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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 17 Feb 2017

Metal-Free Synthesis of C-4 Substituted Pyridine Derivatives Using Pyridine-boryl Radicals *via* a Radical Addition/Coupling Mechanism: A Combined Computational and Experimental Study

Guoqiang Wang,[a] Jia Cao,[a,c] Liuzhou Gao,[a] Wenxin Chen,[b] Wenhao Huang,[b] Xu Cheng,[b,d,*] and Shuhua Li[a,*]

[a]Key Laboratory of Mesoscopic Chemistry of Ministry of Education, Institute of Theoretical and Computational Chemistry, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, P. R. China

[b]Institute of Chemistry and Biomedical Sciences, Jiangsu Key Laboratory of Advanced Organic Material, School of Chemistry and Chemical Engineering, Nanjing University 210023, P. R. China

[c]College of Chemistry and Chemical engineering, Yan'an University, Yan'an 716000, P. R. China

[d]State Key Laboratory of Elemento-organic Chemistry, Nankai University, P. R. China

Supporting Information Placeholder

ABSTRACT: Density functional theory investigations revealed that the pyridine-boryl radical generated *in situ* using 4-cyanopyridine and bis(pinacolato)diboron could be used as a bifunctional "reagent", which serves as not only a pyridine precursor but also a boryl radical. With the unique reactivity of such radicals, 4-substituted pyridine derivatives could be synthesized using α, β-unsaturated ketones and 4-cyanopyridine *via* a novel radical addition/C-C coupling mechanism. Several controlled experiments were conducted to provide supportive evidence for the proposed mechanism. In addition to enones, the scope could be extended to a wide range of boryl radical acceptors, including various aldehydes and ketones, aryl imines and alkynones. Lastly, this transformation was applied in the late-stage modification of a complicated pharmaceutical molecule.

1. INTRODUCTION

Organoboron reagents are commonly described as reactive radical precursors in many organic reactions.[1] For example, organoboranes are usually used as radical initiators or for generating carbon radicals.[2, 3] Lewis-borane complexes, especially N-heterocyclic carbene boranes[4] can be readily used in radical reductive reactions[4a,b] and as co-initiators[4e] in photopolymerizations. In these systems, the radical reactions always occur *via* an innate chain mechanism.

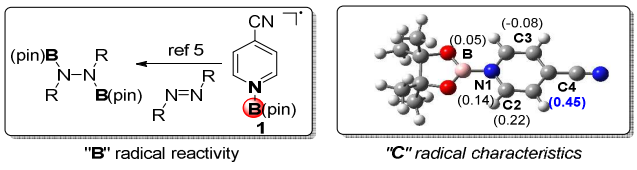


Figure 1. The dual characteristics of pyridine-boryl radical (1). Left: B radical reactivity; Right: calculated spin density distribution of 1 (at the UM06-2X/6-31G(d,p) level).

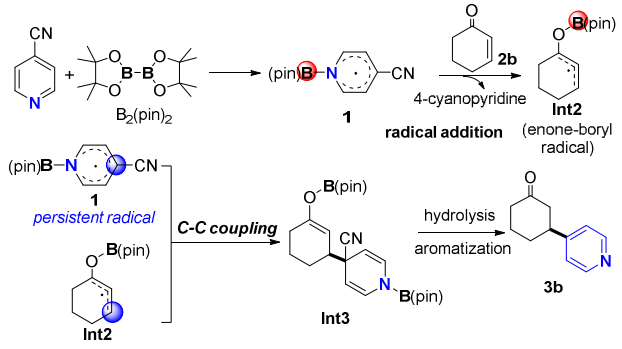
Recently, we reported that the B-B bond of bis(pinacolato)diboron ($B_2(pin)_2$) could be homolytically cleaved to generate a pyridine-boryl radical (**1**) through a cooperative catalysis involving two 4-cyanopyridine molecules.[5] The radical **1** could react as a base-stabilized boryl radical in the catalytic reduction of azo-benzene compounds (Figure 1, left).[5, 6] Furthermore, our theoretical calculations (see Figure S1 for details) suggest that the spin density in **1** is mainly localized on C_4 rather than on B (Figure 1, right).[7, 8] Thus, the radical **1** may act as a carbon radical in some reactions. The *in situ* generated pyridine-boryl radical (**1**) from 4-cyanopyridine and $B_2(pin)_2$ may provide opportunities for the development of other new reactions, in particular reactions that lead to the synthesis of pyridine derivatives *via* the carbon-carbon radical coupling reactions.

From a synthetic view, the synthesis of diverse functionalized pyridine derivatives is of particular interest, given that the pyridine core is an important class of structural unit found in pharmaceutical compounds[9] and functional materials.[10] Transition metal catalysts have played privileged roles in the synthesis of pyridine derivatives, including the direct C-H bond activation, radical reactions, and cross-coupling reactions.[11-13] On the other hand, the use of organometallic reagents such as organolithium and Grignard reagents, provides a transition-metal-free strategy for synthesis of 2- or 4-substituted pyridines.[14-16] In these systems, preactivated pyridines or stoichiometric amounts of Lewis acids are usually required.[16] Given the considerable importance of pyridine derivatives, it is highly desirable to develop other effective strategies for the synthesis of pyridine derivatives.

Thus, we speculate that the pyridine-boryl radical (**1**) could be used as a precursor to synthesize the 4-substituted pyridines *via* a persistent radical cross-coupling mechanism.[17, 18] α, β-unsaturated ketones (enones) are selected as functionalization reagents due to their high boryl radical stabilization

energies. The proposed mechanism is shown in Scheme 1. First, the homolytical cleavage of the B-B bond of $B_2(pin)_2$ by 4-cyanopyridine generates boryl radical **1**;[5] then the boryl radical addition from **1** to enone **2b** generates a new radical intermediate (**Int2**); and then the radical cross-coupling reaction of **1** and **Int2** generates a dearomitized pyridine intermediate (**Int3**). Subsequently, the hydrolysis and aromatization of **Int3** lead to 4-substituted pyridine (**3b**). In this process, the radical **1** generated in situ could be considered as a bifunctional "reagent", which not only serves as a pyridine precursor but also acts as a boryl radical. Herein, we report a combined computational and experimental study to show that the above proposed strategy provides a metal-free approach for synthesis of 4-substituted pyridine derivatives. In addition to α, β-unsaturated ketones, a broad range of some other commercially available compounds, for example, aldehydes, ketones, alkyne ketones and aryl imines can be used as functionalization reagents.

Scheme 1. Speculated mechanism for the synthesis of 4-substituted pyridine using the pyridine-boryl radical (1) *via* radical addition/coupling pathway.

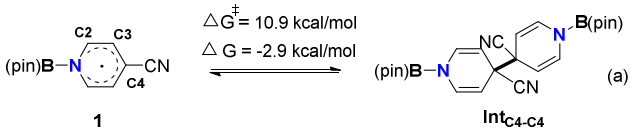


2. RESULTS AND DISCUSSIONS

2.1 Computational investigations

Initially, we performed unrestricted density functional theory (DFT) calculations with the M06-2X funtional[19] to investigate the thermodynamic change for the homo-coupling of radical **1** (see Supporting information for computational details). As displayed in Scheme 2, the formation of the dimeric species of **1**, $\mathbf{Int}_{C4\text{-}C4}$, via C_4-C_4 bond formation is exothermic by 2.9 kcal/mol with a barrier of 10.9 kcal/mol, suggesting the dimerization reaction of radical **1** is reversible (See Figure S2 in supporting information for other possible dimerization pathways). The existence of the dimeric species of **1** was further verified by ^{1}H NMR and HRMS studies (See Figure S8 in Supporting information). Thus, the radical **1** might be considered as a persistent radical for subsequent cross-coupling reactions.

Scheme 2. Calculated free energy change (ΔG) for the dimerization reaction of pyridine-boryl radical 1.



For the model reaction between the radical **1** and 2-cyclohexenone (**2b**), we have computationally investigated the energetics of the proposed mechanism. The free energy profile is shown in Figure 2 (see supporting information for details). First, the coordination of 2-cyclohexenone to the boron atom of the pyridine-boryl radical **1** generates a tetra-coordinated boryl intermediate (**Int1**) *via* **TS1**, with a barrier of 10.6 kcal/mol. Then, the dissociation of 4-cyanopyridine from **Int1** yields an enone-boryl radical (**Int2**). Due to the formation of a strong B-O bond and the resonance stabilization effect, this radical intermediate is only 1.8 kcal/mol in free energy above the separated **1** and 2-cyclohexenone, and the corresponding barrier is 8.4 kcal/mol. These results suggest that the formation of a new radical (**Int2**) with enone (**2b**) *via* the boryl radical addition is possible, and **Int2** may be consider as a transient radical for subsequent cross coupling reactions. Then, the C-C coupling reaction between radical **1** and **Int2** at β-carbon atom of **Int2** generates a 1,4-addition intermediate (**Int3**) *via* **TS3** (Figure 2, blue line), with a barrier of 11.5 kcal/mol, and the whole process is exothermic by 20.5 kcal/mol (with respect to the radical **1** and reactant **2b**). In addition to the 1, 4-addition pathway, the radical coupling reaction between **1** and **Int2** can also generate a 1,2-addition intermediate (**Int4**) *via* **TS4**, with a lower barrier of 10.5 kcal/mol (Figure 2, red line). However, the generation of **Int4** is only exothermic by 18.6 kcal/mol (with respect to the radical **1** and reactant **2b**). A possible equilibrium between 1,4-addition and 1, 2-addition pathway is suggested in Scheme 3. The dissociation barrier for the carbon-carbon bond of **Int4** is 29.1 kcal/mol, suggesting a reversible dynamic process for the 1,2-addition pathway. Thus, we speculate that the 1,4-addition pathway would be a thermodynamically favorable pathway, and the 1,4-addition product **3b** might be the major product.

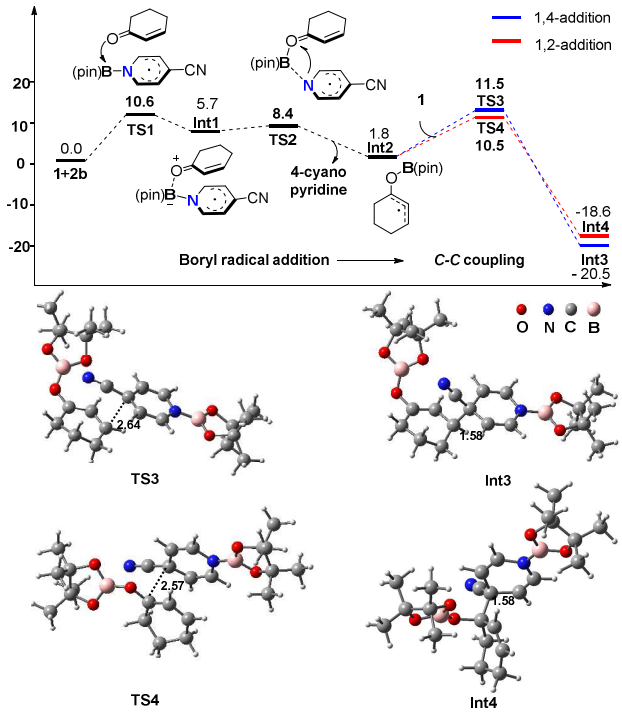
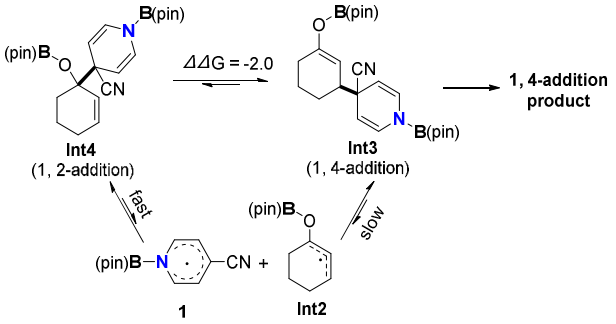


Figure 2. Computed Gibbs free energy (in kcal/mol) profile for the reaction between the radical **1** and 2-cyclohexenone (**2b**) in benzene. The blue line denotes the 1,4-addition pathway and the red line corresponds to the 1,2-addition pathway. Distances are in Å.

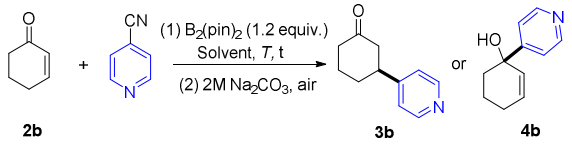
Scheme 3. A possible equilibrium between 1,4-addition and 1,2-addition pathway (Energy is in kcal/mol).



2.2 Experimental studies

In order to validate the predicted reactivity of the pyridine-boryl radical (**1**) and its reaction with enones, we conducted initial reactions using 2-cyclohexenone (**2b**) as the substrate (Table 1). Preliminary attempts generated the pyridine addition product in 59% yield and with a mixture of regioisomers (**3b**/ **4b** = 42%:17%, entry 1). After further optimization of the reaction conditions, methyl *tert*-butyl ether (MTBE) was found to be a suitable solvent for this reaction, the reaction yield and regioselectivity increased to 81% and 62:19, respectively, at 70 °C in the presence of 1.5 equivalent 4-cyanopyridine (entry 10). One can see from Table 1 that the reaction temperature is important for improving the regioselectivity (entries 8-10). At room temperature and 40°C, **3b** and **4b** were formed with lower 1,4-addition/1,2-addition selectivity.

Table 1. Optimization of the reaction conditions.[a]

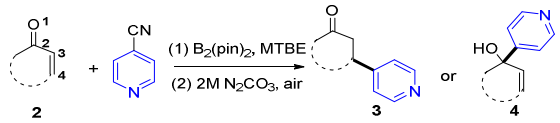


Entry	t (h)	*T* (°C)	Solvent	Ratio (3b/4b)[b]
1	16	40	EA	42%:17%
2	16	40	CH_2Cl_2	19%:7%
3	16	40	CH_3CN	28%:8%
4	16	40	THF	42%:11%
5	16	40	Toluene	38%:19%
6	16	40	Pentane	40%:18%
7	16	40	MTBE	43%:17%
8[c]	24	40	MTBE	61%:23%
9[c]	48	r.t.	MTBE	55%:20%
10[c]	24	70	MTBE	62%:19% (70%, 3.7:1)[d]

[a]Reaction conditions: 2-cyclohexenone (0.2 mmol), 4-cyanopyridine (0.2 mmol), $B_2(pin)_2$ (0.24 mmol), solvent (1.0 mL). [b]Yields and the ratio of **3b** to **4b** were determined by ^{1}H NMR analysis of the crude reaction mixture with CH_3NO_2 as an internal standard. [c]0.3 mmol 4-cyanopyridine was used. [d] Isolated yield.

With cyclopent-2-en-1-one (**2a**) and cyclohept-2-en-1-one (**2c**) as the substrates (Table 2), 1,4-addition also occurred more favorably than 1,2-addition at 70°C, as observed for **2b**. These results suggest that 1,4-addition is thermodynamically favorable, which is consistent with our DFT calculations.

Table 2. Temperature effect on the product distribution.[a]



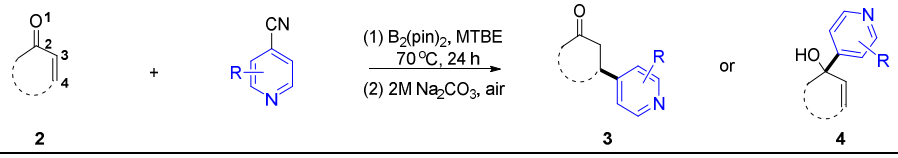
Substrates	Yield (ratio, 3:4) (*T*= 70 °C)	Yield (ratio, 3:4) (*T*= r.t.)
 (**2a**)	43% (1.8:1)[b, e]	50% (1:1)[c, e]
 (**2c**)	62% (>20:1)[d]	59% (4:1)[c]

[a]Reaction conditions: enones (0.2 mmol), 4-cyanopyridine (0.3 mmol), $B_2(pin)_2$ (0.24 mmol), MTBE (1.0 mL), isolated yield refer to the combined yield of all isomers, the ratio was determined by ^{1}H NMR analysis of the crude mixture. [b]The reaction time was 24h. [c]The reaction time were 48h. [d]The reaction time was 36h. [e]The ratio was determined by GC-MS analysis of the crude mixture due to the peak overlap in the ^{1}H NMR spectrum.

With the optimized condition in hand (Table 1, entry 10), we explored the radical addition/coupling reaction with various combinations of enones and pyridines (Table 3). At first, cyclic enones with different patterns of substitution were evaluated. It was found that even with β-methyl group the 1,4-addition products were generated with moderate selectivity in the case of **3e**-**3f**. Dimethyl substituted cyclohexeone **2g** reversed the selectivity and the 1,2-addition product **4g** became the major product. **2h** with α-phenyl group gave the 1, 4-addition **3h** in trans configuration only. The reaction of acetylcyclohexene-2 (**2i**) and 4-cyanopyridine produced a mixture of **3i** and **4i** in a 1.8:1 ratio. The more bulky substrate **3j** offered only the 1,4-addition product **3j** in 62% yield with trans configuration as predominant species. When β-ionone **2k** was adopted, the corresponding 1, 2-addition product **3k** could be prepared in 59% yield. Subsequently, a variety of acyclic enones were subjected to this transformation. Enone **2l** gave the 1,4-addition product **3l** with a ratio of 3.6:1 to its 1,2-addition product **4l**. By introducing a phenyl group into the enone molecule, complete regioselectivity of 1,4-addition could be achieved and **3m**-**3o** could be furnished in moderate to acceptable yield. In turn, several dimethyl acyclic enones were screened with standard condition. The 1,4-addition could offer the pyridine substituted with quaternary carbon center as the major product for **3q** and **3r** and the only product for **3s**-**3u**.

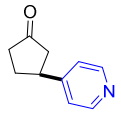
To obtain more functionalized pyridine derivatives, we surveyed the reactions of 2-cyclohepten-1-one with other 4-cyanopyridine derivatives, as shown in Table 3. 4-cyanopyridines bearing substituents at C-3 position, such as F, Cl, and methyl, provided 1,4-addition products **3v**, **3w** and **3x** in 60%, 63% and

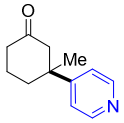
Table 3. Substrate scope.[a]

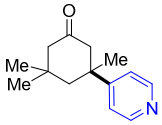


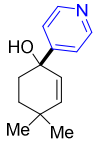
2 3 4

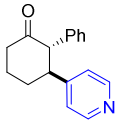
A. Enones

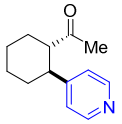

40%
3d/4d (2.6:1)


86%
3e/4e (1.8:1)[c]


82%
3f/4f (3.5:1)[c]


83%
3g/4g (1:1.6)[c]


53%
only **3h**[b]
trans only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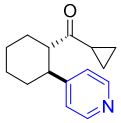
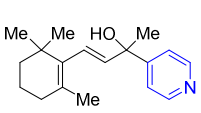
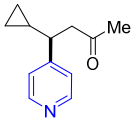
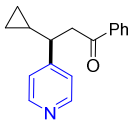
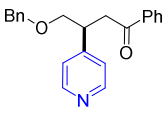
3i/4i (1.8:1)
d.r. > 10:1

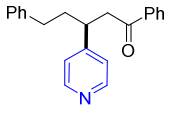

62%
only **3j**
d.r. = 10:1

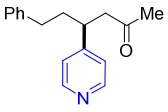

59%
only **3k**

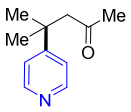

60%
3l/4l (3.6:1)


52%
only **3m**


44%
only **3n**


50%
only **3o**


71%
3p/4p (4:1)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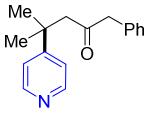
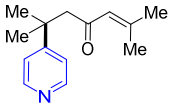
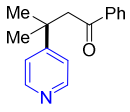
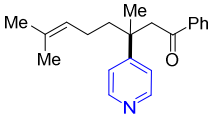
3q/4q (7.9:1)

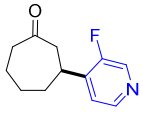

69%
3r/4r (14:1)

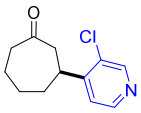

70%
only **3s**


81%
only **3t**


71%
only **3u**

B. Pyridines


60%
only **3v**[c]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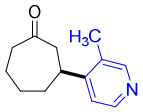
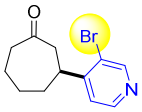
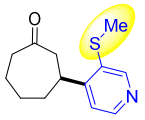
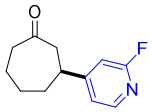
only **3w**[c]


51%
only **3x**[c]


38%
only **3y**[d]


48%
only **3z**[d]

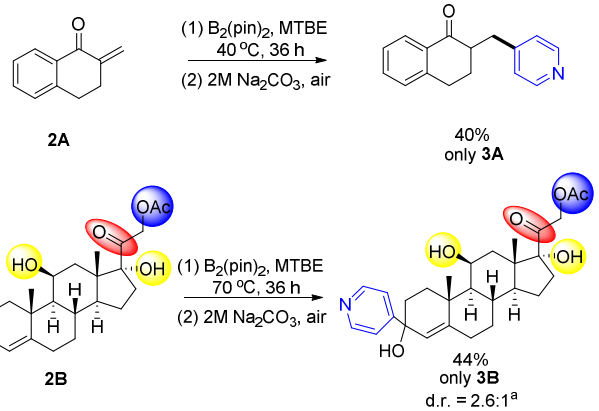

n.d.

[a]Reaction conditions: enones (0.2 mmol), 4-cyanopyridine (0.3mmol), $B_2(pin)_2$ (0.24 mmol), MTBE (1.0 mL), 24h, 70 °C, isolated yields refer to the combined yield of all isomers, the major isomer is depicted, the ratio was determined by ^{1}H NMR analysis of the crude mixture. [b]Reacted at room temperature, for 48h. [c]For 36 h. [d]Reacted at 40 °C, for 36h.

51% isolated yield, respectively. Highly sensitive thioether and bromo moieties which usually lead to side reactions under transition-metal catalysis were tolerated well in the present boryl radical system. Corresponding 1, 4-addition products **3y** and **3z** were obtained in moderate yields. However, with the 4-cyanopyridines bearing a substituent at C-2 position (for example, 2-fluorine-4-cyanopyridine), desired product was not detected.[20]

We further demonstrated the synthetic application of this protocol in the synthesis or modification of medicinally related molecules (Scheme 4). When enone **2A** was subjected to our reaction conditions in the presence of 4-cyanopyridine (1.5 equiv) and $B_2(pin)_2$ (1.2 equiv), the aromatase inhibitor **3A**[9] could be obtained in 40% yield. Hydrocortisone acetate **2B**, a pharmaceutical reagent featuring an ester, two unprotected alcohols and an alkyl ketone, can be facilely converted into the tertiary alcohol adduct **3B** in moderate yield (44%, d.r.= 2.6:1) with these sensitive groups remaining intact. Although the relative configuration of the major isomer could not be assigned, our protocol exhibits good functional group tolerance indeed.

Scheme 4. Applications to medicinally relevant substrates.



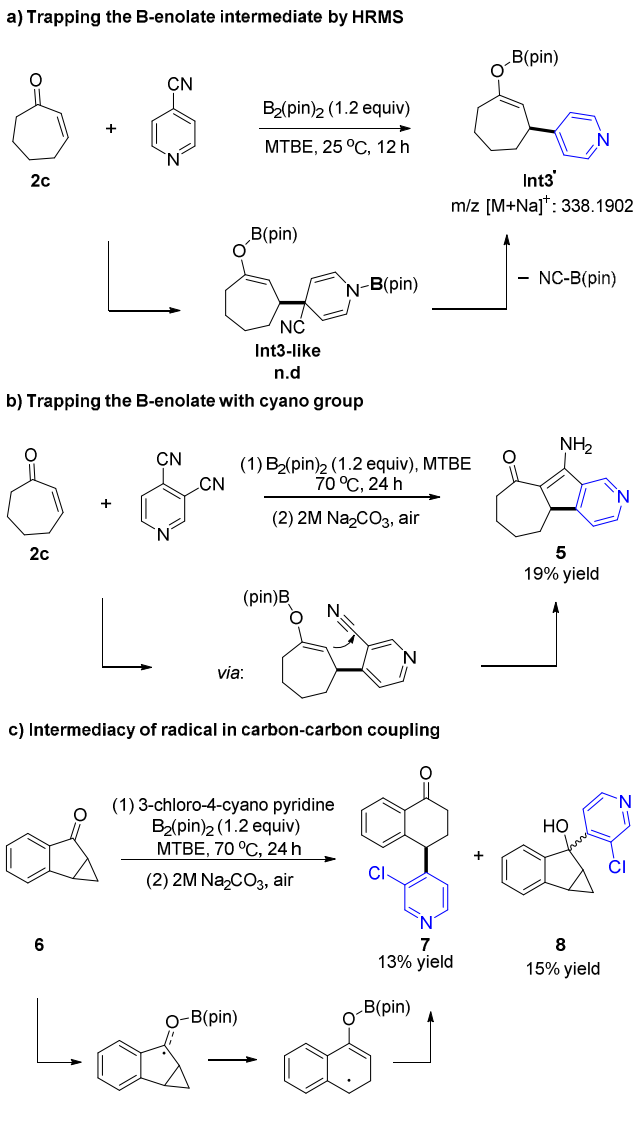
[a]Determined by ^{1}H NMR analysis of the isolated mixture of diastereomers.

2.3 Mechanistic investigations

In addition to the investigations of the temperature effect on the regioselectivity, further experimental studies were conducted to verify the proposed reaction pathway. Firstly,

HRMS was performed to detect the possible intermediate. As shown in Scheme 5a, an aromatized boron-enolate intermediate (**Int$_3$'**) could be detected by crude HRMS analysis of the reaction mixture of **2c** and 4-cyanopyridine. However, the direct detection of the **Int3-like** species was not successful, possibly due to its rapid aromatization.

Scheme 5. Controlled experiments.

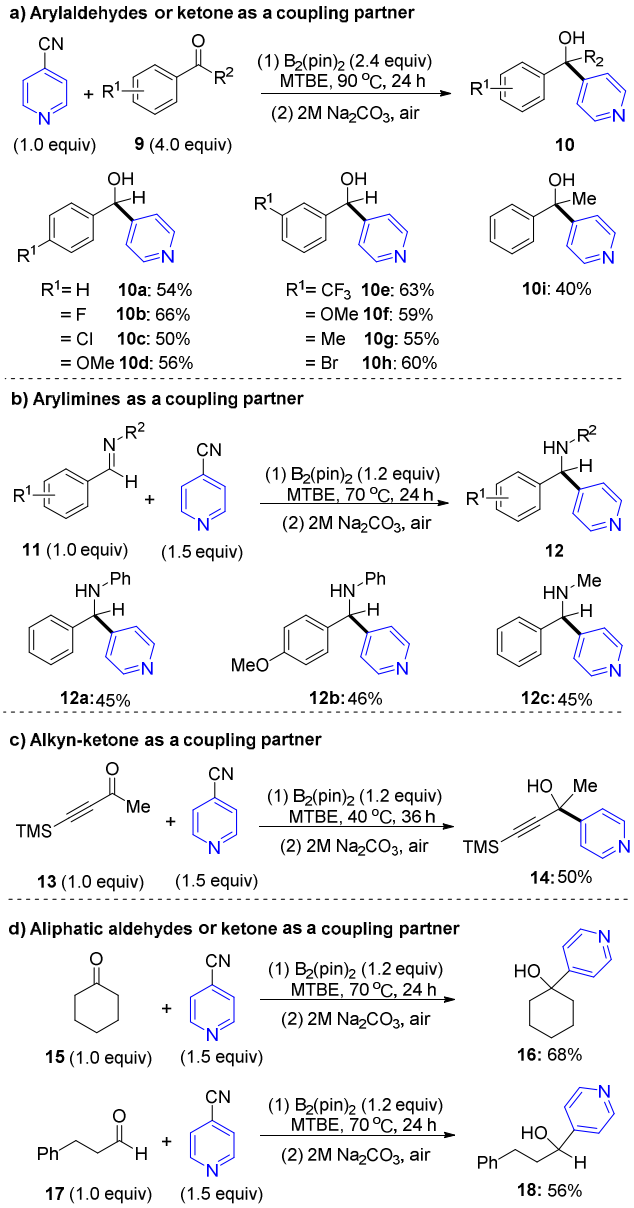


Secondly, the generation of the boron-enolate species was confirmed by intramolecular trapping reaction (Scheme 5b). When the 3, 4-dicyanopyridine was subjected to the standard conditions, compound **5** with fused ring scaffold was isolated, indicating that an intramolecular trapping of the boron-enolate *via* a nucleophilic addition reaction occurred. The conformation of fused ring **5** can be determined by DFT calculations (See Scheme S4 in supporting information for details).

Thirdly, the involvement of radical intermediate was probed with the rigid cycloprop[a]inden-6(1*H*)-one **6** *as radical clock*. In the presence of 3-chloro-4-cycano pyridine and $B_2(pin)_2$ at 70 °C, the product **7** was generated from the opening of fused cyclopropyl group (another 1, 2-addition product **8** was obtained, Scheme 5c). This result also indicates the involvement of radical intermediate in the proposed pathways.

2.4 Expanding the substrate scope

Scheme 6. The extended scope of the radical addition/coupling mechanism.



In order to test the protocol's diversity, we explored whether other commercially available carbonyl derivatives could be used as coupling partners for the synthesis of 4-substituted pyridines. Further experiments indicated that aryl aldehydes, aryl ketone, arylimines, 4-(trimethylsilyl)-3-butyn-2-one, as well as aliphatic aldehyde or ketone were suitable substrates for the synthesis of 4-substituted pyridines *via* our proposed strategy (Scheme 6). As shown in Scheme 6a, under slightly modified reaction conditions (see Table S1 in supporting information for details), benzaldehydes with either electron-donating or electron-withdrawing group (**9b-d**) underwent the reaction to give **10b-d** in moderate to good yields. Halides, such as F, Cl, and Br were well tolerated (**10b**, **10c** and **10h**) with this radical protocol. The position of substituents on the phenyl ring showed weak

influence on the reactivity (**9e**-**g**). Acetophenone (**9i**) afforded pyridine moiety containing a tertiary alcohol in 40% yield. Commercially available arylimines (**11a**-**c**) were also converted to substituted 4-pyridinemethanamines (**12a**-**c**) in moderate yields. Furthermore, alkynone **13**, was also tested, and the corresponding product **14** was isolated in moderate yield (50%), leaving the carbon-carbon triple bond and trimethylsilyl substituent untouched. Encouragingly, aliphatic aldehyde or ketone (**15**, **17**) could also be used as a coupling partner for the synthesis 4-substituted pyridines **16** and **18** in good yield, demonstrating the broad substrate scope of this method.

3. CONCLUSIONS

In summary, a metal-free approach to the synthesis of C-4 substituted pyridine derivatives was predicted computationally and verified experimentally. Theoretical calculations revealed that the *in situ* generated pyridine-boryl radical using 4-cyanopyridine and $B_2(pin)_2$ exhibits a carbon-radical characteristic, and this boryl radical can be used as a bifunctional "reagent", which acts as not only a pyridine precursor but also a boryl radical. The combined computational and experimental study showed that the 4-substituted pyridine derivatives could be synthesized using α, β-unsaturated ketones *via* the proposed radical addition/coupling mechanism with 4-cyanopyridine and $B_2(pin)_2$ as starting material. Several controlled experiments were conducted to probe the mechanistic details. Then, the reaction was further expanded to a wide range of boryl radical acceptors, including various aldehydes and ketones, aryl imines and alkynone. Application of this transformation in the modification of a complicated pharmaceutical molecule was described. The reactions occur under mild conditions without the use of any transition-metal catalysts or organometallic reagents. Efforts to apply this *in situ* generated new boryl radical to other reactions with the help of combined theoretical and experimental studies are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Computational investigations, experiment procedure, compound characterization, spectra. This material is available free of charge *via* the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*shuhua@nju.edu.cn
*chengxu@nju.edu.cn

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work was supported by the National Natural Science Foundation of China (Grants No. 21333004, No. 21361140376, No. 21572099 and No. 21332005). This work was partially sponsored by Qing Lan Project. All calculations in this work have been done on the IBM Blade cluster system in the High Performance Computing Center of Nanjing University. We dedicate this work to professor Qi-Lin Zhou on the occasion of his 60th birthday.

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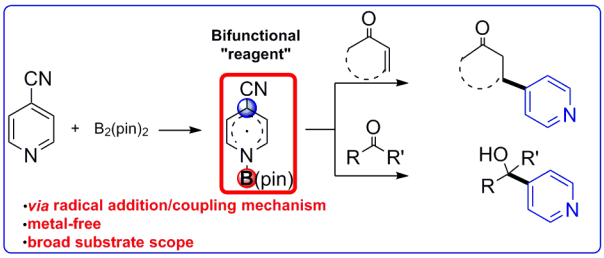
Bifunctional
"reagent"
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N
+ B2(pin)2
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N
B(pin)
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O
R
R'
O
N
HO
R'
R
N
•via radical addition/coupling mechanism
•metal-free
•broad substrate scope