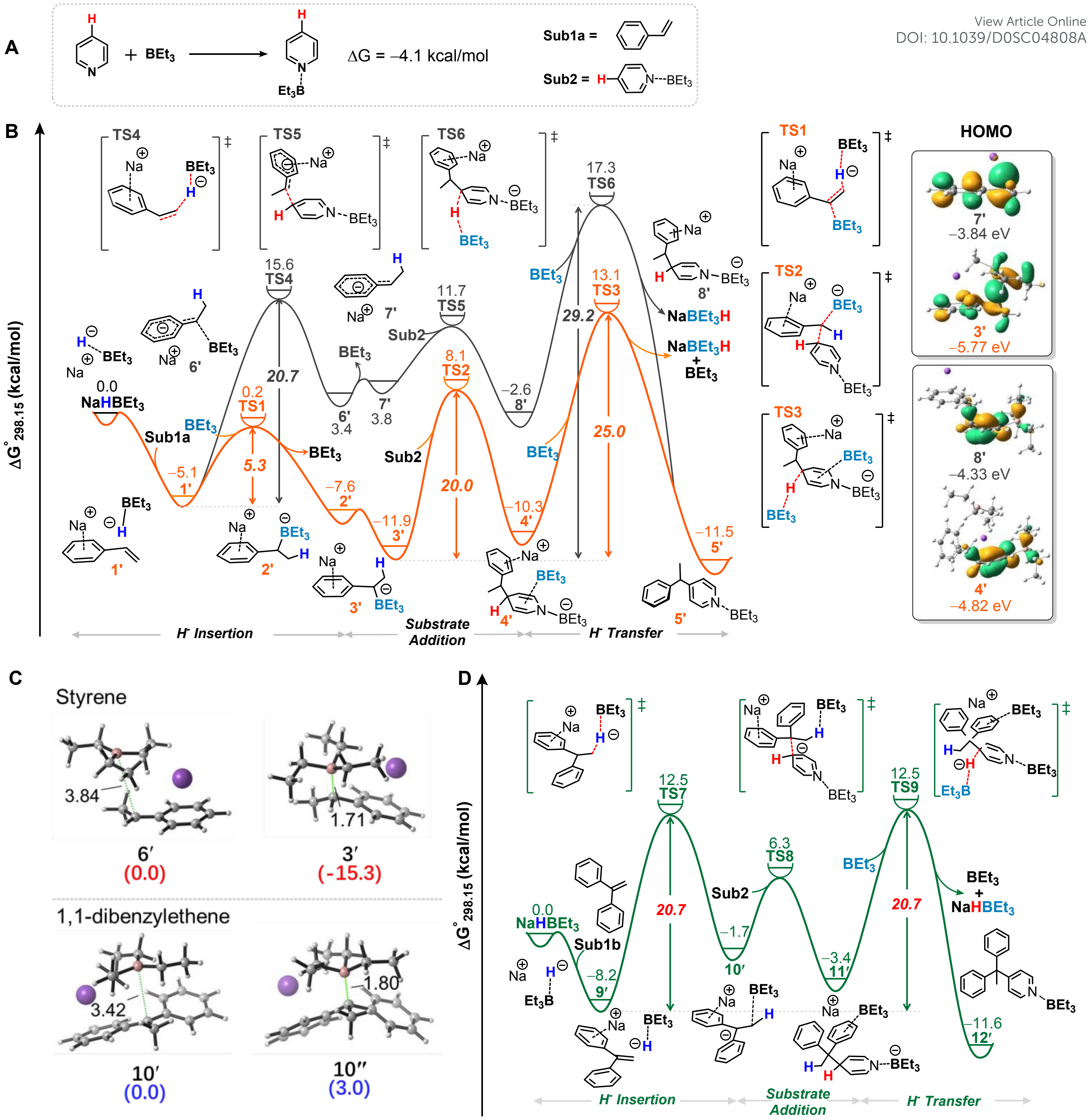
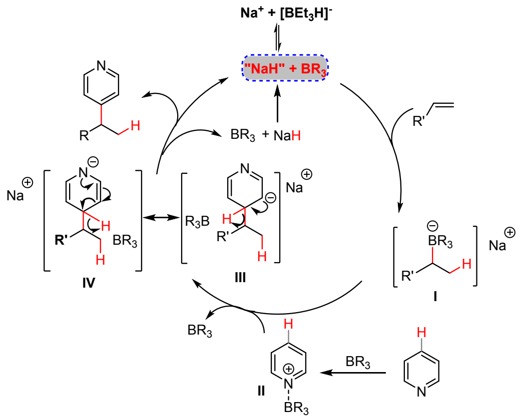


Figure 2. Calculated energy profiles of NaBEt3H-catalyzed alkylation reaction of pyridine with alkene. A, Calculated energy profile of pyridine with BEt3. B, DFT-computed reaction pathway for NaBEt3H -catalysed alkylation of styrene with pyridine. C, The relative Gibbs energies and structures of different C–B interactions between styrene and 1,1-diphenylethene. D, DFT-computed reaction pathway for NaBEt3H -catalysed alkylation of diphenylethene with pyridine

supported by DFT calculations. The formation of C–B bond during this process is energetically disfavored (Figure 2C, bottom, **10’→10”**, 3.0 kcal/mol endergonic). Whereas the C–B bond could significantly stabilize similar intermediate **6’** in the alkylation of pyridine with styrene (Figure 2C, top, **6’ →3’**, 15.3 kcal/mol exergonic). Moreover, the Gibbs energy profiles of the alkylation between 1,1-diphenylethene and pyridine was also provided (Figure 2D), and calculated result showed that the Gibbs activation energy of the rate-determining step is 20.7 kcal/mol relative to **9’**, lower than that of styrene (25 kcal/mol). This is also consistent with the experimental results.

On the basis of above experimental observations and computational studies, a plausible mechanism of this $NaBEt_3H$-catalyzed Chichibabin-type alkylation reaction is depicted in Scheme 4. An addition of the hydride catalyst to alkene could occur firstly in the presence of organoborane, furnishing “organoborate” intermediate **I**,[22] which has been recognized as a class of particularly versatile synthetic intermediate in organic synthesis.[23] Intermediate **I** could then undergo an intermolecular regioselective addition to organoborane-activated heteroarenes **II** leading to σ^{H}-adduct intermediate **III** and **IV**. Finally, an elimination of hydride anion, a Chichibabin-type-like process,[11] could occur with the assistance of organoborane to furnish the expected alkylation product simultaneously regenerate the hydride catalyst to participate the next catalytic cycle. For the mechanism of alkylation of pyridine with 1,1-diaryl alkenes, according to the experimental phenomenon and computational studies, free 1,1-diphenyl stabilized carbon anion intermediate rather than its tetradentate benzylorganoborate species might react directly with intermediate **II** to provide the product **4** and regenerate the hydride catalyst. The relatively high loading of $NaBEt_3H$ and BEt_3 under the present catalytic conditions might be ascribed to the ineluctable trace amount of water in the reaction, the strong interaction of BEt_3 with pyridine cores and the decomposition of BEt_3.



Scheme 4 Plausible mechanism.

Conclusions

In summary, we have developed the first $NaBEt_3H$-catalyzed Chichibabin-type alkylation of pyridines with alkenes in the presence of BEt_3 in a perfect atom-economical and regiospecific fashion. This method allows for facile access an array of branched C4-alkylation pyridines, without the requirement of conventional transition metal catalyst, prior formation of *N*-activated pyridines, organometallic reagents, and oxidation process. Moreover, the highly congested all-carbon quaternary center-containing triarylmethanes could also be efficiently synthesized. The corresponding mechanism and the key roles of organoborane were also elaborated by the combination of H/D scrambling experiments, ^{11}B NMR studies, intermediate trapping experiments and computational studies. This novel and mechanically complementary methodology could not only open a new door for the classical but still infantile Chichibabin-type reaction, but also set up a new platform for the development of novel C–C bond-forming methods. Explorations of the potential of this organoborohydride catalysis for C–C bond formations is currently underway in our lab.

Conflicts of interest

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There are no conflicts to declare.

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