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Direct regioselective C-3 halogenation of pyridines

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Chao Li[1,4], Xinyao Li[2,4], Jiaxing Li[1,4], Zhixing Wang[1], Dunhuang Ouyang[1], Ning Jiao[1] ✉ & Song Song[1,3] ✉

Pyridine derivatives are one of the most common heterocycles in chemistry. The 3-halopyridines are generally synthesized by indirect methods, including functional group conversion or a temporary dearomatization–rearomatization process. Although the direct electrophilic halogenation of pyridines provides straightforward access to 3-halopyridines, it has been rarely reported owing to the poor π nucleophilicity of pyridines. Here we describe a general direct regioselective C-3 halogenation of pyridines promoted by an ether solvation effect. This radical process enables the regioselective reaction to occur at the C-3 position of pyridines, rather than other aromatic C–H bonds, and can be applied to the late-stage halogenation of complex molecules. The mechanistic studies show that the interaction between the pyridine substrate, ether solvent and haleniums plays a dominant role in the reactivity and regioselectivity.

As one of the most common heterocycles, pyridine derivatives are widely used in diverse fields[1,2]. The 3-halopyridines display distinct physiological, pharmacokinetic and pharmacological properties due to the characteristic halogen-atom effect[3,4]. These compounds not only form the core structures of approved drugs like nicergoline and roflumilast[5,6], but also act as essential synthons for preparing 3-functionalized pyridines via subsequent bond-forming reactions[7,8] (Fig. 1a). Thus, developing synthetic methods for regioselective halogenation of pyridines is of high importance. Nevertheless, such methods have only been developed in recent years. In 2013, Hartwig and co-workers reported the direct C-2 fluorination of pyridines[9]. Recently, McNally[10], Ritter[11] and our group[12] described the C-4 halogenation of pyridines. In spite of the reports on C-3 functionalization of pyridines[13–19], those on the direct regioselective C-3 halogenation of pyridines are lacking.

Electrophilic aromatic halogenation is the most convenient method for synthesizing aryl halides[20,21]. Over the past 150 years, substantial advances, including new halogenating reagents[22–25], catalytic systems[26–32] and activation strategies[33–38] have enabled halogenation of challenging aromatic substrates. However, owing to the inherent inertness of pyridines[39,40], these strategies have proven largely applicable only to pyridines bearing electron-donating groups[25–27,30,35]. Therefore, the halogenation of pyridines bearing electron-withdrawing groups (for example NO_2, CF_3 and CN) has not been achieved (Fig. 1b, left). On the other hand, the reported late-stage halogenation of complex molecules bearing both pyridine and other aromatics almost exclusively delivers halogenated products at the benzene ring[25–27,30]; the corresponding regioselective halogenation occurring at the pyridine rings via a one-step strategy has rarely been reported (Fig. 1b, right). So far, 3-halopyridines have generally been synthesized by indirect methods (Fig. 1c). For example, Knochel and co-workers realized C-3 iodination of pyridines through preinstalled directing groups at the C-4 position[41]. The Hartwig group reported the preparation of 3-halopyridines via iridium-catalysed borylation followed by *ipso* halogenation with copper salts[42]. The decarboxylative halogenation of pyridine carboxylic acids was realized by the MacMillan group[43]. Recently, a temporary dearomatization–rearomatization strategy has been employed for the synthesis of 3-halopyridines. In 2022, McNally and co-workers reported C-3 halogenation of pyridines[44] through a Zincke imine intermediate[45–47]. At the same time, the Studer group developed C-3 halogenation of pyridines[48] via an oxazino pyridine intermediate[49–52]. Despite these advances, regioselective and direct C-3 halogenation of pyridines, which is the most straightforward and step-economical

[1]State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing, China. [2]Department of Chemistry, College of Sciences, Shanghai Engineering Research Center of Organ Repair, Shanghai University, Shanghai, China. [3]Beijing Advanced Center of Cellular Homeostasis and Aging-Related Diseases, Peking University, Beijing, China. [4]These authors contributed equally: Chao Li, Xinyao Li, Jiaxing Li.
✉e-mail: jiaoning@pku.edu.cn; ssong@bjmu.edu.cn

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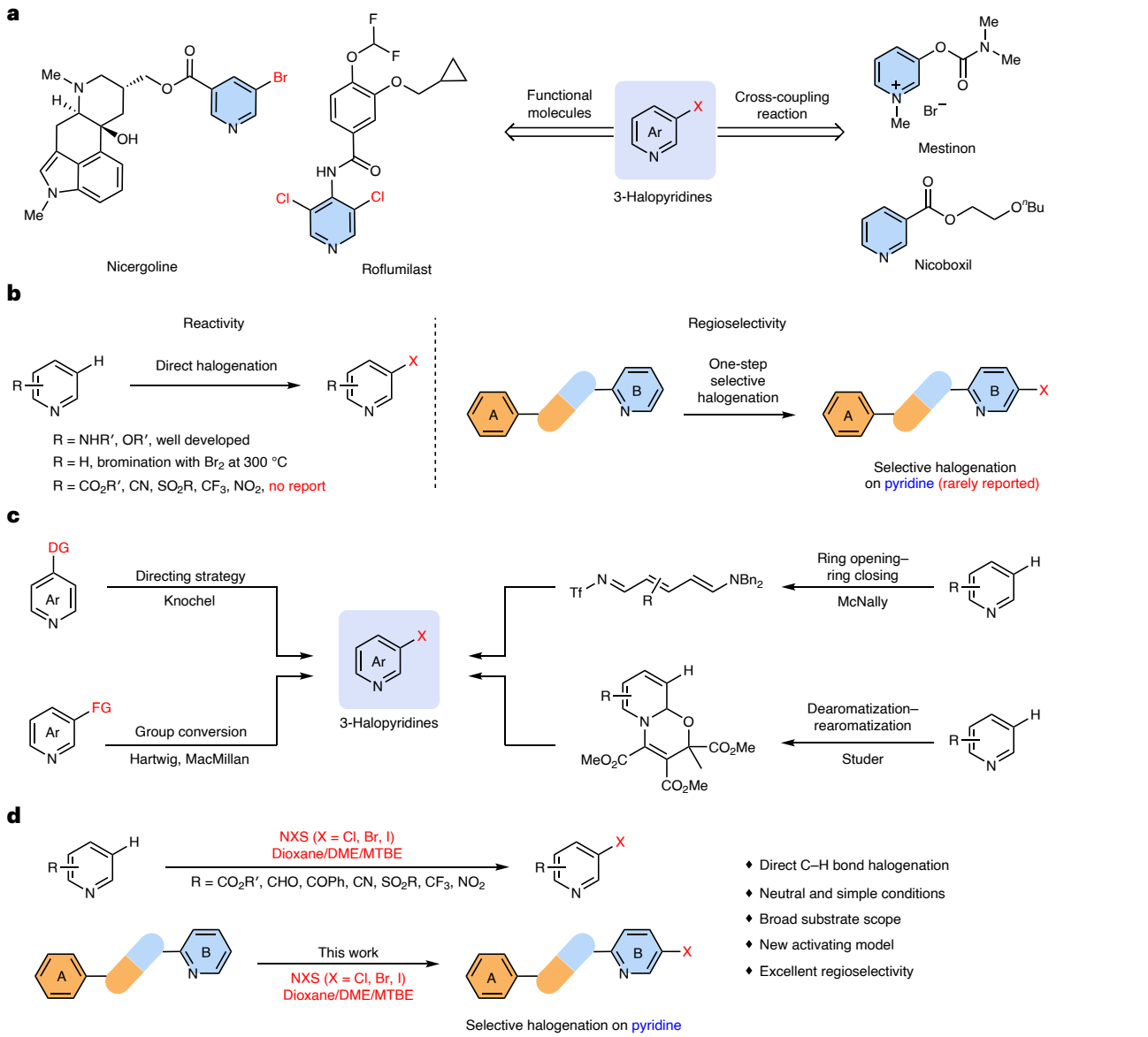

Fig. 1 | Strategies for regioselective C-3 halogenation of pyridines. **a**, 3-Halopyridines in pharmaceuticals and synthetic chemistry. **b**, The challenges in C-3 halogenation of pyridines. NHR, substituted amino; OR, substituted ether. **c**, The synthesis of 3-halopyridines via indirect methods. **d**, This work: direct regioselective C-3 halogenation of pyridines. Dioxane, 1,4-dioxane; DME, 1,2-dimethoxyethane; MTBE, *tert*-butyl methyl ether; NXS, *N*-halosuccinimide; DG, directing group; FG, functional group; Ar, aryl group; X, halogen group. Red and blue text labels highlight key points. The blue and orange shadings represent the differences between pyridine and aromatic rings in the molecule to highlight chemoselectivity.

route to 3-halopyridines, needs urgent development. Following our continuous development of halogenation strategies[53], in this Article we report a highly regioselective and direct C-3 halogenation of pyridines promoted by an ether solvent (Fig. 1d). We note that pyridines bearing electron-withdrawing groups were halogenated with high efficiency. The simple conditions and good functional group tolerance of this protocol allow it to be successfully applied to the late-stage synthesis and modification of bioactive molecules.

Results and discussion

Reaction development and substrate scope of C-3 halogenation of pyridines

Initially, we attempted to achieve C-3 halogenation of pyridine through a Lewis acid activation strategy[54]. Surprisingly, decreasing the Lewis acid loading enhanced the reaction efficiency, and the highest yield of product was obtained without the Lewis acid additive in dioxane (see Supplementary Table 1 for details). After careful screening of the reaction conditions, we were delighted to find that dioxane could promote C-3 bromination of pyridines efficiently in the presence of *N*-bromosuccinimide (NBS) without any other activator. Other ether solvents such as tetrahydrofuran (THF) and methyl *tert*-butyl ether (MTBE) were also suitable for promoting the *meta* bromination with relatively low yields. Meanwhile, no desired product **1** was detected in other solvents (see Supplementary Table 2 and Supplementary Scheme 1 for details). Under the optimized conditions, the bromination of various pyridines was explored to test the generality of this protocol (Fig. 2a). The pyridines bearing electron-withdrawing substituents including ester, cyano, nitro, trifluoromethyl, aldehyde, ketone, amide, sulfonamide or halogen at the *meta* position were halogenated to the corresponding products **1**–**12** in moderate to good yields. In addition, benzyl-, alkyl- or phenoxy-substituted pyridines also underwent bromination to afford products **13**–**15** in moderate yields. To our delight, the 2,3′-bipyridyl could be mono-brominated with high selectivity at the less sterically hindered pyridine in this reaction system

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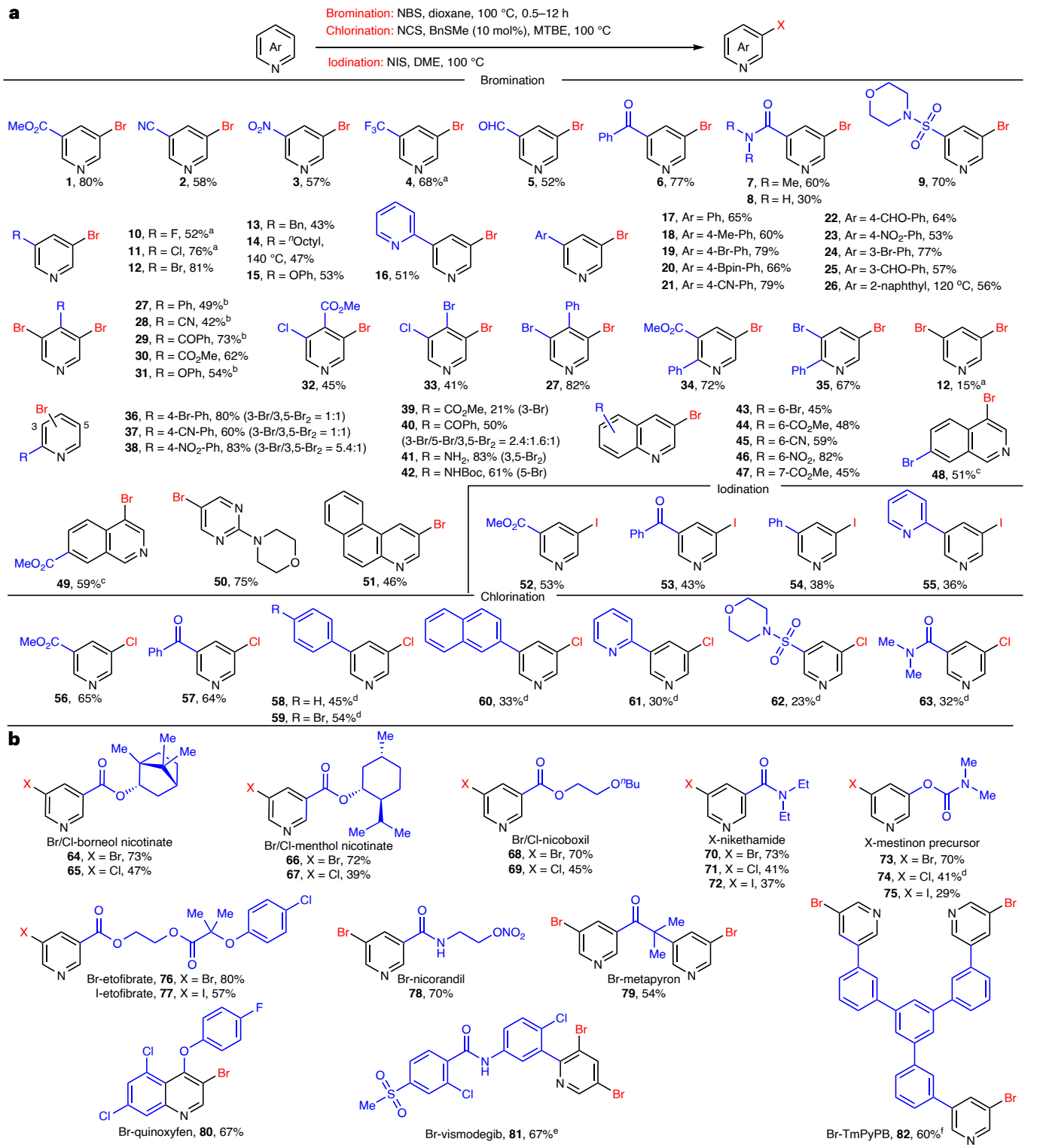

Fig. 2 | C-3 halogenation of pyridines. a, Substrate scope of the halogenation of pyridines. **b**, Late-stage halogenation of drugs and materials. See Supplementary Section 3 for experimental details for each substrate. Conditions for bromination: substrate (0.5 mmol) and NBS (1.0–2.5 mmol) in dioxane (2 ml) were stirred under air for 0.5–12 h. Unless otherwise specified in the substrate scope, the reaction temperature was 100 °C. The ratios given in brackets are based on the constituents of the total yield. Conditions for iodination: substrate (0.5 mmol) and NIS (2.5 mmol) in DME (1 ml) were stirred in a sealed tube at 100 °C for 18 h. Conditions for chlorination: substrate (0.5 mmol), *N*-chlorosuccinimide (NCS) (1.5 mmol) and BnSMe (10 mol%) in MTBE (2 ml) were stirred in a sealed tube at 100 °C for 12 h. [a]NMR spectroscopy yields are reported due to the low boiling point of the product. [b]NBP (2 mmol), 120 °C for 12 h. [c]TBCA (0.33 mmol). [d]NCP (1.5 mmol). [e]NBS (2.5 mmol), 120 °C for 1 h. [f]NBS (3.0 mmol) in dioxane (6 ml), 100 °C for 18 h. Bn, benzyl; Ar, aryl; Bpin, boronic acid pinacol ester; Boc, *tert*-butoxycarbonyl; TmPyPB, 3,3′-[5′-[3-(3-pyridinyl)phenyl][1,1′:3′,1″-terphenyl]-3,3″-diyl]bispyridine; NBP, *N*-bromophthalimide; TBCA, tribromocyanuric acid; NCP, *N*-chlorophthalimide.

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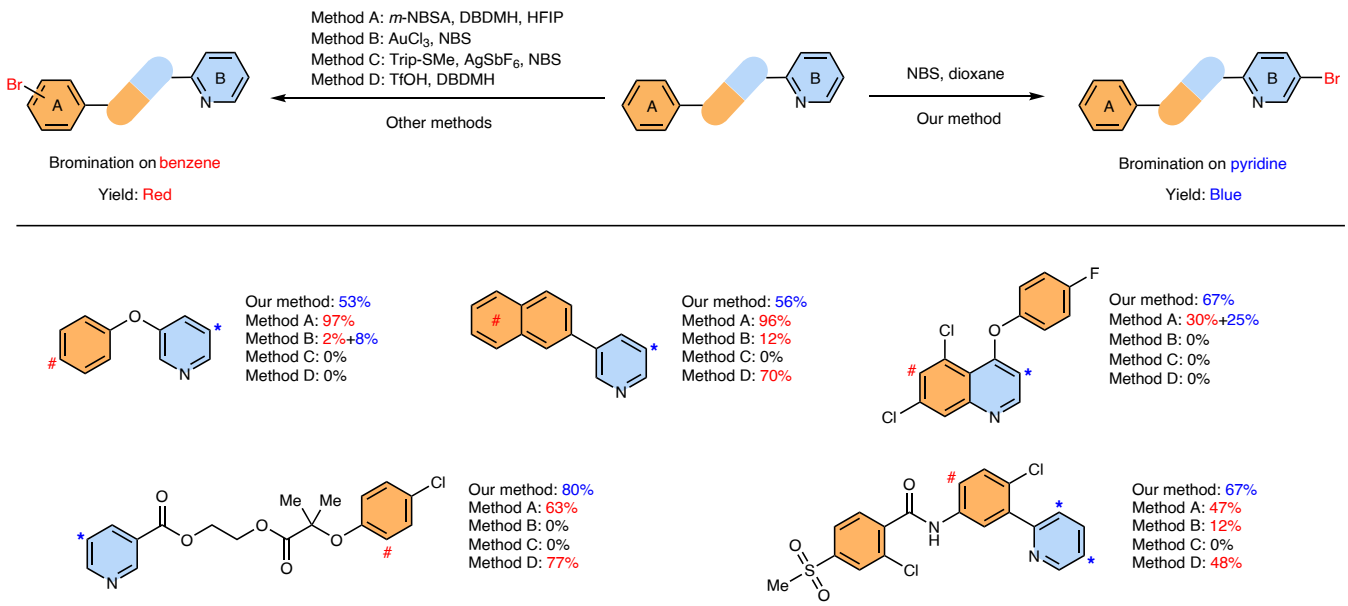

Fig. 3 | Comparison of selectivity with literature methods. Our method: substrate (0.5 mmol) and NBS (1.0–2.5 mmol) in dioxane (2 ml) were stirred under air at 100 °C for 0.5–12 h. Method A: substrate (0.5 mmol), DBDMH (0.30 mmol) and *m*-NBSA (0.025 mmol) in HFIP (2 ml) were stirred under air at 60 °C for 24 h. Method B: substrate (0.5 mmol), NBS (0.50 mmol) and $AuCl_3$ (0.025 mmol) in 1,2-dichloroethane (DCE) (2 ml) were stirred under air at 80 °C for 12 h. Method C: substrate (0.5 mmol), NBS (0.50 mmol), Trip-SMe (0.025 mmol) and $AgSbF_6$ (0.005 mmol) in DCE (3 ml) were stirred under air at room temperature for 12 h. Method D: substrate (0.5 mmol), DBDMH (0.25 mmol) and TfOH (0.5 mmol) in DCE (2 ml) were stirred under air at room temperature for 2 h. The sites of halogenation reactions are denoted by the symbols * and #. The red and blue text indicate bromination on benzene and pyridine rings, respectively. *m*-NBSA, *m*-nitrobenzenesulfonic acid; DBDMH, 1,3-dibromo-5,5-dimethylhydantoin; HFIP, 1,1,1,3,3,3-hexafluoro-2-propanol; Trip-SMe, 9,10-[1,2]benzenoanthracen-9(10*H*)-yl(methyl)sulfane; TfOH, trifluoromethanesulfonic acid.

(to give **16**). Furthermore, *meta*-aryl substituted pyridines furnished the halogenation with high efficiency and good regioselectivity to afford **17**–**26** in moderate to good yields. Moreover, 4-substituted pyridines were converted into the corresponding di-bromination products **27**–**31** in moderate yields. The disubstituted pyridines showed good reactivity under optimized conditions (to give **27** and **32**–**35**). However, the unsubstituted pyridine was dibrominated in only 15% yield (to give **12**), along with significant substrate degradation. The *ortho*-substituted pyridines bearing an electron-deficient benzene ring, ester or ketone or an electron-donating amino group could also be brominated to deliver mono- and di-substituted products **36**–**42**. In addition, this method could be extended to the halogenation of isoquinoline, quinoline, pyrimidine and benzoquinoline scaffolds (to give **43**–**51**). This system was also successfully applied to the chlorination and iodination of various pyridines, albeit with slightly lower yields (see Supplementary Tables 3 and 4 for details). The iodination of 3-substituted pyridines bearing an ester, a ketone, an aryl or a heteroaryl group went smoothly to afford **52**–**55** with dimethyl ether (DME) as the solvent. We note that catalytic benzyl methyl sulfide could improve the chlorination with MTBE as the solvent. A series of pyridines bearing an ester, a ketone, an aryl, a heteroaryl, a sulfamide or an amide group was chlorinated with moderate yields (to give **56**–**63**).

Halogen atoms significantly modulate the properties of drug compounds[3,4]. Consequently, late-stage halogenation provides a reliable strategy for rapid modification of pharmaceuticals and materials, circumventing de novo synthesis[5,6]. Therefore, we applied our method to achieve late-stage halogenation of bioactive molecules (Fig. 2b). Borneol nicotinate, menthol nicotinate and nicoboxil, bearing electron-withdrawing ester groups, underwent halogenation smoothly with high efficiency (to give **64, 66 and 68**). Nikethamide was converted into the corresponding halogenated product **70** in 73% yield. A precursor of mestinon bearing an amide ester group was brominated in 70% yield (to give **73**). The bromination of etofibrate and nicorandil delivered **76** and **78** with the tolerance of the ester, ether or nitro group. The two pyridine rings in metapyron were both brominated under the modified conditions tolerating the ketone group (to give **79**). Quinoxyfen with a quinoline scaffold was also tolerated to afford **80** in 67% yield. The bromination of vismodegib delivered dibrominated product **81** with excellent selectivity on the pyridine ring. The photoelectric material TmPyPb was also compatible with the present reaction system, affording the corresponding product **82** in 60% yield. In addition to bromination, the late-stage chlorination and iodination of the drugs also went smoothly to afford the halogenated products **65, 67, 69, 71, 72, 74, 75** and **77** with relatively lower yields under the present conditions.

Comparison of methods

We compared our method with established bromination methods for late-stage functionalization of pharmaceuticals containing pyridine and benzene rings, which are the two most prevalent arenes in drug design (Fig. 3; see Supplementary Section 4 for details). To our delight, our method showed largely improved efficiency compared to a Lewis acid-catalysed system ($AuCl_3$ (ref. 28)), a Brønsted acid-catalysed system (*m*-nitrobenzenesulfonic acid (*m*-NBSA)/1,1,1,3,3,3-hexafluoroisopropanol (HFIP) (ref. 26), TfOH (ref. 33)) and a Lewis base-catalysed system (triptycenyl sulfide (Trip-SMe) (ref. 29)). We note that good regioselectivity on the C-3 position of pyridine was observed in our bromination system, while the bromination under *m*-NBSA/HFIP, TfOH and Trip-SMe conditions occurred on the benzene ring or on both the benzene and pyridine rings (Fig. 3). These experiments revealed that our present NBS/ether system showed high reactivity and different regioselectivity compared to the above-mentioned methods.

Synthetic applications

3-Bromopyridine **1** can be easily converted into other value-added motifs. For example, brominated pyridine **1** underwent Suzuki–Miyaura reaction to deliver alkyl pyridine **83**. In addition, alkenyl and alkynyl pyridines **84** and **85** were obtained from 3-bromopyridine **1** via Heck

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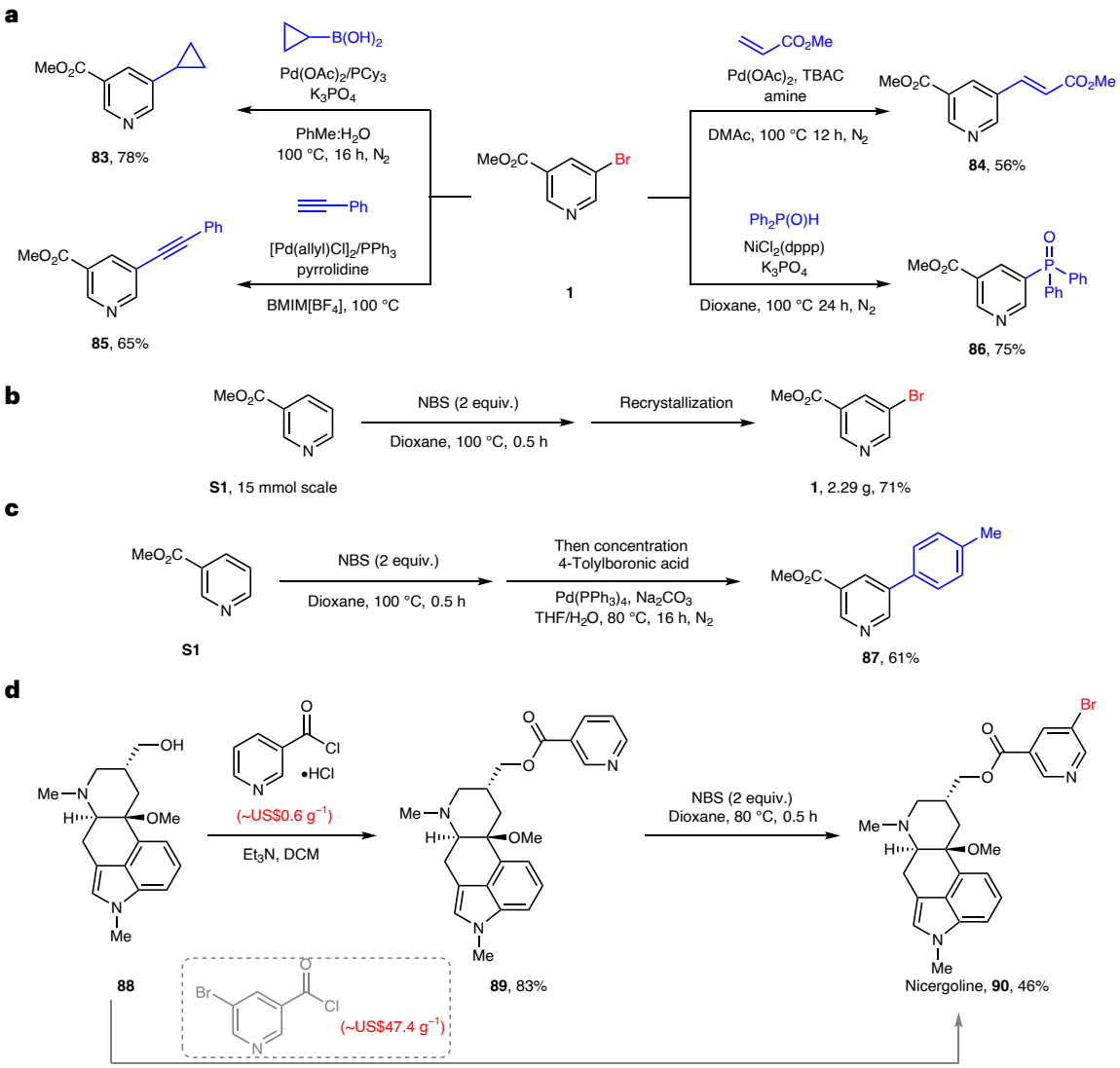

Fig. 4 | Applications of 3-halopyridines. a, 3-Bromopyridine **1** can be easily converted into other 3-functionalized pyridine derivatives. **b**, The scale-up experiment was conducted without column chromatography. **c**, The one-pot C-3 arylation of pyridine was achieved via the developed halogenation method. **d**, The late-stage bromination served as the key step in the synthesis of nicergoline. The grey dotted line and grey structure represent two different strategies for synthesizing nicergoline, highlighting the advantages of our method. Ac, acetyl; PCy_3, tricyclohexyl phosphine; TBAC, tetrabutyl ammonium chloride; DMAc, *N,N*-dimethylacetamide; BMIM[BF_4], 1-butyl-3-methylimidazolium tetrafluoroborate; dppp, 1,3-bis(diphenylphosphino)propane; THF, tetrahydrofuran; DCM, dichloromethane.

or Sonogashira reaction. Furthermore, the reaction between **1** and diphenylphosphine oxide delivered methyl 5-(diphenylphosphoryl) nicotinate **86** in good yield (Fig. 4a). A scale-up experiment was conducted to afford 3-bromopyridine **1** in 71% yield without column chromatography, demonstrating the good operability of this halogenation (Fig. 4b). The C-3 arylation of pyridine **S1** to **87** was achieved in 61% yield via halogenation followed by a Suzuki–Miyaura reaction in a one-pot process (Fig. 4c), showing a convenient protocol for pyridine functionalization. With this bromination reaction as the key step, nicergoline **90** was conveniently prepared through the late-stage bromination of nicergoline precursor **89** (Fig. 4d). Compared to the reported method[55], our strategy exhibits exceptional advantages in raw material cost saving (approximately US\$0.6 g^{-1} for nicotinoyl chloride hydrochloride versus approximately US\$47.4 g^{-1} for 5-bromonicotinoyl chloride).

Mechanistic studies

Control experiments were systematically conducted to elucidate the reaction mechanism (Fig. 5a). No bromination was observed when NBS was replaced with molecular bromine (Br_2), indicating that Br_2 was not the active source of bromine (equation (1) in Fig. 5a). No desired product **1** was detected when NaBr or tetrabutylammonium bromide (TBAB) was used as the bromo-source, which ruled out the nucleophilic substitution pathway (equation (2) in Fig. 5a). The bromination of **S1** was restrained by (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), revealing this bromination is likely to undergo a radical process (equation (3) in Fig. 5a). The yield of **1** was unaffected when the reaction was performed in the dark, ruling out the influence of light (equation (4) in Fig. 5a). When 1,1-diphenylethylene was added to the standard conditions, brominated diphenylethylene **91** was observed in 75% yield with trace amount of **1**, indicating the possibility of a radical mechanism (equation (5) in Fig. 5a). However, when 1,1-diphenylethylene was mixed with NBS in dioxane, no **91** was detected (equation (6) in Fig. 5a). These experiments showed that pyridine was crucial for the generation of bromo-radicals (equations (5 and 6) in Fig. 5a). On changing pyridine to methyl benzoate **92**, no brominated product was detected under standard conditions (equation (7) in Fig. 5a). Moreover, protonated pyridine **93** could not be brominated in the presence of NBS and dioxane (equation (8) in Fig. 5a). 2,6-Disubstituted pyridine **94** with significant

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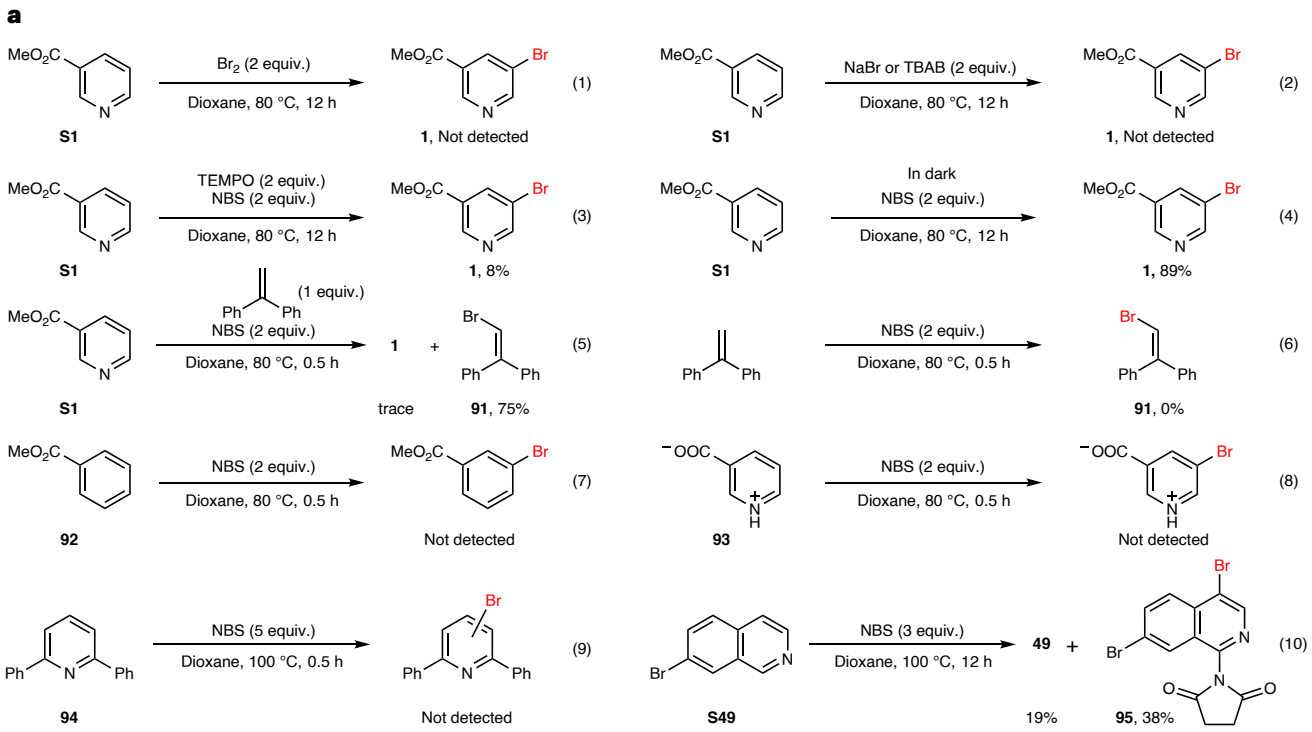

Fig. 5 | Mechanistic investigations. a, Control experiments were performed to understand the mechanism. **b**, ^{13}C NMR spectroscopy studies were conducted to investigate the interaction between pyridine and NBS. **c**, ^{13}C NMR spectroscopy studies were conducted to investigate the interaction between the ether solvent and NBS. TBAB, tetrabutylammonium bromide; TEMPO, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl.

steric hindrance at positions 2 and 6 also could not be brominated (equation (9) in Fig. 5a). These results imply that the nitrogen atom on the pyridine ring could interact with NBS to enable the bromination (equations (7–9) in Fig. 5a). We note that, when isoquinoline **S49** participated in this reaction in the presence of NBS, unexpected amination product **95** was obtained (equation (10) in Fig. 5a), revealing that the succinimide was likely to participate in the halogenation process.

To further prove the interaction between pyridine and NBS, ^{13}C NMR spectroscopy studies were conducted (Fig. 5b). The ^{13}C NMR spectroscopy signal of the carbonyl group in NBS shifted to a lower

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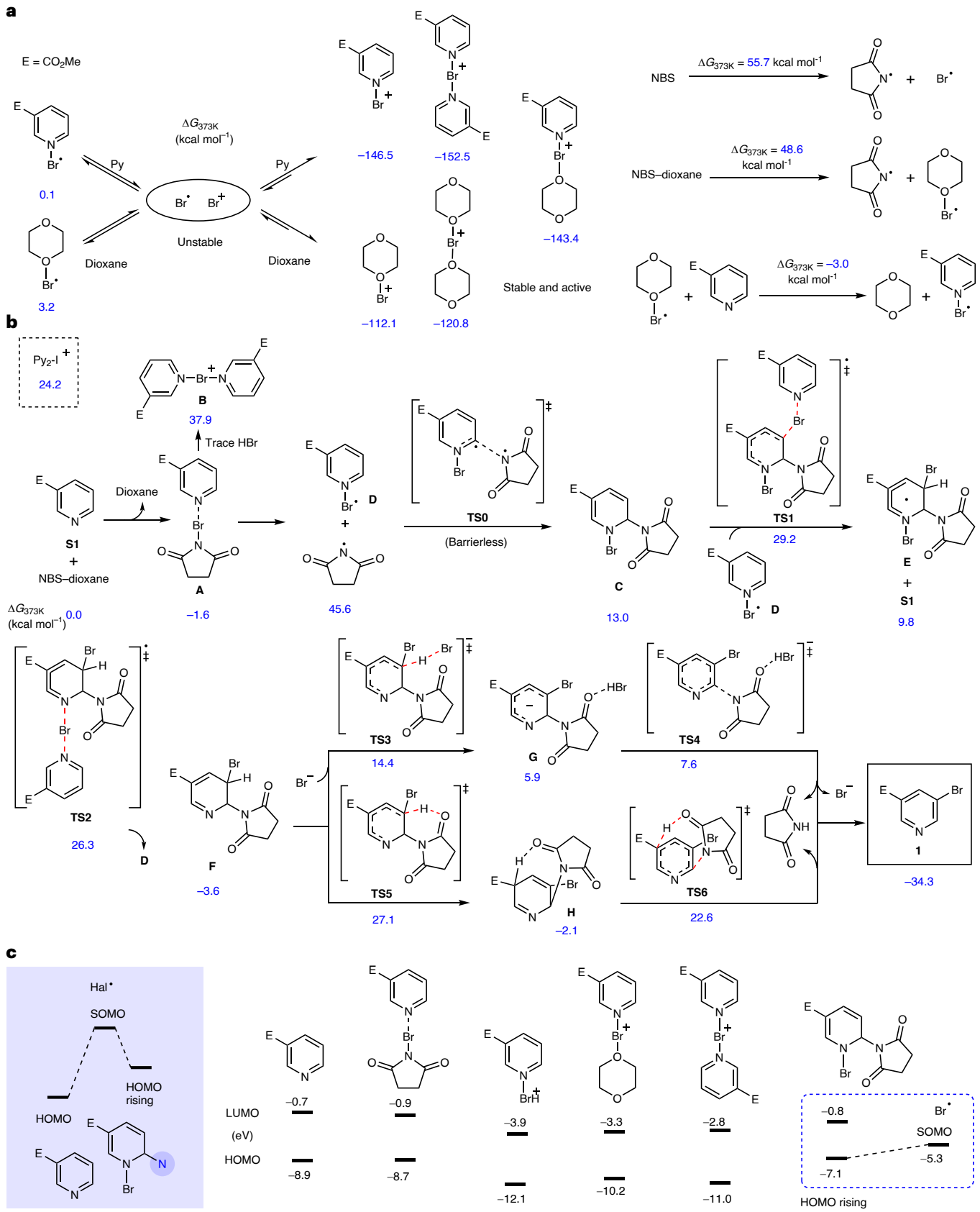

Fig. 6 | Density functional theory analysis of C-3 halogenation of pyridines. **a**, Br^+ and Br· species can be substantially stabilized by pyridine and dioxane. All calculations were performed at the M06-2X-D3(SMD, dioxane)/def2-TZVP//M06-2X-D3(SMD, dioxane)/def2-SVP level of theory. **b**, The possible pathway of regioselective C-3 bromination is proposed. **c**, The energy of frontier molecular orbitals was calculated to explain the distinct reactivity of pyridine–Br species. The shading in **c** emphasizes FMO modulation strategy. The dashed outlines are used to emphasize content. Py, pyridine.

field in the presence of pyridine **S1**, indicating that the electron density of the carbonyl group decreased. In addition, no significant difference was observed in the ^{13}C NMR spectroscopy signal of the carbonyl group in succinimide. These experiments confirmed the interaction between pyridine and the bromine atom of NBS. NBS showed a substantial change to a lower field in the presence of dioxane (Fig. 5c). This result is similar to that of a typical Lewis base, Ph_3PO (see Supplementary Scheme 18 for details), suggesting that the ether solvent functioned as a potential Lewis base. Furthermore, when pyridine and *N*-iodosuccinimide (NIS) in DME were stirred for 1 h, the formation of Py_2–I^+ (py, pyridyl) was detected by high-resolution mass spectrometry-electrospray ionization (HRMS-ESI) analysis (see Supplementary Scheme 20 for details).

Density functional theory calculations were then used to further understand the mechanism of C-3 halogenation of pyridines in dioxane (Fig. 6a–c). First, the treatment of halogenating agents such as NBS under heat conditions can generate the unstable Br^+ and Br· species[21,56,57]. However, Br^+ species can be significantly stabilized by pyridine and dioxane with stabilization free energies of 112.1–152.5 kcal mol^{-1} and Br· species can also have interactions with pyridine and dioxane (Fig. 6a, left). Especially in dioxane solution, the conversion of NBS into the succinimide radical and Br· species required a lower energy (48.6 versus 55.7 kcal mol^{-1}). Further bromine radical transfer provided a more stable pyridine bromine radical[58] (Fig. 6a, right). Then the regioselective C-3 bromination pathway of pyridine in dioxane as the model reaction was explored (Fig. 6b). Pyridine and NBS–dioxane form a complex Py–NBS (**A**), which can further convert into Py_2–Br^+ (**B**) together with trace HBr or Py–Br· (**D**) and the succinimide radical. This pair of radicals can undergo a radical-coupling reaction through the barrierless transition state **TS0** (see Supplementary Scheme 22 for details) to deliver Py–Br–NS (**C**) with a relatively lower free energy of 13.0 kcal mol^{-1}. The formation of **C** was confirmed by HRMS-ESI analysis[59] (see Supplementary Scheme 21 for details). For the NIS system, Py_2-I^+ was more stable than Py_2–Br^+, consistent with the experimental observation from HRMS analysis. Once **C** was formed, the stabilized Py–Br· (**D**) tended to attack the C-3 position of **C** through transition state **TS1** with an activation free energy of 29.2 kcal mol^{-1}, providing the intermediate **E**. With the release of the Br· species via **TS2** with an activation free energy of 16.5 kcal mol^{-1}, 3-Br(H)Py (**F**) was obtained as a stable species. The subsequent deprotonation step proceeds through two distinct pathways. In the presence of trace bromide ions, 3-H abstraction occurs via transition state **TS3** ($\Delta G^{\ddagger}$ = 18.0 kcal mol^{-1}), generating intermediate **G**. Subsequent succinimide departure proceeds with an extremely low barrier (**TS4**, $\Delta G^{\ddagger}$ = 1.7 kcal mol^{-1}) to afford the final product **1**. Alternatively, the intramolecular deprotonation by the carbonyl group of the succinimide moiety through **TS5** requires an activation free energy of 30.7 kcal mol^{-1}, followed by H-migration to the 5-position, yielding intermediate **H**. Succinimide elimination then occurs via **TS6** ($\Delta G^{\ddagger}$ = 24.7 kcal mol^{-1}), releasing the final product **1** along with free succinimide.

Finally, as the frontier molecular orbital (FMO) modulation strategy, including lowest unoccupied molecular orbital (LUMO), highest occupied molecular orbital (HOMO) or singly occupied molecular orbital (SOMO) activation has been well realized in the organocatalytic field, the energy of the frontier molecular orbitals was calculated to explain the distinct reactivity of the pyridine–Br species and bromine radicals (Fig. 6c). The HOMOs of Py, Py–NBS (**A**) and Py–Br^+ species were found at −8.7 to −12.1 eV and the SOMO energy level of the bromine radical was found at −5.3 eV. The relatively smaller energy difference (1.8 eV) between the HOMO of Py–Br–NS (**C**) and the SOMO of the bromine radical explains the outstanding reactivity observed for **C**.

Conclusions

In summary, we have reported a direct regioselective C-3 halogenation of pyridines. The commercially accessible reagents, broad functional group tolerance, operational simplicity and excellent selectivity of this reaction allow it to be successfully applied to the synthesis of 3-functionalized pyridines, late-stage functionalization of bioactive molecules and the concise syntheses of pharmaceuticals. The mechanistic studies showed that a halo-radical was generated under the reaction conditions and the interaction between pyridine and ether solvent with haleniums played a dominant role in the reactivity and regioselectivity.

Methods

Typical procedure for C-3 bromination of pyridines

A pyridine substrate (0.50 mmol, if solid) and NBS (1.0 mmol) were added to a sealed tube with a magnetic stir bar at room temperature. Then dioxane (2 ml) and a pyridine substrate (0.50 mmol, if liquid) were added in sequence and then the mixture was stirred at 600 r.p.m. at 100 °C for 0.5–12 h. After cooling down to room temperature, the solvent was removed by rotary evaporation. The residue was purified by chromatography on a silica gel (petroleum ether/ethyl acetate) to afford the brominated product. For complete experimental details, including procedures and full characterization (^1H and ^{13}C NMR spectroscopy, HRMS spectrometry) of all new compounds, see the Supplementary Information.

Data availability

The data that support the findings of this study are available in the Article and its Supplementary Information. Source data are provided with this paper.

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Author contributions

C.L. and S.S. conceived and designed the experiments. X.L. supervised the mechanistic studies. C.L., J.L., Z.W. and D.O. performed the experiments. C.L., J.L., Z.W., D.O., N.J. and S.S. analysed data. C.L., N.J. and S.S. wrote the paper. N.J. and S.S. directed the project.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Ning Jiao or Song Song.

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