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Letter

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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.9b03798 • Publication Date (Web): 07 Oct 2019

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Lewis Acid-Catalyzed Selective Reductive Decarboxylative Pyridylation of N-Hydroxyphthalimide Esters: Synthesis of Congested Pyridine-Substituted Quaternary Carbons

Liuzhou Gao,[a,‡] Guoqiang Wang,[a,‡] Jia Cao,[a] Hui Chen,[a] Yuming Gu,[a] Xueting Liu,[a] Xu Cheng,[a,b] Jing Ma[a] 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

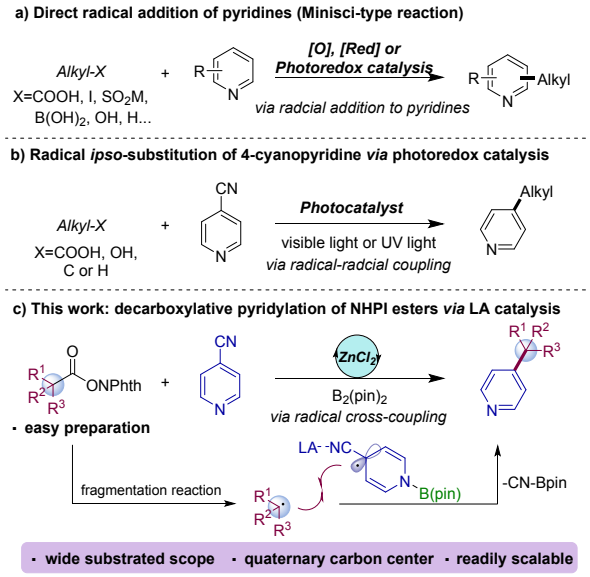
[b]Institute of Chemistry and Biomedical Sciences, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, P. R. China

ABSTRACT: A practical and efficient Lewis acid-catalyzed radical-radical coupling reaction of N-hydroxyphthalimide esters and 4-cyanopyridines with inexpensive bis(pinacolato)diboron as reductant has been developed. With $ZnCl_2$ as the catalyst, a wide range of quaternary 4-substituted pyridines, including highly congested diarylmethyl- and triarylmethyl-substituents, could be selectively obtained in moderated to good yields with broad functional group tolerance. Combined theoretical calculations and experimental studies indicate that the Lewis acid could coordinate with the cyano group of pyridine-boryl radical to lower the activation barrier of the C-C coupling pathway, leading to the formation of 4-substituted pyridines. Moreover, it could also facilitate the decyanation/aromatization of the radical-radical coupling intermediate.

KEYWORDS: Lewis acid catalysis, radical-radical coupling, pyridines, quaternary carbons, late-stage.

Pyridines are essential structural units that exist in a wide range of biologically active molecules,[1] natural products[2] and functional materials.[3] Functionalization of pyridines with conventional two-electron process, including nucleophilic aromatic substitution (S_NAr),[4] and transition-metal catalyzed C-H activation,[5] has been broadly investigated. However, sensitive organometallic reagents[6] or transition-metal catalysts[7] are always required in these processes. Moreover, the introduction of congested tertiary substituents toward pyridines with two-electron strategies is rather challenging.[4a,8]

With the prosperity of radical chemistry, we could construct complex molecules *via* radical-mediated processes.[9,10] For example, the classical Minisci-type reactions[11] with different kinds of radical precursors, including alkyl carboxylic acid,[12] boronates,[13] alkyl halides,[14] sulfinates,[15] sulfonyl halides,[16] alcohols,[17] olefins,[18] and alkanes,[19] have been extensively developed for the C-H functionalization of electron-deficient heteroarenes. This strategy proceeds through the direct addition of carbon radical to heteroaromtic bases, which always involves competitive low-energy pathways, and therefore the regioselectivity of this type reaction is difficult to control.[20] Although Baran[21] and co-workers have performed systematic investigations on the regiochemistry of Minisci reactions and provided some practical guidelines to this issue, the tunability of

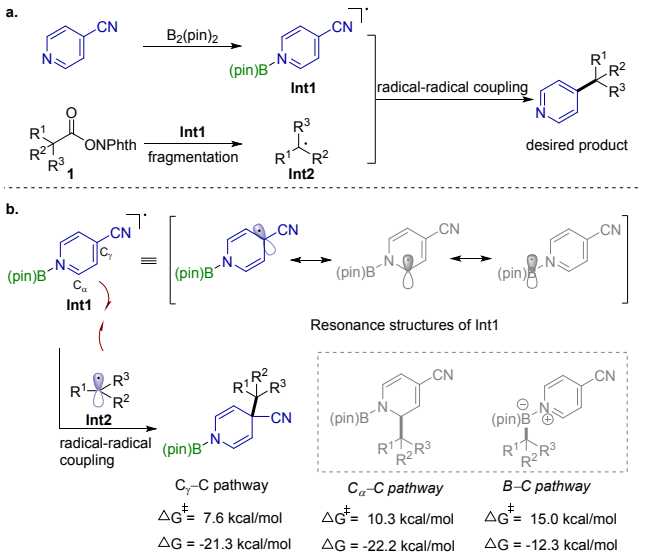


Scheme 1. Radical-mediated strategies for the functionalization of pyridines.

regioselectivity of pyridine is difficult. In addition to Minisci reactions, radical based *ipso*-substitution of pyridine nitriles is another approach for the synthesis of substituted pyridines. Recently, MacMillan,[22] Opatz's[23] and Inoue[24] groups have independently reported the pyridylation of alkyl carboxylic acid, alcohol oxalate salts,

C-C or sp^3 C-H bond (Scheme 1b) with pyridine nitriles under the irradiation of visible light or UV-light. These methods always involve the radical-radical coupling between the pyridine nitrile radical anions with another in situ generated carbon radical, leading to *ipso*-substituted pyridine products. However, transition-metal photocatalysts or the nearly stoichiometric amount of organic photocatalysts and UV-light irradiation are required in those transformations. In this regard, the development of practical and efficient strategies that enables to generate substituted pyridines under mild condition would be of great synthetic value. We herein report a $ZnCl_2$-catalyzed reductive decarboxylative pyridylation of N-hydroxyphthalimide (NHPI) esters *via* the radical-radical coupling of the neutral 4-cyanopyridine-boryl radical[25] with the decarboxylative carbon radical, which is mechanistically different from Minisci-type reactions or photoredox catalyzed *ipso*-substitution strategy. Moreover, the protocol reported here could avoid the regioselectivity issue in Minisci reactions, and a series of quaternary carbons containing pyridine-4-yl moiety could be obtained in good efficiency.

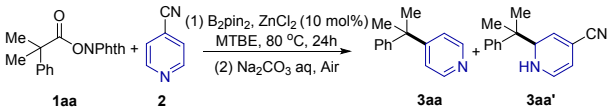
Reaction Design



Scheme 2. Reaction design of the decarboxylative pyridylation of NHPI ester.

Recently, our group[25c] and Fu group[26] independently described that the persistent pyridine-boryl radical[27] generated from the B_2pin_2 and pyridines induce the reductive fragmentation of redox-active esters (RAEs) to form carbon radicals, which could be further trapped by 1,1-disubtituted alkenes or the boryl radical to generate the C-C or C-B products. This strategy intrigued our interest in construction of the synthetically valuable 4-subtituted pyridines *via* the *ipso*-substitution of 4-cyanopyridines with RAEs as the radical precursors, which are easily available from the abundant carboxylic acids, as shown in Scheme 2a. One can see from Scheme 2b that the radical-radical coupling reaction between the pyridine-boryl radical (**Int1**) and carbon radical (**Int2**) may proceed through three different pathways (C_γ-C, C_α-C, and B-C pathways), due to three different resonance structures of **Int1**. With 2-phenyl-propan radical and 4-cyanopyridine-boryl radical as the model reactants, the activation barriers of these three pathways calculated with M06-2X at the 6-31G** level are 7.6, 10.3 and 15.0 kcal/mol, respectively (see Fig. S2 in SI for details). Although the B-C coupling pathway might be excluded, we still need to tune the reaction condition to suppress the competitive C_α-C pathway, which is a major challenge to achieve the desired reaction. In addition, the possible H-atom abstraction reaction or self-reaction of the decarboxylative carbon radicals should also be suppressed by tuning the reaction condition.

Using 4-cyanopyridine and NHPI ester **1aa** as model substrates in the decarboxylative pyridylation reaction in the presence of B_2pin_2, we observed the formation of C_γ-C coupling product **3aa** in 48% yield at 80 °C, with 10% yield of byproduct **3aa'** (Figure 1, entry 3, see Table S1 and Fig. S15 in SI for details). After extensive examination of different reaction parameters, the optimal reaction conditions were achieved with 10 mol% of $ZnCl_2$ as the catalyst. The desired coupling product **3aa** could be obtained in 76% yield (74% isolated yield) with excellent regioselectivity (C_γ/C_α>20:1). Other Lewis acids[28] (such as $B(C_6F_5)_3$, $AlMe_2Cl$, $MgCl_2$, $AlCl_3$, $FeCl_3$, $Zn(OAc)_2$) could also facilitate the C_γ-C coupling pathway, providing the target **3aa** in 51% to 72% yields, while the use of $BF_3{\cdot}Et_2O$ as the catalyst led to a decreased yield (30%).

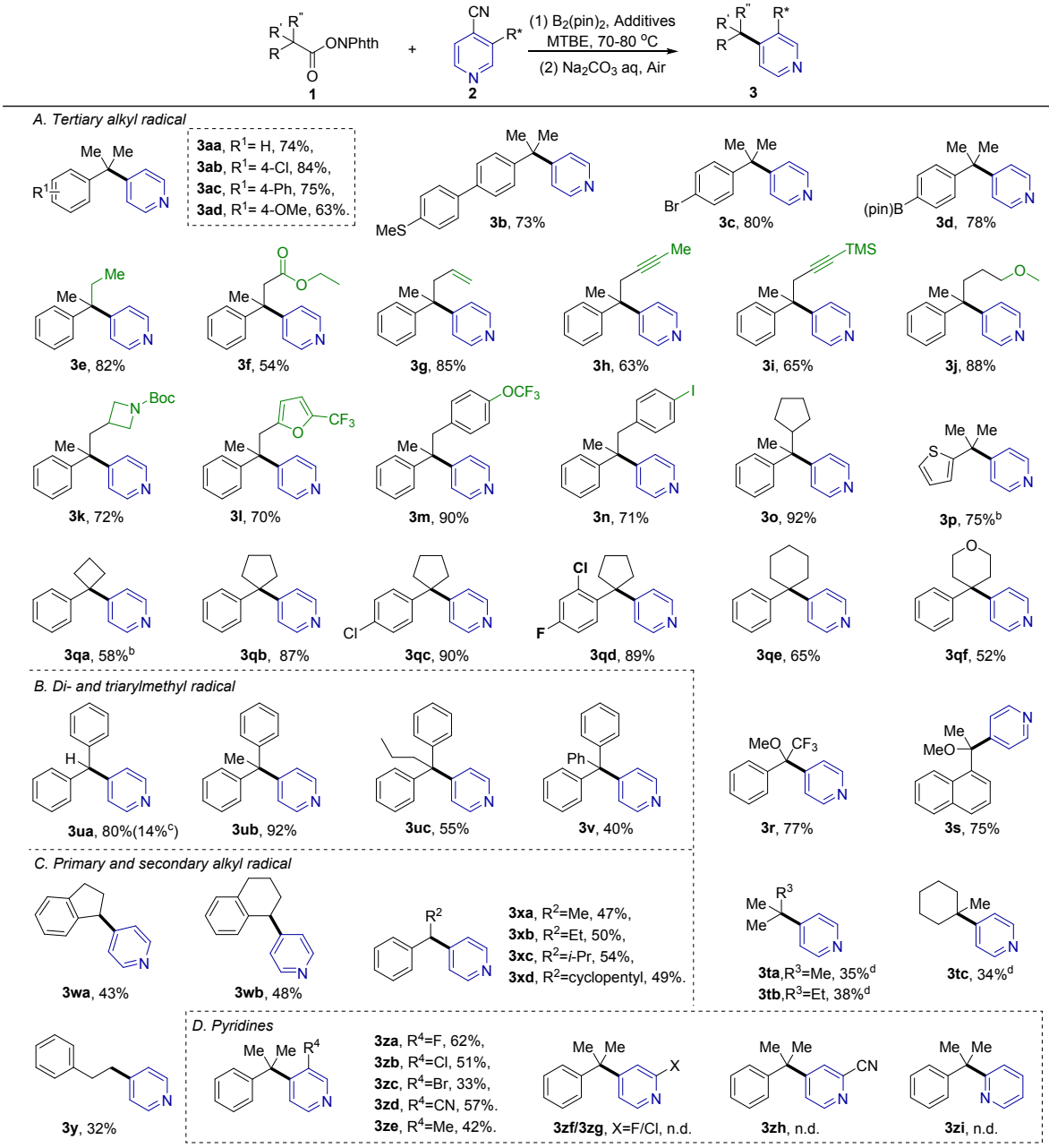


entry	deviation from standard condition	yield (%)[b]	ratio (3aa:3aa')[c]
1	none	76%	>20:1
2	no B_2pin_2	N.R.	N.R.
3	no $ZnCl_2$	48%	4.8:1
4	$BF_3{\cdot}Et_2O$, $B(C_6F_5)_3$, $AlMe_2Cl$ instead of $ZnCl_2$	30%-58%	5.8:1-13:1
5	$MgCl_2$, $AlCl_3$, $FeCl_3$, $Zn(OAc)_2$ instead of $ZnCl_2$	56%-72%	8:1-19:1

Figure 1. Optimization of the decarboxylative pyridylation of NHPI **1aa**. [a]Reaction conditions: **1aa** (0.2 mmol), 2 (0.3 mmol), $B_2(pin)_2$ (0.24 mmol), $ZnCl_2$ (10 mol%) in MTBE (1.0 mL), under Ar. [a]NMR yield, using benzyl ether as internal standard. [c]Ratio was determined by the GC-MS analysis.

After identifying the optimal conditions, we next explored the scope and generality of this decarboxylative pyridylation protocol. As shown in Table 1, a broad range of N-hydroxyphthalimide derivatives of tertiary carboxylic acids could be served as radical precursors to react with 4-cyanopyridine-boryl radical to afford the corresponding 4-substituted pyridines with a quaternary carbon in good to high yields. This protocol exhibits wide functional group tolerances, and we obtained the desired products in good to excellent yields, including products containing halogens (F (**3qd**), Cl (**3ab**, **3qc**), Br (**3c**)), esters (**3f**), alkene (**3g**), alkyne (**3h**, **3i**), ether (**3j**), Boc carbamate

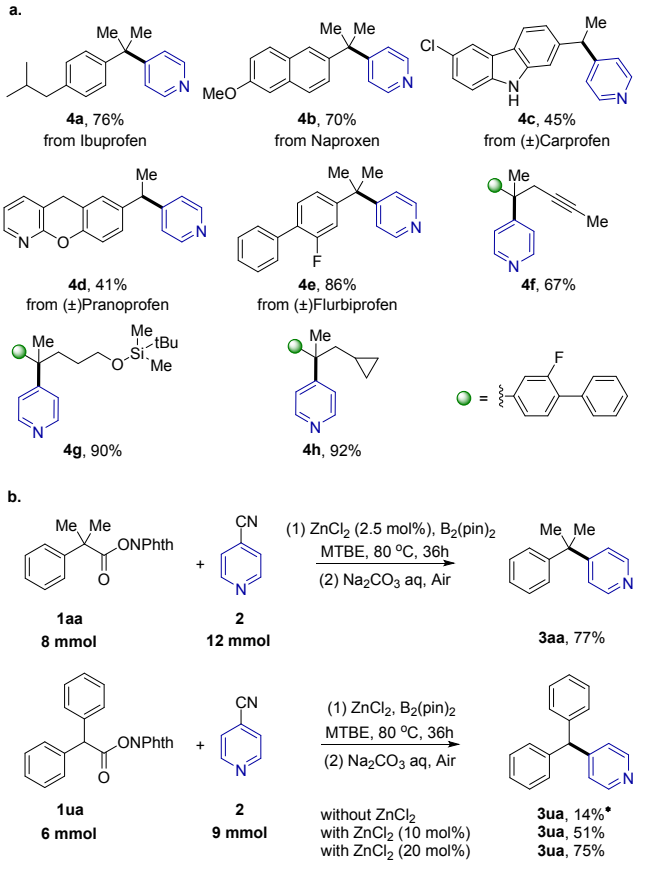
Table 1. Substrate scope of the NHPI ester and pyridine.[a]



[a]Reaction conditions: [a]NHPI ester 1 (0.2 mmol), $B_2(pin)_2$ (1.2 equiv.), 4-cyanopyridine (1.5 equiv.), $ZnCl_2$ (10 mol%), MTBE (1.0 mL), 80 °C, 24 hours. [b]70 °C. [c]Without $ZnCl_2$. [d]With 2.0 equiv. 4-cyanopyridine. (n.d.=not detected).

(**3k**), heterocycles (azetidine (**3k**), furan (**3l**), thiophene (**3p**), tetrahydropyrane (**3qf**)). More importantly, functional groups, such as aryl boronic ester, aryl iodide, alkyne silane were also well tolerated with this protocol, and desired product **3d**, **3i**, **3n** was obtained in good yields. Compounds **3r** and **3s** with α-methoxyl α-trifluoromethyl subsitutents were also generated in 77% and 75% yields, respectively. In addition to the broad functional group compatibility, another feature of our protocol is in the construction of sterically congested structures, which are difficult in the classical Minisci-type reactions.[8,17d,29] For example, the transformation could afford the congested quaternary carbon pyridines in 52-92% yields (**3e-3s**). Moreover, RAEs derived from α-quaternary aliphatic acids could also smoothly transform into the corresponding pyridylation products **3ta-3tc** in acceptable yields (34%-38%). Tri- or tetraarylmethane derivatives are important building blocks with wide applications in molecular devices,[30] organic frameworks,[31] and pharmaceutical chemistry.[32] But they have not been widely investigated due to the difficulty of synthesis.[33] With our method, NHPI ester of 2,2-diphenylacetic acid **1ua-1uc** and 2,2,2-triphenylacetic acid **1v** could be employed as the radical precursor, leading to **3ua-3v** in

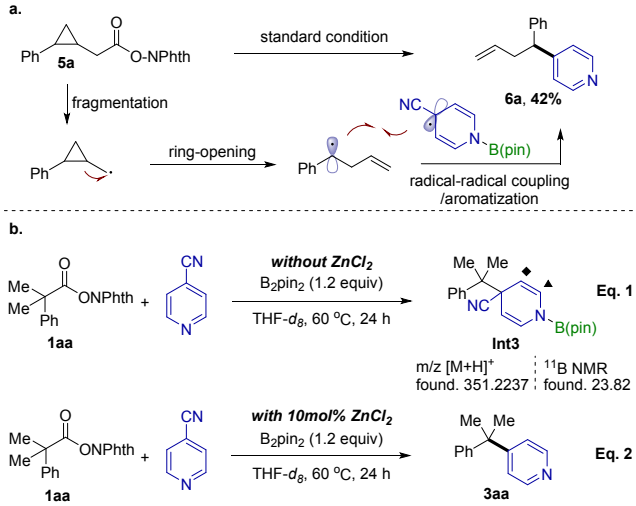
40-92% yield. Our method is not limited to tertiary carboxylic acids. The secondary carboxylic acid NHPIs are also good alkyl radical precursors, affording the corresponding pyridine derivatives (**3ua**, **3wa-3xd**) in moderate to good yields (43%-80%). However, the primary carboxylic acid NHPI **1y** (derived from 3-phenylpropanoic acid) gave a yield of only 32% (**3y**) due to several competing pathways.[34] Thus, this protocol is less effective for primary carboxylic acids. Next, we also probed the scope of the pyridines in the reaction. Under similar condition, 4-cyano-substituted pyridines with halides (F, Cl, Br), cyano or methyl substituents at the C_3-position of pyridine ring were well tolerated and the corresponding pyridylation products **3za-3ze** were obtained in 33-62% yields. However, 2-position substituted pyridines, including 2-fluoro-4-cyanopyridine, 2-chloro-4-cyanopyridine, 2,4-dicyanopyridine and 2-cyanopyridine were not tolerated in this reaction (**3zf-3zh**), presumably due to the fact that these pyridines are not able to activate the B-B bond of $B_2(pin)_2$ to generate the corresponding pyridine-boryl radical for initiating the radical-radical coupling reaction.



Scheme 3. Synthetic potentials. **a.** Late-stage 4-pyridiylation of drug molecules. **b.** Gram-scale experiments. *(0.2mmol scale).

To demonstrate the synthetic potentials of this transformation in medicinal chemistry, a series of NHPI esters derived from commercially available anti-inflammatory drugs (Scheme 3a) were synthesized and subjected to standard conditions. Decarboxylative pyridylation products derived from ibuprofen, naproxen, carprofen, pranoprofen, flurbiprofen could be obtained in good to high yields (**4a-4h**, 41-92%). Finally, this $ZnCl_2$ catalyzed C_γ selective decarboxylative pyridylation process was amenable to gram-scale synthesis. As shown in Scheme 3b, in the presence of 2.5 mol% $ZnCl_2$ catalyst loading, gram quantities of pyridine-4-yl substituted quaternary alkanes **3aa** could be prepared with the NHPI esters **1aa** in 77% yield. For the 2,2-diphenylacetic acid NHPI ester **1ua**, in the absence of $ZnCl_2$, only 14% yield of the pyridylation product was obtained. With 20 mol% $ZnCl_2$ as the catalyst, the yield of the desired product **3ua** could significantly increase to 75%.

Mechanistic investigations. To gain more mechanistic insight into this reaction, the control experiments and density functional theory (DFT) calculations were conducted. First, the involvement of a free carbon radical intermediate (obtained from the decarboxylation of NHPI esters) could be confirmed by the isolation of ring-opening product **6a** in 42% yield under standard conditions, using substrate **5a** as the radical clock (Scheme 4a).



Scheme 4. a. Radical clock experiment performed under standard condition. **b.** NMR and HRMS analysis on the crude reaction mixtures.

Then, DFT calculations with M06-2X functional[35] were conducted to probe the role of $ZnCl_2$ in this reductive coupling reaction of RAE and 4-cyanoppyridine. Our calculations suggest that the introduction of $ZnCl_2$ do not have significant effect on the reaction between pyridine-boryl radical **Int1** and NHPI ester **1aa**, the corresponding barrier of the key transition state (cleavage of N-O bond) is slightly lowered from 23.7 kcal/mol to 22.1 kcal/mol (see Fig. S1 and S3, SI). Therefore, the coupling between radicals **Int1** and **Int2** with $ZnCl_2$ was investigated to elucidate the impact of $ZnCl_2$ on this reaction (Figure 2a). The computed free energy profile and the key transition states of this reaction are listed in Figure 2b and 2c. First, $ZnCl_2$ and 4-cyanopyridine-boryl radical could form a stable Lewis adduct (**Int1-$ZnCl_2$**), in which the nitrogen

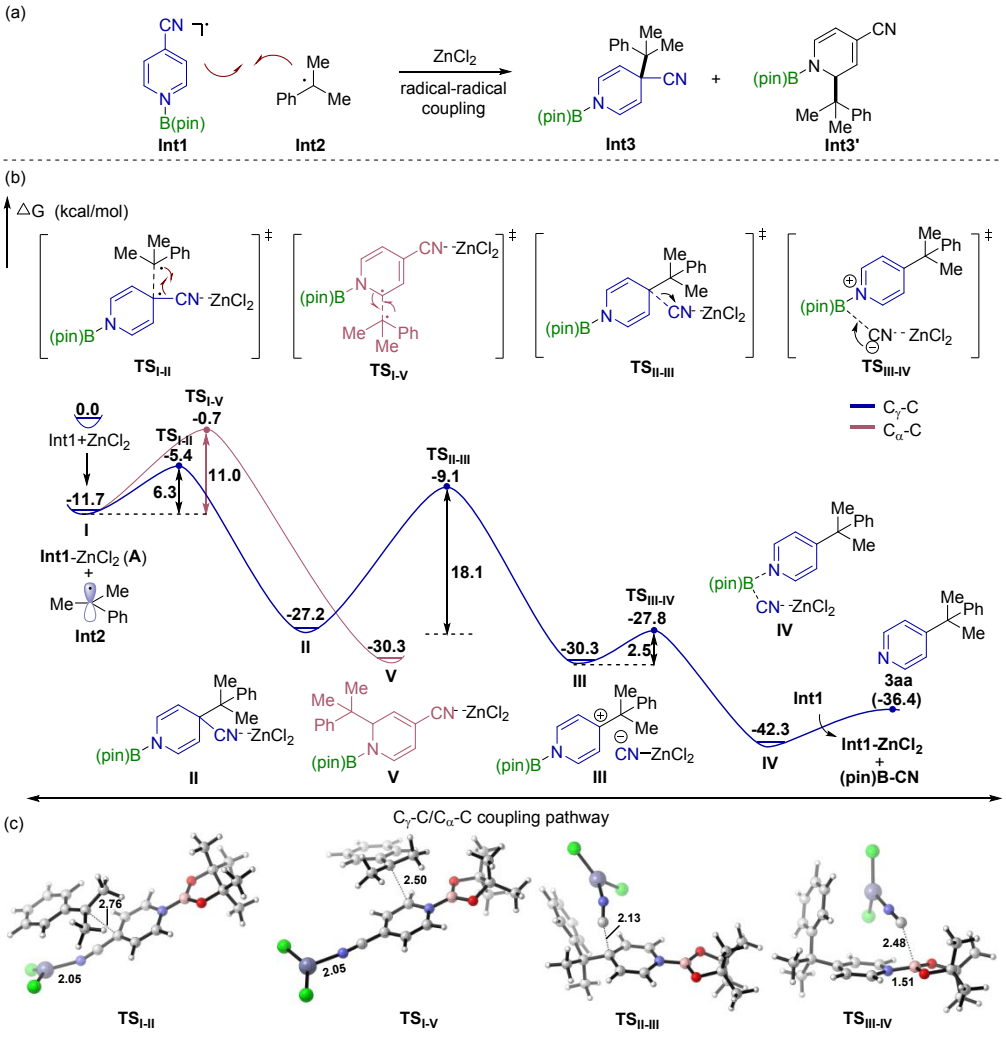
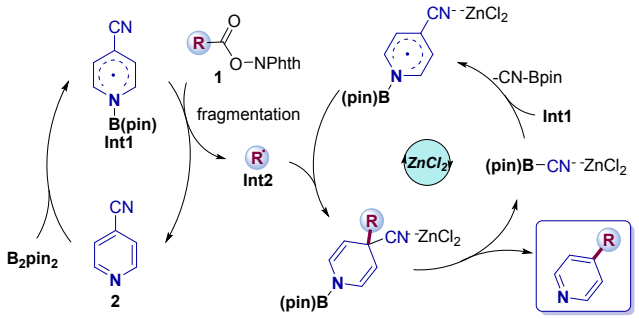


Figure 2. (a) Model reaction used in the computational study of the Mechanism. (b) Potential energy surfaces of the $ZnCl_2$ catalyzed selectivity radical-radical coupling reaction of **Int1** and **Int2** (All energies are with respect to the separate reactant and $ZnCl_2$). (c) Optimized structures of transition states.

atom of cyano is coordinated to the Zn(II) center (ΔG = -11.7 kcal/mol). Then, the radical-radical coupling reaction between radicals **Int2** and **Int1-ZnCl$_2$** at the C_γ position or C_α position generates 1,4-dihydropyridine intermediate **II** (*via* **TS$_{I\text{-}II}$**), and 1,2-dihydropyridine intermediate **V** (*via* **TS$_{I\text{-}V}$**). The C_γ-C pathway is the kinetically more favorable pathway, which requires a much lower barrier than the C_α-C coupling pathway (6.3 *v.s.* 11.0 kcal/mol). The free energy barrier of the C_γ-C coupling pathway is somewhat lowered in the presence of $ZnCl_2$ (reduced from 7.6 kcal/mol to 6.3 kcal/mol). For **TS$_{I\text{-}II}$** and **TS$_{I\text{-}V}$**, the enlarged energy barrier difference ($\Delta\Delta G^{\neq}$= -4.7 kcal/mol) between these two competing pathways could account for the experimental observed improvement in product-selectivity with $ZnCl_2$ as the catalyst (**3aa**/**3aa'**, from 4.8:1 to >20:1). Additionally, $ZnCl_2$ could also facilitate the decyanation/aromatization of the 1,4-dihydropyridine intermediate **Int3**. Dissociation of cyanide from **II** with the assistance of $ZnCl_2$ (**TS$_{II\text{-}III}$**) followed by migration of the cyanide from $ZnCl_2$-CN to the Bpin center (**TS$_{III\text{-}IV}$**) gives the desired decarboxylative/pyridylation product. The activation barrier of these two transition states are 18.1 and 2.5 kcal/mol, respectively. For the dissociation of cyanide from intermediate **II**, our post-Hartree-Fock calculations with the cluster-in-molecule local correlation method[36] (see supporting information for details) also lead to a barrier of 22.0 kcal/mol, being slightly higher than the M06-2X result (**TS$_{II\text{-}III}$**, 18.1 kcal/mol). Without $ZnCl_2$, the dissociation of cyanide requires a free energy barrier of 35.7 kcal/mol, which is difficult to occur at the present condition (see Fig. S5 in SI for details). Furthermore, NMR experiments were performed to verify the calculated mechanism for this $ZnCl_2$-catalyzed reductive coupling reaction. The reaction of **1aa**, 4-cyanopyridine and B_2pin_2 was analyzed by ^{1}H NMR spectroscopy in the presence or absence of $ZnCl_2$ (Scheme 4b, see Fig. S11-12 in SI). Without $ZnCl_2$ (**Eq. 1**), a set of signals observed at δ_H = 6.35 and 4.45 ppm could be assigned to a 1,4-dihydropyridine intermediate **Int3**. The calculated ^{1}H NMR chemical shift (δ_H = 6.91 and 4.78 ppm) of **Int3** by the Gauge-independent atomic orbital (GIAO) method at B97-2/pcSseg-2 level[37] is consistent

with experimental values described above. Additionally, the structure of **Int3** was further confirmed by HRMS and ^{11}B NMR experiments (see Fig. S13 and S14 in SI for details). Therefore, the involvement of 1,4-dihydropyridine (*via* C_γ-C coupling pathway) could be confirmed by our experimental studies. Under a similar condition, when a catalytic amount of $ZnCl_2$ was added (**Eq. 2**), the signals that correspond to 1,4-dihydropyridine intermediate disappeared and the aromatized product **3aa** was observed (Scheme 4b, see Fig. S13). This result indicates that the use of $ZnCl_2$ is crucial to prompt the rearomatization of 1,4-dihydropyridine intermediate, which is consistent with our DFT calculations. In addition, a trace amount of 4-cyanopyridine-boryl radical dimer of **Int1** was also detected by the ^{1}H NMR and confirmed by our calculated ^{1}H NMR chemical shift (see Fig. S11 and S12). Taking these experimental and computational results into consideration, a $ZnCl_2$ catalyzed decarboxylative coupling pathway is proposed in Scheme 5. First, the pyridine-boryl radical **Int1** mediated fragmentation of NHPI ester **1** leads to the generation of carbon radical **Int2** as evidenced by radical-clock experiment. Then, the radical-radical coupling of **Int1-$ZnCl_2$** complex and **Int2** at the γ-position of the pyridine-boryl radical generates the 1,4-dihydropyridine intermediate. Subsequent elimination of the cyano-Bpin with the assistance of $ZnCl_2$ forms the desired 4-substituted pyridines and regenerates the $ZnCl_2$ catalyst. Along the reaction pathway, $ZnCl_2$ works as a bifunctional catalyst. It not only facilitates the C_γ-C coupling pathway, but also contributes to the lowering of the activation barrier of the rearomatization of 1,4-dihydropyridine intermediate.



Scheme 5. Proposed reaction pathway.

In conclusion, the reductive decarboxylative pyridylation of N-hydroxyphthalimide esters has been established with $ZnCl_2$ as the catalyst. This protocol features good selectivity, excellent functional group compatibility, and a variety of congested pyridine-substituted quaternary carbons could be readily prepared in good to excellent yields. The combination of DFT calculations and experimental investigations suggests that $ZnCl_2$ could promote the regioselectivity of the radical-radical coupling step and lower the activation barrier of the rearomatization of the 1,4-dihydropyridine intermediate. The role of $ZnCl_2$ proposed here might provide new inspiration of the utility of Lewis acid in radical chemistry.

ASSOCIATED CONTENT

Supporting Information.
This material is available free of charge via the Internet at http://pubs.acs.org. Free energy profiles. Optimization geometries. Experiment procedure, compound characterization, and spectra.

AUTHOR INFORMATION

Corresponding Author

*shuhua@nju.edu.cn.

Author Contributions

‡L.Z.G. and G.Q.W. contributed equally to this work.

Funding Sources

This work was supported by the National Natural Science Foundation of China (21833002 and 21673110), and the program B for Outstanding PhD candidate of Nanjing University (201901B021).

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

All calculations in this work were performed on the IBM Blade cluster system in the High Performance Computing Center of Nanjing University. We also thank Dr. Zhigang Ni (Nanjing University) for his help in doing post-Hartree-Fock calculations for the rate-determining step.

REFERENCES

(1) (a) Swainston Harrison, T.; Scott, L. J. Atazanavir. *Drugs* **2005**, *65*, 2309–2336. (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among US FDA Approved Pharmaceuticals: Miniperspective. *J. Med. Chem.* **2014**, *57*, 10257–10274. (c) Lee, K. N.; Lei, Z.; Ngai, M. Y. β-Selective Reductive Coupling of Alkenylpyridines with Aldehydes and Imines via Synergistic Lewis acid/Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 5003–5006.

(2) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry, and Applications;* 2nd ed, John Wiley & Sons Wiley: Hoboken, **2011**; pp 139–143.

(3) (a) Guan, A. Y.; Liu, C. L.; Sun, X.-F.; Xie, Y.; Wang, M. A. Discovery of Pyridine-Based Agrochemicals by Using Intermediate Derivatization Methods. *Bioorg. Med. Chem.* **2016**, *24*, 342–353. (b) Zafar, M. N.; Atif, A. H.; Nazar, M. F.; Sumrra, S. H.; Gul-E-Saba; Paracha, R. Pyridine and Related Ligands in Transition Metal Homogeneous Catalysis. *Russ. J. Coord. Chem.* **2016**, *42*, 1-18.

(4) (a) Hill, M. D. Recent Strategies for the Synthesis of Pyridine Derivatives. *Chem. -Eur. J.* **2010**, *16*, 12052–12062. (b) Goetz, A. E.; Garg, N. K. Regioselective Reactions of 3, 4-Pyridynes Enabled by the Aryne Distortion Model. *Nat. Chem.* **2013**, *5*, 54–60. (c) Hilton, M. C.; Dolewski, R. D.; McNally, A. Selective Functionalization of Pyridines via Heterocyclic Phosphonium Salts. *J. Am. Chem. Soc.* **2016**, *138*, 13806–13809. (d) Dolewski, R. D.; Fricke, P. J.; McNally, A. Site-Selective Switching Strategies to Functionalize Polyazines. *J. Am. Chem. Soc.* **2018**, *140*, 8020–8026. (e) Dolewski, R. D.; Hilton, M. C.; McNally, A.

4-Selective Pyridine Functionalization Reactions via Heterocyclic Phosphonium Salts. *Synlett* **2018**, *29*, 8–14. (f) Moser, D.; Duan, Y.; Wang, F.; Ma, Y.; O'Neill, M. J.; Cornella, J. Selective Functionalization of Aminoheterocycles by a Pyrylium Salt *Angew. Chem., Int. Ed.* **2018**, *57*, 11035–11039. (g) Zhang, X.; McNally, A. Cobalt-Catalyzed Alkylation of Drug-Like Molecules and Pharmaceuticals Using Heterocyclic Phosphonium Salts. *ACS Catal.* **2019**, *9*, 4862–4866.

(5) For selected examples of the metal-catalyzed C-H alkylation of pyridines (a) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. Rh(I)-Catalyzed Alkylation of Quinolines and Pyridines via C–H Bond Activation. *J. Am. Chem. Soc.* **2007**, *129*, 5332–5333. (b) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. A Strategy for C–H Activation of Pyridines: Direct C-2 Selective Alkenylation of Pyridines by Nickel/Lewis Acid Catalysis. *J. Am. Chem. Soc.* **2008**, *130*, 2448–2449. (c) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. Selective C-4 Alkylation of Pyridine by Nickel/Lewis Acid Catalysis. *J. Am. Chem. Soc.* **2010**, *132*, 13666–13668. (d) Guo, P.; Joo, J. M.; Rakshit, S.; Sames, D. C–H Arylation of Pyridines: High Regioselectivity as a Consequence of the Electronic Character of C–H Bonds and Heteroarene Ring. *J. Am. Chem. Soc.* **2011**, *133*, 16338–16341. (e) Guan, B.-T.; Hou, Z. Rare-Earth-Catalyzed C–H Bond Addition of Pyridines to Olefins. *J. Am. Chem. Soc.* **2011**, *133*, 18086–18089. (f) Ye, M.; Gao, G.-L.; Yu, J.-Q. Ligand-Promoted C-3 Selective C–H Olefination of Pyridines with Pd Catalysts. *J. Am. Chem. Soc.* **2011**, *133*, 6964–6967. (g) Ryu, J.; Cho, S. H.; Chang, S. A Versatile Rhodium(I) Catalyst System for the Addition of Heteroarenes to both Alkenes and Alkynes by a C–H Bond Activation. *Angew. Chem., Int. Ed.* **2012**, *51*, 3677–3681. (h) Andou, T.; Saga, Y.; Komai, H.; Matsunaga, S.; Kanai, M. Cobalt–Catalyzed C4–Selective Direct Alkylation of Pyridines. *Angew., Chem. Int. Ed.* **2013**, *52*, 3213–3216. (i) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. Palladium-Catalyzed C–H Activation/Cross-Coupling of Pyridine N-Oxides with Nonactivated Secondary Alkyl Bromides. *J. Am. Chem. Soc.* **2013**, *135*, 616–619. (j) Fischer, D. F.; Sarpong, R. Total Synthesis of (+)-Complanadine A Using an Iridium-Catalyzed Pyridine C–H Functionalization. *J. Am. Chem. Soc.* **2010**, *132*, 5926–5927. (k) Song, G.; O, W. W. N.; Hou, Z. Enantioselective C–H Bond Addition of Pyridines to Alkenes Catalyzed by Chiral Half-Sandwich Rare-Earth Complexes. *J. Am. Chem. Soc.* 2014, *136*, 12209–12212. (l) Xie, H.; Shao, Y.; Gui, J.; Lan, J.; Liu, Z.; Ke, Z.; Deng, Y.; Jiang, H.; Zeng, W. Co(II)-Catalyzed Regioselective Pyridine C–H Coupling with Diazoacetates. *Org. Lett.* **2019**, *21*, 3427–3430.

(6) (a) Schlosser, M.; Mongin, F. Pyridine Elaboration through Organometallic Intermediates: Regiochemical Control and Completeness. *Chem. Soc. Rev.* **2007**, *36*, 1161–1172. (b) Andersson, H.; Almqvist, F.; Olsson, R. Synthesis of 2-Substituted Pyridines via a Regiospecific Alkylation, Alkynylation, and Arylation of Pyridine N-Oxides. *Org. Lett.* **2007**, *9*, 1335–1337. (c) Zhang, F.; Duan, X.-F. Facile One-Pot Direct Arylation and Alkylation of Nitropyridine N-Oxides with Grignard Reagents. *Org. Lett.* **2011**, *13*, 6102–6105.

(7) (a) Nakao, Y. Transition-Metal-Catalyzed CH Functionalization for the Synthesis of Substituted Pyridines. *Synthesis* **2011**, *20*, 3209–3219. (b) Zhang, X.; McNally, A. Phosphonium Salts as Pseudohalides: Regioselective Nickel-Catalyzed Cross-Coupling of Complex Pyridines and Diazines. *Angew. Chem., Int. Ed.* **2017**, *56*, 9833–9836. (c) Diesel, J.; Finogenova, A. M.; Cramer, N. Nickel-Catalyzed Enantioselective Pyridone C–H Functionalizations Enabled by a Bulky N-Heterocyclic Carbene Ligand. *J. Am. Chem. Soc.* **2018**, *140*, 4489–4493. (d) Zhang, W. -B.; Yang, X. -T., Ma, J. -B.; Su, Z. -M.; Shi, S. -L. Regio- and Enantioselective C–H Cyclization of Pyridines with Alkenes Enabled by a Nickel/N-Heterocyclic Carbene Catalysis. *J. Am. Chem. Soc.* **2019**, *141*, 5628–5634.

(8) (a) Kröhnke, F. The Specific Synthesis of Pyridines and Oligopyridines. *Synthesis* **1976**, *1976*, 1–24. (b) Murakami, K.; Yamada, S.; Kaneda, T.; Itami, K. C–H Functionalization of Azines. *Chem. Rev.* **2017**, *117*, 9302–9332. (c) Feng, J.; Holmes, M.; Krische, M. J. Acyclic Quaternary Carbon Stereocenters via Enantioselective Transition Metal Catalysis. *Chem. Rev.* **2017**, *117*, 12564–12580.

(9) (a) Yan, M.; Lo, J. L. C.; Edwards, J. T.; Baran, P. S. Radicals: Reac-tive Intermediates with Translational Potential. *J. Am. Chem. Soc.* **2016**, *138*, 12692–12714. (b) Studer, A.; Curran, D. P. Catalysis of Radical Reactions: A Radical Chemistry Perspective. *Angew. Chem., Int. Ed.* **2016**, 55, 58–102. (c) Xuan, J.; Studer, A. Radical Cascade Cyclization of 1,n-Enynes and Diynes for the Synthesis of Carbocycles and Heterocycles. *Chem. Soc. Rev.* **2017**, *46*, 4329–4346. (d) Smith, J. M.; Harwood, S. J.; Baran, P. S. Radical Retrosynthesis. *Acc. Chem. Res.* **2018**, *51*, 1807–1817.

(10) For selected examples of the radical based pyridylation reactions (a) Lima, F.; Kabeshov, M.; Tran, A. D. N.; Battilocchio, C.; Sedelmeier, J.; Sedelmeier, G.; Schenkel, B.; Ley, S. V. Visible Light Activation of Boronic Esters Enables Efficient Photoredox C(sp^2)-C(sp^3) Cross-Couplings in Flow. *Angew. Chem., Int. Ed.* **2016**, *55*, 14085–14089. (b) Boyington, A. J.; Riu, M. Y.; Jui, N. T. Anti-Markovnikov Hydroarylation of Unactivated Olefins via Pyridyl Radical Intermediates. *J. Am. Chem. Soc.* **2017**, *139*, 6582–6585. (c) Zhang, X.; Feng, X.; Zhou, C.; Yu, X.; Yamamoto, Y.; Bao, M. Transition-Metal-Free Decarboxylative Arylation of 2-Picolinic Acids with Arenes under Air Conditions. *Org. Lett.* **2018**, *20*, 7095–7099. (d) Seath, C. P.; Vogt, D. B.; Xu, Z.; Boyington, A. J.; Jui, N. T. Radical Hydroarylation of Functionalized Olefins and Mechanistic Investigation of Photocatalytic Pyridyl Radical Reactions. *J. Am. Chem. Soc.* **2018**, *140*, 15525–15534. (e) Lei, Y.; Yang, J.; Qi, R.; Wang, S.; Wang, R.; Xu, Z. Arylation of Benzyl Amines with Aromatic Nitriles. *Chem. Commun.* **2018**, *54*, 11881–11884. (f) Sun, A. C.; McClain, E. J.; Beatty, J. W.; Stephenson, C. R. J. Visible Light-Mediated Decarboxylative Alkylation of Pharmaceutically Relevant Heterocycles. *Org. Lett.* **2018**, *20*, 3487–3490. (g) He, Y.; Kang, D.; Kim, I.; Hong, S. Metal-Free Photocatalytic Trifluoromethylative Pyridylation of Unactivated Alkenes. *Green Chem.* **2018**, *20*, 5209–5214. (h) Chen, D.; Xu, L.; Long, T.; Zhu, S.; Yang, J.; Chu, L. Metal-Free, Intermolecular Carbopyridylation of Alkenes via Visible-Light-Induced Reductive Radical Coupling. *Chem. Sci.*, **2018**, *9*, 9012–9017. (i) Zhu, S.; Qin, J.; Wang, F.; Li, H.; Chu, L. Photoredox-Catalyzed Branch-Selective Pyridylation of Alkenes for the Expedient Synthesis of Triprolidine. Nat. Commun. **2019**, *10*, 749. (j) Boyington, A. J.; Seath, C. P.; Zearfoss, A. M.; Xu, Z. Jui, N. T. Catalytic Strategy for Regioselective Arylethylamine Synthesis. *J. Am. Chem. Soc.* **2019**, *141*, 4147–4153.

(11) For selected examples of Minisci alkylation of N-heteroarenes (a) Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinummo, M. Nucleophilic Character of Alkyl Radicals-VI: A New Convenient Selective Alkylation of Heteroaromatic Bases. *Tetrahedron* **1971**, *27*, 3575–3579. (b) Minisci, F.; Citterio, A.; Giordano, C. Electron-Transfer Processes: Peroxydisulfate, a Useful and Versatile Reagent in Organic Chemistry. *Acc. Chem. Res.* **1983**, *16*, 27–32. (c) Minisci, F.; Vismara, E.; Fontana, F. Recent Developments of Free-Radical Substitutions of Heteroaromatic Bases. *Heterocycles*, **1989**, *28*, 489–519. (d) Cheng, W.; Shang, R.; Fu, Y. Photoredox/Brønsted Acid Co-Catalysis Enabling Decarboxylative Coupling of Amino Acid and Peptide Redoxactive Esters with N-Heteroarenes. *ACS Catal.* **2017**, *7*, 907–911. (e) Cheng, W.; Shang, R.; Fu, M.; Fu, Y. Photoredox-Catalysed Decarboxylative Alkylation of N-Heteroarenes with N-(Acyloxy)phthalimides. *Chem. -Eur. J.* **2017**, *23*, 2537–2541. (f) Wu, X.; Zhang, H.; Tang, N.; Wu, Z.; Wang, D.; Ji, M.; Xu, Y.; Wang, M.; Zhu, C. Metal-Free Alcohol-Directed Regioselective Heteroarylation of Remote Unactivated C(sp^3)–H

Bonds. *Nat. Commun.*, **2018**, *9*, 3343. (g) Zhang, X.; Weng, W.; Liang, H.; Yang, H.; Zhang, B. Visible-Light-Initiated, Photocatalyst-Free Decarboxylative Coupling of Carboxylic Acids with N-Heterocycles. *Org. Lett.* **2018**, *20*, 4686–4690. (h) Sutherland, D. R.; Veguillas, M.; Oates, C. L.; Lee, A. Metal-, Photocatalyst-, and Light-Free, Late-Stage C–H Alkylation of Heteroarenes and 1, 4-Quinones Using Carboxylic Acids. *Org. Lett.* **2018**, *20*, 6863–6867. (i) Liu, P.; Liu, W.; Li, C. Catalyst-Free and Redox-Neutral Innate Trifluoromethylation and Alkylation of Aromatics Enabled by Light. *J. Am. Chem. Soc.* **2017**, *139*, 14315-14321. (j) Fu, M.; Shang, R.; Zhao, B.; Wang, B.; Fu, Y. Photocatalytic Decarboxylative Alkylations Mediated by Triphenylphosphine and Sodium Iodide. *Science* **2019**, *363*, 1429–1434.

(12) (a) Xia, R.; Xie, M.-S.; Niu, H.-Y.; Qu, G.-R.; Guo, H.-M. Radical Route for the Alkylation of Purine Nucleosides at C6 via Minisci Reaction. *Org. Lett.* **2014**, *16*, 444–447. (b) Mai, D. N.; Baxter, R. D. Unprotected Amino Acids as Stable Radical Precursors for Heterocycle C–H Functionalization. *Org. Lett.* **2016**, *18*, 3738–3741. (c) Garza-Sanchez, R. A.; Tlahuext-Aca, A.; Tavakoli, G.; Glorius, F. Visible Light-Mediated Direct Decarboxylative C–H Functionalization of Heteroarenes. *ACS. Catal.* **2017**, *7*, 4057–4061. (d) Li, Z.; Wang, X.; Xia, S.; Jin, J. Ligand-Accelerated Iron Photocatalysis Enabling Decarboxylative Alkylation of Heteroarenes. *Org. Lett.* **2019**, *21*, 4259–4265.

(13) (a) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. Direct C–H Arylation of Electron-Deficient Heterocycles with Arylboronic Acids. *J. Am. Chem. Soc.* **2010**, *132*, 13194–13196. (b) Li, G.-X.; Morales-Rivera, C. A.; Wang, Y.; Gao, F.; He, G.; Liu, P.; Chen, G. Photoredox-Mediated Minisci C–H Alkylation of N-Heteroarenes Using Boronic acids and Hypervalent Iodine. *Chem. Sci.* **2016**, *7*, 6407-6412.

(14) (a) Ye, Y.; Sanford, M. S. Merging Visible-Light Photocatalysis and Transition-Metal Catalysis in the Copper-Catalyzed Trifluoromethylation of Boronic Acids with CF_3I. *J. Am. Chem. Soc.* **2012**, *134*, 9034–9037. (b) McCallum, T.; Barriault, L. Direct Alkylation of Heteroarenes with Unactivated Bromoalkanes Using Photoredox Gold Catalysis. *Chem. Sci.* **2016**, *7*, 4754–4758.

(15) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara. Y.; Baran, P. S. Practical and Innate Carbon–hydrogen Functionalization of Heterocycles. *Nature* **2012**, *492*, 95.

(16) Nagib, D. A.; MacMillan, D. W. C. Trifluoromethylation of Arenes and Heteroarenes by Means of Photoredox Catalysis. *Nature* **2011**, *480*, 224–228.

(17) (a) Jin, J.; MacMillan, D. W. C. Alcohols as Alkylating agents in Heteroarene C–H Functionalization. *Nature* **2015**, *525*, 87–90. (b) McCallum, T.; Pitre, S. P.; Morin, M.; Scaiano, J. C.; Barriault, L. The Photochemical Alkylation and Reduction of Heteroarenes. *Chem. Sci.* **2017**, *8*, 7412–7418. (c) Dong, J.; Wang, Z.; Wang, X.; Song, H.; Liu, Y., Wang, Q. Metal-, Photocatalyst-, and Light-Free Minisci C–H Alkylation of N-Heteroarenes with Oxalates. *J. Org. Chem.* **2019**, *84*, 7532–7540. (d) Pitre, S. P.; Muuronen, M.; Fishman, D. A.; Overman, L. E. Tertiary Alcohols as Radical Precursors for the Introduction of Tertiary Substituents into Heteroarenes. *ACS Catal.* **2019**, *9*, 3413–3418.

(18) (a) Ma, X.; Herzon, S. B. Intermolecular Hydropyridylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **2016**, *138*, 8718–8721. (b) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev.* **2016**, *116*, 8912–9000. (c) Lo, J. C.; Kim, D.; Pan, C. M.; Edwards, J. T.; Yabe, Y.; Gui, J.; Qin, T.; Gutierrez, S.; Giacoboni, J.; Smith, M. W.; Holland, P. L.; Baran, P. S. Fe-Catalyzed C–C Bond Construction from Olefins via Radicals. *J. Am. Chem. Soc.* **2017**, *139*, 2484–2503. (d) Ma, X.; Dang, H.; Rose, J. A.; Rablen, P.; Herzon, S. B. Hydroheteroarylation of Unactivated Alkenes Using N-Methoxyheteroarenium Salts. *J. Am. Chem. Soc.* **2017**, *139*, 5998–6007. (e) Buquoi, J. Q.; Lear, J. M.; Gu, X.; Nagib, D. A. Heteroarene Phosphinylalkylation via a Catalytic, Polarity-Reversing Radical Cascade. *ACS Catal.* **2019**, *9*, 5330–5335.

(19) (a) Deng, G.; Li, C.-J. $Sc(OTf)_3$-Catalyzed Direct Alkylation of Quinolines and Pyridines with Alkanes. *Org. Lett.* **2009**, *11*, 1171–1174. (b) Deng, G.; Ueda, K.; Yanagisawa, S.; Itami, K.; Li, C.-J. Coupling of Nitrogen Heteroaromatics and Alkanes without Transition Metals: A New Oxidative Cross-Coupling at C-H/C-H Bonds. *Chem. -Eur. J.* **2009**, *15*, 333–337. (c) Jin, J.; MacMillan, D. W. C. Direct α-Arylation of Ethers through the Combination of Photoredox-Mediated C-H Functionalization and the Minisci Reaction. *Angew. Chem., Int. Ed.* **2015**, *54*, 1565–1569. (d) Li, G.; Hu, X.; He, G.; Chen. G. Photoredox-Mediated Remote C(sp^3)–H Heteroarylation of Free Alcohols. *Chem. Sci.*, **2019**, *10*, 688–693. (e) Huang, C.-Y.; Li, J.; Liu, W.; Li, C.-J. Diacetyl as a "Traceless" Visible Light Photosensitizer in Metal-Free Cross-Dehydrogenative Coupling Reactions. *Chem. Sci.* **2019**, *10*, 5018–5024.

(20) (a) Brueckl, Y. Ji, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. Innate C-H Trifluoromethylation of Heterocycles. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, 108, 14411–14415. (b) Proctor, R. S. J.; Phipps, R. J. Recent Advances in Minisci-Type Reactions. *Angew. Chem., Int. Ed.* **2019**, *58*, 2-36.

(21) O'Hara, F.; Blackmond D. G.; Baran, P. S. Radical-Based Regioselective C–H Functionalization of Electron-Deficient Heteroarenes: Scope, Tunability, and Predictability. *J. Am. Chem. Soc.* **2013**, *135*, 12122-12134.

(22) (a) McNally, A.; Prier, C. K.; MacMillan, D. W. C. Discovery of An Alpha-Amino C-H Arylation Reactionusing the Strategy of Accelerated Serendipity. *Science* **2011**, *334*, 1114-1117. (b) Pirnot, M. T.; Rankic, D. A.; Martin D. B. C.; MacMillan, D. W. C. Photoredox Activation for the Direct Beta-Arylation of Ketones and Aldehydes. *Science*, **2013**, *339*, 1593-1596. (c) Zuo, Z.; MacMillan, D. W. C. Decarboxylative Arylation of Alpha-Amino Acids via Photoredox Catalysis: A One-Step Conversion of Biomass to Drug Pharmacophore. *J. Am. Chem. Soc.* **2014**, *136*, 5257–5260. (d) Cuthbertson, J. D.; MacMillan, D. W. C. The Direct Arylation of Allylic sp^3 C-H Bonds via Organic and Photoredox Catalysis. *Nature* **2015**, *519*, 74–77.

(23) (a) Lipp, B.; Nauth, A.; Opatz, T. Transition-Metal-Free Decarboxylative Photoredox Coupling of Carboxylic Acids and Alcohols with Aromatic Nitriles. *J. Org. Chem.* **2016**, *81*, 6875–6882. (b) Lipp, B.; Lipp, A.; Detert, H.; Opatz, T. Light-Induced Alkylation of (Hetero)aromatic Nitriles in a Transition-Metal-Free C-C-Bond Metathesis. *Org. Lett.* **2017**, *19*, 2054–2057.

(24) Hoshikawa, T.; Inoue, M. Photoinduced Direct 4-Pyridination of C(sp^3)-H Bonds. *Chem. Sci.*, **2013**, *4*, 3118–3123.

(25) (a) Wang, G.; Zhang, H.; Zhao, J.; Li, W.; Cao, J.; Zhu, C.; Li, S. Homolytic Cleavage of a B–B Bond by the Cooperative Catalysis of two Lewis Bases: Computational Design and Experimental Verification. *Angew. Chem, Int. Ed.* **2016**, 55, 5985–5989. (b) Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. Diboron(4) Compounds: From Structural Curiosity to Synthetic Workhorse. *Chem. Rev.* **2016**, *116*, 9091–9161. (c) Gao, L.; Wang, G.; Cao, J.; Yuan, D.; Cheng, X.; Guo, X. W.; Li, S. Organocatalytic Decarboxylative Alkylation of N-hydroxy-phthalimide Esters Enabled by Pyridine-Boryl Radicals. *Chem. Commun.* **2018**, *54*, 11534–11537. (d) Zhang, L.; Jiao, L. Pyridine-Catalyzed Radical Borylation of Aryl Halides. *J. Am. Chem. Soc.* **2017**, *139*, 607-610. (e) Zhang, L.; Jiao, L. Super Electron Donors Derived from Diboron. *Chem. Sci.* **2018**, *9*, 2711-

2722. (f) Koniarczyk, J. L.; Greenwood, J. W.; Alegre-Requena, J. V.; Paton R. S.; McNally, A. A Pyridine-Pyridine Cross-Coupling Reaction via Dearomatized Radical Intermediates. *Angew. Chem., Int. Ed.*, **2019**, DOI: 10.1002/anie.201906267 (in press). (g) Cao, J.; Wang, G.; Gao, L.; Chen, H.; Liu, X.; Cheng, X.; Li, S. Perfluoroalkylative Pyridylation of Alkenes via 4-Cyanopyridine-Boryl Radicals. *Chem. Sci.* **2019**, *10*, 2767–2772.

(26) Cheng, W.; Shang, R.; Zhao, B.; Xing W.; Fu, Y. Isonicotinate Ester Catalyzed Decarboxylative Borylation of (Hetero)Aryl and Alkenyl Carboxylic Acids through N-Hydroxyphthalimide Esters. *Org. Lett.* **2017**, *19*, 4291–4294.

(27) For reviews on persistent radical effect (a) Fischer, H. The Persistent Radical Effect: A Principle for Selective Radical Reactions and Living Radical Polymerizations. *Chem. Rev.* **2001**, 101, 3581–3610. (b) Studer, A. The Persistent Radical Effect in Organic Synthesis. *Chem.–Eur. J.* **2001**, *7*, 1159–1164. (c) Studer, A. Tin-Free Radical Chemistry Using the Persistent Radical Effect: Alkoxyamine Isomerization, Addition Reactions and Polymerizations. *Chem. Soc. Rev.* **2004**, *33*, 267–273.

(28) For reviews on Lewis acid promoted radical reactions, see: (a) Renaud, P.; Gerster, M. Use of Lewis acids in free radical reactions. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562–2579. (b) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163-171. (c) Sibi, M. P.; Manyem, S.; Zimmerman, J. Enantioselective Radical Processes. *Chem. Rev.* **2003**, *103*, 3263–3295. (d) Merna, J.; Vlcek, P.; Volkis, V.; Michl, J. Li^+ Catalysis and Other New Methodologies for the Radical Polymerization of Less Activated Olefins. *Chem. Rev.* **2016**, 116, 771–785. (e) Skubi, K. L.; Blum T. R.; Yoon, T. P. Dual Catalysis Strategies in Photochemical Synthesis. *Chem. Rev.* **2016**, *116*, 10035–10074. (f) Yoon, T. P. Photochemical Stereocontrol Using Tandem Photoredox-Chiral Lewis Acid Catalysis. *Acc. Chem. Res.* **2016**, *49*, 2307–2315.

(29) Wang, C.-S.; Dixneuf, P. H.; Soule, J.-F. Photoredox Catalysis for Building C–C Bonds from $C(sp^2)$–H Bonds. *Chem. Rev.* **2018**, *118*, 7532–7585.

(30) (a) ErbasCakmak, S.; Leigh, D. A.; McTernan, C. T.; Nussbaumer, A. L. Artificial Molecular Machines. *Chem. Rev.* **2015**, 115, 10081–10206. (b) Wang, X.; Li, W.; Wang, W.; Yang, H. Heterorotaxanes. *Chem. Commun.* **2018**, *54*, 13303–13318.

(31) Dong, J.; Liu Y.; Cui, Y. Chiral Porous Organic Frameworks for Asymmetric Heterogeneous Catalysis and Gas Chromatographic Separation. *Chem. Commun.* **2014**, *50*, 14949–14952.

(32) Huang, X.; Jeong, Y.; Moon, B. K.; Zhang, L.; Kang, D. H.; Kim, I. Self-Assembly of Morphology-Tunable Architectures from Tetraarylmethane Derivatives for Targeted Drug Delivery. *Langmuir*, **2013**, *29*, 3223–3233.

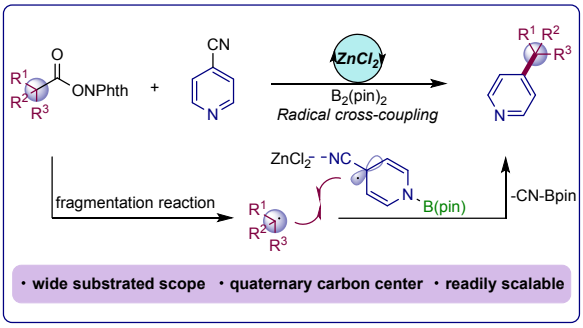
(33) Zhang, S.; Kim, B. S.; Wu, C.; Mao, J.; Walsh, P. J. Palladium-Catalysed Synthesis of Triaryl(heteroaryl)methanes. *Nat. Commun.* **2017**, *8*, 14641.

(34) For 3-phenylpropanoic acid, the H-atom abstraction and homo-coupling byproducts of the alkyl radical were detected by GC-MS analysis (see Fig. S19 in Supporting Information for details).

(35) (a) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. Design of Density Functionals by Combining the Method of Constraint Satisfaction with Parametrization for Thermochemistry, Thermochemical Kinetics, and Noncovalent Interactions. *J. Chem. Theory. Comput.* **2006**, *2*, 364–382. (b) Zhao, Y. Truhlar, D. G. A New Local Density Functional for Main-Group Thermochemistry, Transition Metal Bonding, Thermochemical Kinetics, and NonCovalent Interactions. *J. Chem. Phys.* **2006**, *125*, 194101. (c) Zhao, Y. Truhlar, D. G. Density Functional for Spectroscopy: No Long-range Self-Interaction Error, Good Performance for Rydberg and Charge-Transfer States, and Better Performance on Average than B3LYP for Ground States. *J. Phys. Chem. A.* **2006**, *110*, 13126–13130.

(36) (a) Li, S.; Ma, J.; Jiang, Y. Linear Scaling Local Correlation Approach for Solving the Coupled Cluster Equations of Large Systems. *J. Comput. Chem.* **2002**, *23*, 237–24. (b) Li, W.; Ni, Z.; Li, S. Cluster-in-Molecule Local Correlation Method for post-Hartree–Fock Calculations of Large Systems. *Mol. Phys.* **2016**, *114*, 1447–1460. (c) Ni, Z.; Li, W.; Li, S. Fully Optimized Implementation of the Cluster-in-Molecule Local Correlation Approach for Electron Correlation Calculations of Large Systems. *J. Comput. Chem.* **2019**, *40*, 1130–1140.

(37) Zhao, D.; Song, R.; Li, W.; Ma, J.; Dong, H.; Li, S. Accurate Prediction of NMR Chemical Shifts in Macromolecular and Condensed-Phase Systems with the Generalized Energy-Based Fragmentation Method. *J. Chem. Theory Comput.* **2017**, *13*, 5231–5239.


ONPhth
CN
ZnCl2
B2(pin)2
Radical cross-coupling
fragmentation reaction
ZnCl2-
-NC
B(pin)
-CN-Bpin
• wide substrated scope • quaternary carbon center • readily scalable