ORGANIC CHEMISTRY

Radical and ionic *meta*-C–H functionalization of pyridines, quinolines, and isoquinolines

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Carbon-hydrogen (C–H) functionalization of pyridines is a powerful tool for the rapid construction and derivatization of many agrochemicals, pharmaceuticals, and materials. Because of the inherent electronic properties of pyridines, selective *meta*-C–H functionalization is challenging. Here, we present a protocol for highly regioselective *meta*-C–H trifluoromethylation, perfluoroalkylation, chlorination, bromination, iodination, nitration, sulfanylation, and selenylation of pyridines through a redox-neutral dearomatization-rearomatization process. The introduced dearomative activation mode provides a diversification platform for meta-selective reactions on pyridines and other azaarenes through radical as well as ionic pathways. The broad scope and high selectivity of these catalyst-free reactions render these processes applicable for late-stage functionalization of drugs.

Pyridines and their derivatives are among the most frequently occurring heteroarenes in pharmaceuticals and agrochemicals that contain N-heterocycles (Fig. 1A) (*1*, *2*). They also play prominent roles in ligands as well as functional materials (*3*, *4*). Selective modification of pyridines without preinstalled transformable functional groups can substantially increase step economy for the preparation of related, more elaborate compounds (*5*). The known methods for carbon-hydrogen (C–H) functionalization of pyridines mainly rely on the electronically biased reactivity of the ortho- and para-positions owing to the electronic deficiency of the π-system as well as the efficient σ-donor property of the nitrogen atom (*5*, *6*). Current strategies for direct functionalization of pyridines include directed metalation (*7*, *8*), Minisci-type radical reactions (*9*), and nucleophilic addition to N-activated pyridines (*10*, *11*). However, for unbiased pyridines, direct meta-functionalization is far more challenging, with limited documented examples (*12*). In particular, meta-selective processes proceeding in both radical and ionic reactivity modes are unavailable.

Although electrophilic aromatic substitutions have been applied to meta-selective halogenation and nitration of pyridines, the harsh acidic conditions limit their usage and frequently lead to regioisomeric products (*13*, *14*). Milder meta-functionalization reactions have been developed in recent decades, mainly through transition-metal catalysis (Fig. 1B) (*15*). On the basis of steric control, iridium-catalyzed C–H borylation and silylation reactions occur regioselectively at the meta position (*16*–*21*). Palladium-catalyzed *meta*-C–H olefination and arylation reactions were pioneered by the Yu group by using designed ligands for regioselectivity control (*22*–*25*). Despite the extensive development and application of those transition metal–catalyzed reactions, the reaction type and scope are still limited; for example, 3-substituted pyridines are required for regioselectivity control in most cases (*15*).

An alternative strategy for the meta-functionalization of pyridines is the temporary dearomatization approach, so that the initially electron-deficient heteroarenes are transformed into activated electron-rich intermediates. The ensuing electrophilic reactions and subsequent rearomatization provide exclusively meta-substituted heteroarenes (Fig. 1C) (*26*–*31*). Several strategies for the reductive dearomatization of pyridines have been developed along those lines (*32*, *33*). However, most of them generate either stable enamines so that rearomatization becomes energetically unfavorable, or alternatively very unstable intermediate *N*-silyl or *N*-boryl species that constrain applicable functionalization reactions. For example, the interrupted reductive dearomatization of pyridiniums allowed for subsequent selective C3-functionalization, but tetrahydropyridines instead of the aromatized heteroarenes were formed as the final products (*34*). meta-Selective silylation, alkylation, and trifluoromethylthiolation have been developed through 1,4-reduction of pyridines by silanes or boranes followed by in situ functionalization and oxidative rearomatization (*28*–*30*). Nevertheless, introduction of the trifluoromethyl and halogen groups to these reductively dearomatized intermediates remains unachieved, most likely because of the sensitivity of these intermediates to oxidation in the presence of electrophilic reagents (*35*). To date, none of the reported methods provide access to stable dearomatized intermediates of pyridines that possess enough redox stability to undergo radical addition and electrophilic halogenation instead of direct oxidative rearomatization yet still rearomatize under specific conditions, such as acid treatment. We present a protocol for versatile and practical *meta*-C–H functionalization of pyridines, quinolines, and isoquinolines through a redox-neutral dearomatization-rearomatization process (Fig. 1D). Pyridines can react with inexpensive and commercially available acetylenedicarboxylates to form Huisgen 1,4-dipoles, which readily undergo high-yielding dearomative cycloaddition reactions with carbonyl dipolarophiles (*36*, *37*). We found that the formed oxazino pyridines are bench-stable intermediates, which could engage in regioselective radical and ionic functionalizations by use of a variety of radical precursors and electrophilic reagents. Acid-promoted rearomatization then provides the corresponding meta-functionalized pyridines. With the redox-neutral activation method of N-heteroarenes, we could achieve exclusively meta-selective C–H functionalization to form trifluoromethyl, perfluoroalkyl, chloro, bromo, iodo, nitro, thio, and seleno N-heteroarenes under mild conditions.

We evaluated first the reaction conditions for redox-neutral dearomatization and rearomatization of pyridines (Fig. 2). A broad range of pyridines engaged in three-component coupling with dimethyl acetylenedicarboxylate (DMAD) and methyl pyruvate (MP) in acetonitrile at room temperature under air (tables S1 to S3), with an excellent average yield of 89% (fig. S5). The generated oxazino pyridine intermediates, used as mixtures of diastereoisomers [in some cases also as a regioisomeric mixture (fig. S5)], were stable toward air, water, and silica-gel-column chromatography (fig. S7), and these activated pyridines could then be used as efficient carbon-radical acceptors as well as nucleophiles in reactions with various electrophilic trapping reagents. Separation of the isomers was not required because they converged to the same product after functionalization and rearomatization. We found that rearomatization of the regioselectively C–H functionalized oxazino pyridine intermediates is readily achieved in aqueous acid at 60°C in quantitative yields (table S4).

Considering the radical *meta*-pyridine functionalization, C–H trifluoromethylation of the oxazino pyridine intermediates merits attention. Although radical trifluoromethylation is a practical method for installing the pharmaceutically highly relevant trifluoromethyl group on arenes (*38*), poor regioselectivity has been observed for unbiased pyridines owing to polarity-mismatch (*39*). A general strategy to directly install a trifluoromethyl or other perfluoroalkyl groups selectively at the meta-position of pyridines under mild conditions is highly desirable. In this work, we realized formal direct meta-selective trifluoromethylation of pyridines by merging the dearomatization-rearomatization strategy with trifluoromethyl radical chemistry. Trifluoroiodomethane, one of the cheapest trifluoromethyl sources (*38*), together with the organic base DBU (1,8-diazabicyclo[5.4.0]

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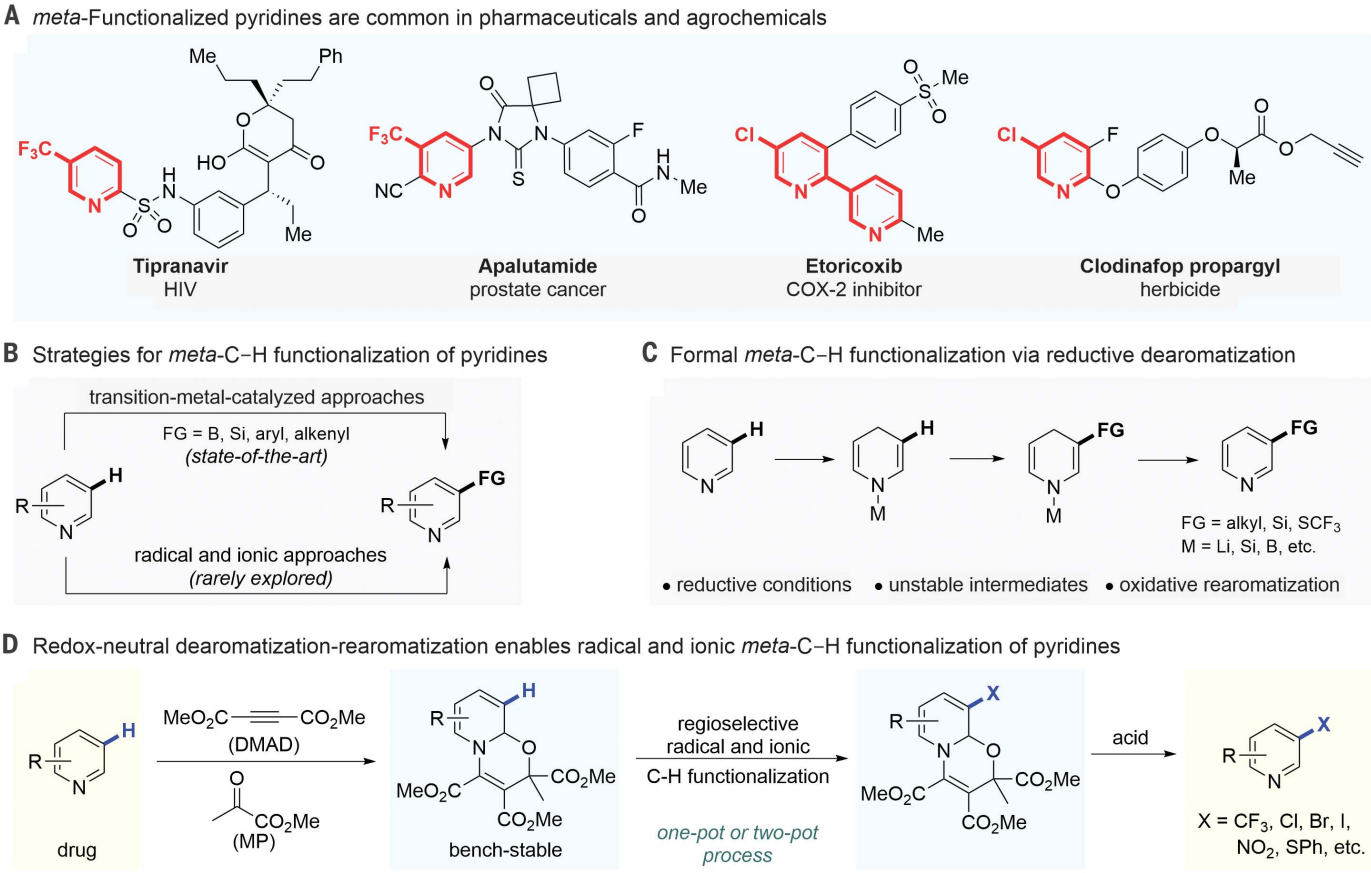


Fig. 1. meta-Functionalization of pyridines. (**A**) Various biologically active compounds containing a meta-functionalized pyridine moiety. (**B**) Established routes for the direct *meta*-C–H functionalization of pyridines. (**C**) meta-Functionalization through reduction to the dihydropyridine. (**D**) Developed strategy through redox-neutral activation of pyridines and subsequent regioselective ionic and radical C–H functionalization. FG, functional group; DMAD, dimethyl acetylenedicarboxylate; MP, methyl pyruvate.

undec-7-ene) effectively promote trifluoromethylation of the oxazino pyridine intermediates under blue light irradiation. We propose that the generated electrophilic trifluoromethyl radical (figs. S12 to S14) should electronically match with the nucleophilic dearomatized intermediates (*40*), which should also be responsible for the high regioselectivity. Blue light was required for chain initiation through carbon-iodine (C–I) bond homolysis, and we assumed that the radical generated by the addition of the trifluoromethyl radical to the oxazino pyridine intermediate further reacts through iodine atom abstraction from CF_3I, sustaining the chain (fig. S14). DBU-mediated HI elimination leads to the C–H trifluoromethylated oxazino pyridine, driving the endothermic I atom transfer step (*41*).

Both electron-donating phenyl (**2**), phenoxy (**3**), alkyl groups (**7**), and electron-withdrawing halo substituents (**9**, **10**, **11**, and **16**) on pyridines at different positions were compatible with the reaction. For substrates with two *meta*-C–H positions available (**1** to **6**), including unsubstituted pyridine (**1**), only mono-functionalized products were obtained. The dienamine entity of the oxazino pyridine intermediates was reactive at the β- and δ-position, and 2-aryl pyridines gave a mixture of 3- and 5-functionalized products (**5** and **6**). The reverse selectivity for products **5** and **6** indicates the inherent steric bias of the radical addition process. Chloro-, bromo-, and iodo-trifluoromethylated pyridines (**9**, **10**, and **11**, respectively), which can serve as versatile precursors to drug-like compounds, were accessible in moderate yields. The reaction was also compatible with other heteroarenes, such as thiophenes (**5**), pyrazoles (**13**), and oxazoles (**14**), with activation (dearomatization) and accordingly C–H functionalization chemoselectively occurring on the pyridine moiety. In general, electron-rich arenes such as thiophenes are better trifluoromethyl radical acceptors than pyridines (*39*), showing that our activation mode overrides innate reactivity patterns. Along these lines, our strategy enables selective trifluoromethylation of pyridines in the presence of electron-rich arenes (**3** and **5**). Multisubstituted pyridines (**15**, **16**, and **20** to **23**) were compatible substrates. Quinolines (**17**), isoquinolines (**18**), and naphthyridines (**19**) also engaged in the transformation on application of the same activation strategy to provide the corresponding trifluoromethylated heteroarenes with complete meta-selectivity. Along with the trifluoromethyl group, other polyfluoroalkyl groups (**4**, **6**, **8**, **12** to **15**, and **20** to **22**) could also be introduced to the meta position of pyridines, quinolines, and isoquinolines under the same conditions by simply varying the radical precursors. As compared with the trifluoromethylation, perfluoroalkylation with the corresponding commercial iodides worked with higher efficiency. The relatively low yields of the trifluoromethylation reactions were mainly due to low conversions (figs. S10 and S11). Varying the oxazino pyridine moiety by using different dipolarophiles for pyridine dearomatization did not provide better results (figs. S8 and S9). With iodoacetonitrile, meta-alkylation of pyridines could be achieved, albeit in low yield (**23**).

Direct meta-halogenation of pyridines under mild conditions has been a longstanding challenge in synthetic chemistry (*42*). Using the redox-neutral dearomatization activation strategy, selective electrophilic halogenation

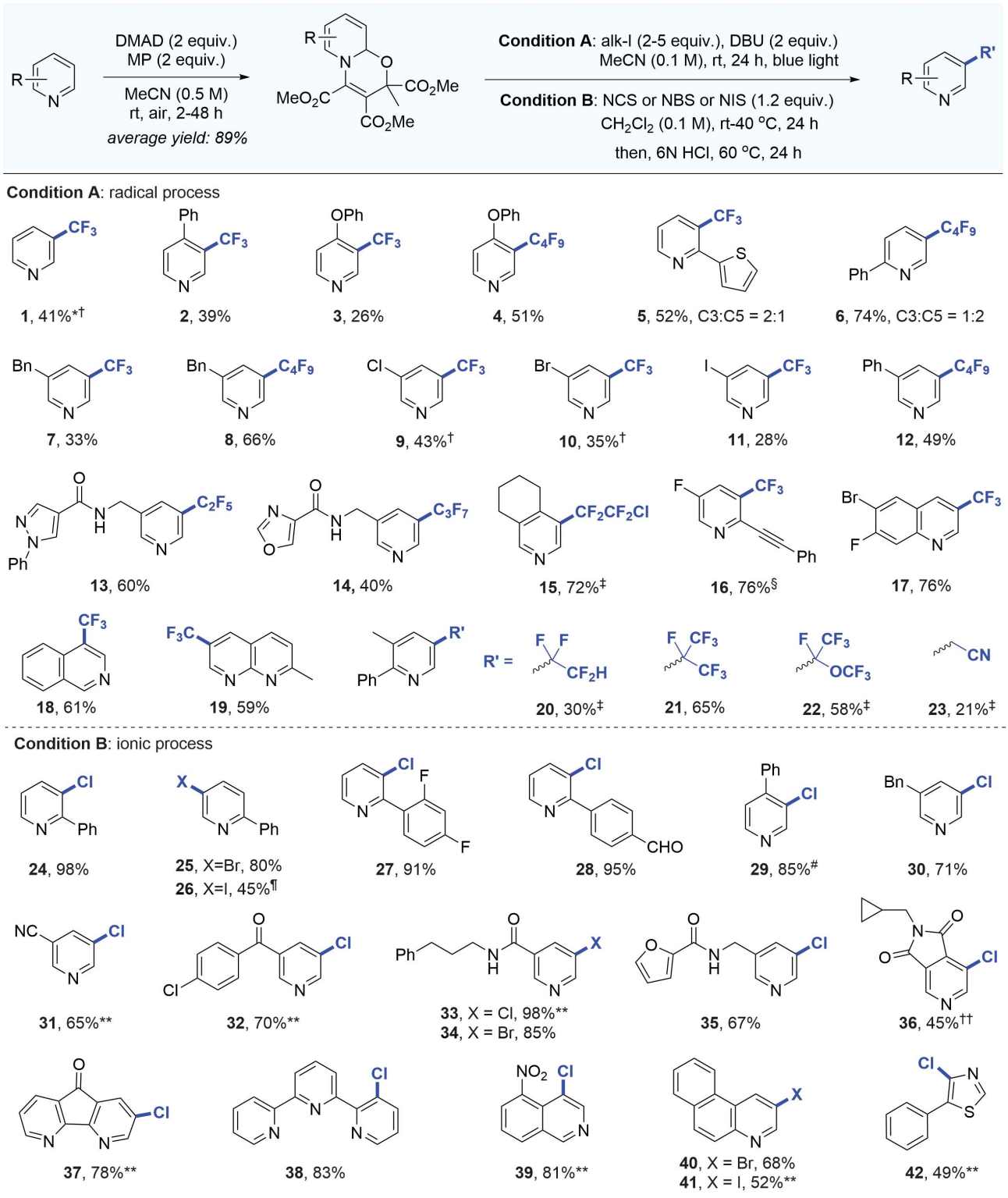
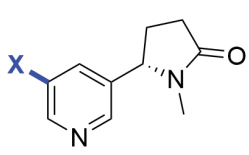
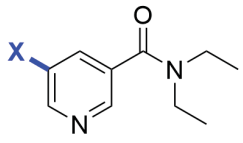


Fig. 2. Scope of radical meta-fluoroalkylation and ionic meta-halogenation. Compounds **1** to **23** are accessible through radical C–H functionalization by using condition A. Ionic functionalization leads to halogenated heteroarenes **24** to **42** by applying condition B. All yields of pyridine products correspond to isolated yields on the basis of the isolated dearomatized intermediates. Asterisk indicates 1.3 equiv alkyl iodide. Dagger symbol (†) indicates that yield was determined by the analysis of ^{1}H nuclear magnetic resonance (NMR) spectra of crude product by using dibromomethane as an internal standard. Double-dagger symbol (‡) indicates 10 equiv alkyl iodide. Section symbol (§) indicates that H_2SO_4 was used instead of HCl. Paragraph symbol (¶) indicates 60% conversion based on the analysis of ^{1}H NMR spectra of crude product by using dibromomethane as an internal standard. Pound symbol (#) indicates mono- and di-chlorination at 3- and 5-positions, with a ratio of 5:1 (mono:di). Two asterisks (**) indicate trimethyl silyl chloride (2.0 equiv) as additive, heating at 40°C. Two dagger symbols (††) indicate trimethyl silyl chloride (2.0 equiv) as additive, heating at 60°C. DMAD, dimethyl acetylenedicarboxylate; MP, methyl pyruvate; MeCN, acetonitrile; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; NCS, *N*-chlorosuccinimide; NBS, *N*-bromosuccinimide; NIS, *N*-iodosuccinimide.

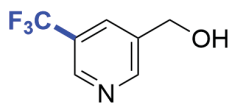


from (-)-cotinine

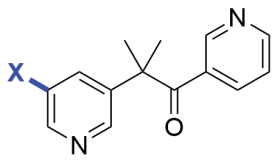
43, X = CF_3, 49%
44, X = C_2F_5, 74%
45, X = Cl, 75%
46, X = Br, 80%
47, X = I, 48%
48, X = NO_2, 30%
49, X = SPh, 42%
50, X = SePh, 40%



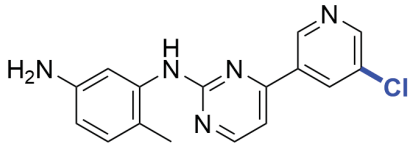
from nikethamide
51, X = Cl, 60%
52, X = SPh, 61%



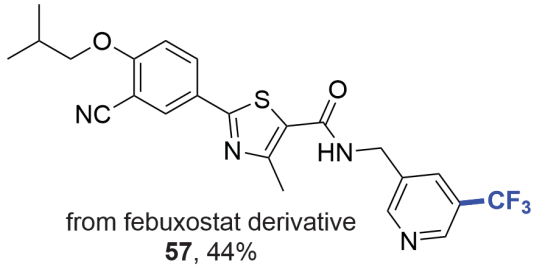
from nicotinyl alcohol
53, 36%*



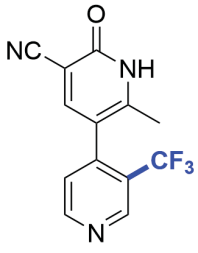
from metyrapone
54, X = CF_3, 47%
55, X = Cl, 68%



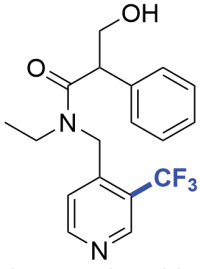
from imatinib precursor
56, 76%†



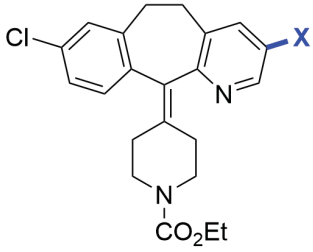
from febuxostat derivative
57, 44%



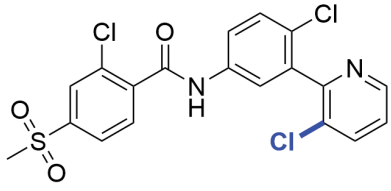
from milrinone
58, 38%, mono:di =1:1



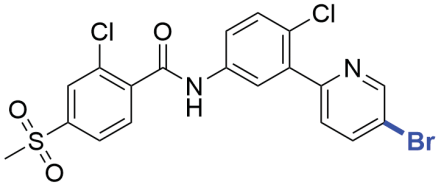
from tropicamide
59, 41%



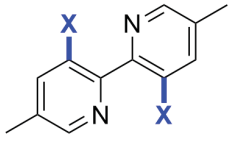
from loratadine
60, X = CF_3, 56%
61, X = C_2F_5, 65%
62, X = Br, 48%



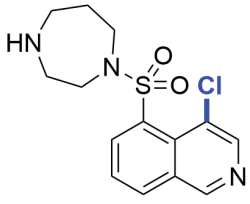
from vismodegib
63, 92%



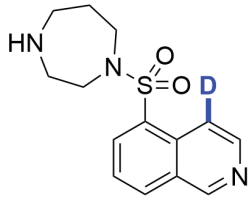
from vismodegib
64, 69%



from abametapir
65, X = Cl, 70%
66, X = Br, 51%



from fasudil
67, 51%‡



from fasudil
68, 86%, >99% D‡

Fig. 3. meta-Functionalization of drugs and drug derivatives. Radical trifluoromethylation of various heteroarene containing biologically active molecules is achieved. The ionic C–H functionalization can be used for *meta*-C–H halogenation, nitration, sulfanylation, selenylation, and deuteration on more complex heteroarenes. All yields of pyridine products correspond to isolated yields on the basis of the isolated dearomatized intermediates. Experimental details are provided in the supplementary materials. Asterisk indicates from the corresponding acetate. Dagger symbol (†) indicates from the corresponding acetamide. Double-dagger symbol (‡) indicates from the corresponding *tert*-butyl carbamate.

at the meta-position of pyridines possessing both electron-rich and electron-poor substituents was readily achieved with commercially available *N*-halosuccinimides (**24** to **42**). For 2-aryl pyridines with two meta-positions available, mono-chlorination and mono-bromination were achieved with opposite regioselectivity (**24** to **28**) as chlorination occurred exclusively at the 3-position, whereas bromination proceeded at the 5-position, addressing the β- or δ-reactivity of the dienamine intermediate, respectively. A plausible explanation is that chlorination occurs irreversibly at the more nucleophilic β-position, delivering the kinetic product, whereas because of the weaker carbon-bromine (C–Br) bond, bromination is reversible and leads to the less sterically hindered and thermodynamically more stable δ-bromo dienamine intermediates (*42*, *43*). This analysis is in line with the iodination that also occurs exclusively at the 5-position (**26**). We observed good selectivity of mono-chlorination for 4-aryl pyridines (**29**). Activation of the chlorinating reagent, *N*-chlorosuccinimide, with trimethylsilyl chloride (*44*) further extended the scope to more electron-deficient pyridines (**31** to **34**, **36**, and **37**) that are virtually unreactive under conventional electrophilic aromatic halogenation conditions (*13*). Moreover, bipyridine and terpyridine ligands, such

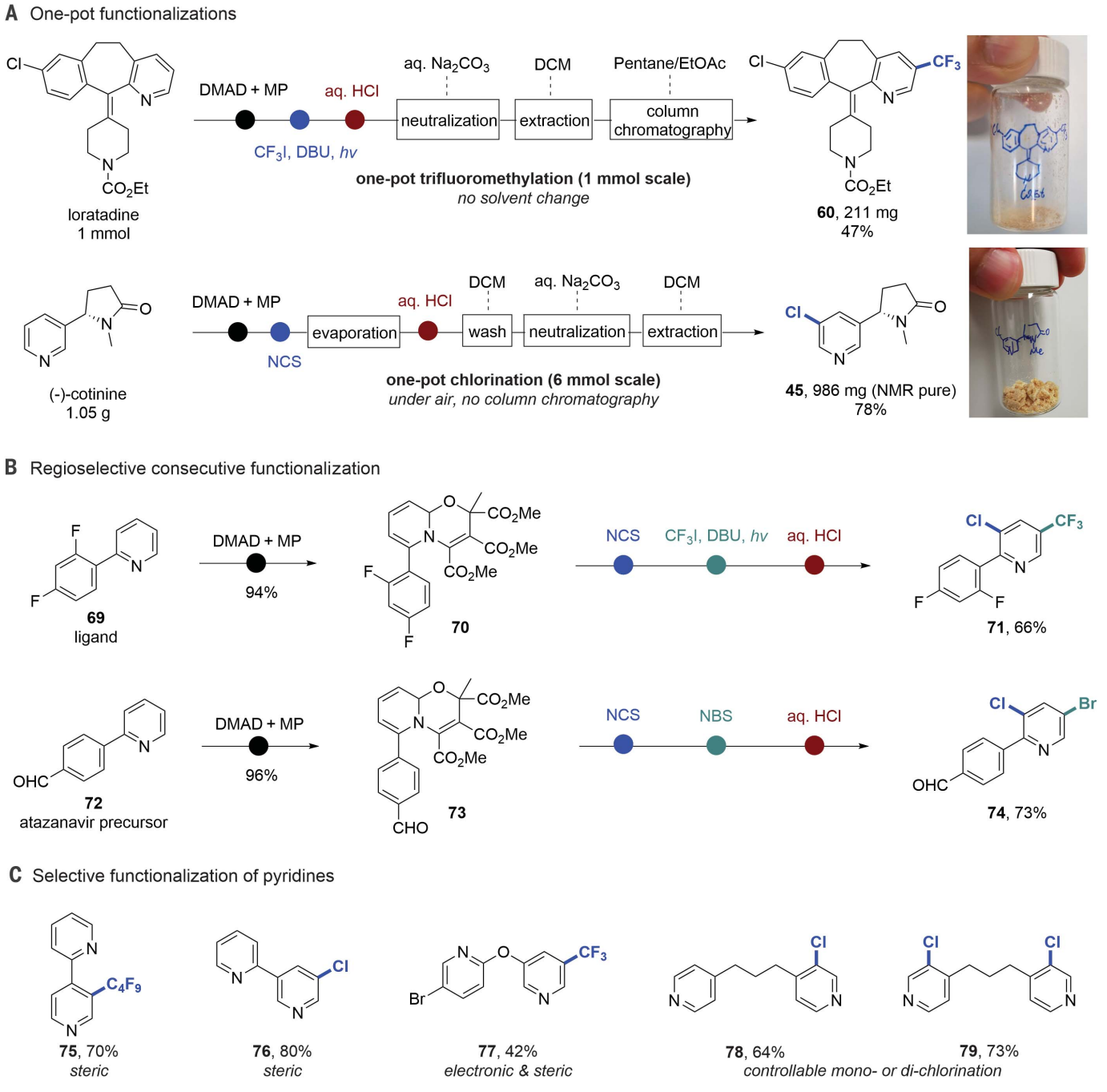


Fig. 4. Synthetic applications. (**A**) meta-Trifluoromethylation of loratadine and meta-chlorination of (–)-cotinine as one-pot processes on a larger scale. (**B**) Sequential radical-ionic or ionic-ionic meta,meta′-difunctionalization of pyridines. (**C**) Chemoselective *meta*-C–H functionalization of molecules containing two pyridine rings.

as **37** and **38**, could be selectively monodearomatized at one of the pyridine rings, delivering after rearomatization monochlorinated products. Isoquinolines (**39**) and 1-azaphenanthrenes (**40** and **41**) can also be selectively halogenated at the meta position of the pyridine core. The potential application of this redox-neutral activation strategy toward other N-heteroarenes could be demonstrated by the successful 4-selective chlorination of a thiazole compound (**42**).

Late-stage functionalization enables rapid modification of drugs, drug candidates, and materials without the need for de novo synthesis (*45*, *46*). We demonstrated that the developed redox-neutral dearomatization-functionalization-rearomatization strategy is a practical method for the direct late-stage modification of drugs that contain pyridine moieties (Fig. 3). Twelve drugs and drug derivatives with varied substitution patterns underwent diverse meta-selective functionalizations in generally good yields (30 to 92%; **43** to **68**). As an illustration, various functionalities—including trifluoromethyl (**43**), pentafluoroethyl (**44**), chloro (**45**), bromo (**46**), iodo (**47**), nitro (**48**), sulfanyl (**49**), and selenyl (**50**) groups—could be selectively introduced into the meta position of the alkaloid (–)-cotinine through radical and ionic pathways. Although some drugs and precursors required protection of the hydroxyl or amino groups before dearomatization (**53**, **56**, **67**, and **68**), acid-promoted rearomatization

expediently furnished the free alcohol or amine products. The relatively electron-rich pyridine ring in metyrapone was selectively trifluoromethylated (**54**) and chlorinated (**55**) in 47 and 68% yield, respectively. The pyrimidine moiety in the imatinib precursor was well tolerated (**56**; 76%). Tropicamide with a 4-alkyl pyridine moiety was mono-trifluoromethylated in moderate yield (**59**), whereas milrinone with a 4-aryl pyridine moiety delivered an isolable mixture of mono- and di-trifluoromethylated products (**58**). Vismodegib furnished 3-chlorinated (**63**; 92%) and 5-brominated (**64**; 69%) products with exclusive regiocontrol. For the drug abametapir with a bipyridine structure, the mono-dearomatized intermediate gave meta, meta′-dichlorination (**65**; 70%) and meta,meta′-dibromination (**66**; 51%) products, probably because of high reactivity of the corresponding dearomatized intermediate. To illustrate the potential use of this redox-neutral activation method for other previously inaccessible meta-functionalization reactions, we achieved selective deuteration of fasudil (**68**; 86%, >99% deuterium) by treating the dearomatized intermediate with deuterated trifluoroacetic acid and deuterium oxide (D_2O).

The meta-functionalizations of pyridines described above were carried out by means of two-pot processes, in which the dearomatized intermediates were isolated before the ensuing C–H functionalization step to guarantee facile isolation of products and limit side reactions. This allowed for ready diversification because various radical precursors and electrophiles engage in the C–H functionalization, as we have documented. However, targeting a single meta-functionalized compound, we found that most reactions can be readily conducted as one-pot processes. To demonstrate the practicality and robustness of the method in both medicinal and process chemistry, we displayed one-pot reactions at a larger scale, starting from loratadine and (–)-cotinine (Fig. 4A and figs. S3 and S4). meta-Trifluoromethylation of loratadine on a 1-mmol scale gave 47% isolated yield of **60** without any solvent change. Gram-scale synthesis of meta-chlorinated (–)-cotinine **45** was achieved under air without the need for column chromatography. Through sequential ionic chlorination and radical trifluoromethylation, regioselective consecutive functionalization of a ligand was realized to generate 3,5-difunctionalized pyridine **71** (66% yield) without isolation of the mono-functionalized intermediates, leveraging the potential of the β- and δ-reactivity of the dienamine intermediates (Fig. 4B). Likewise, sequential ionic-ionic difunctionalization of the atazanavir precursor was accomplished (**74**; 74%). When two differently substituted pyridines were presented in the same molecule, the redox-neutral dearomatization showed high selectivity toward more electron-rich and less sterically hindered pyridines, allowing for chemoselective mono-meta-functionalization of polypyridine compounds [**54** and **55** (Fig. 3) and **75** to **79** (Fig. 4C)]. Even for compounds that contain pyridines in the same chemical environment, such as the linker molecule used to construct metal organic frameworks (**78** and **79**) (*47*), controlled mono- and di-dearomatization can lead to the corresponding mono- and di-chlorination products, respectively, in high yields.

We have developed a general method for radical and ionic *meta*-C–H functionalization of pyridines, quinolines, and isoquinolines through a redox-neutral dearomatization-rearomatization strategy. The high selectivity, robust reaction operations, broad scope of transformations, and late-stage application all contribute to the practicality of the method. Therefore, this redox-neutral activation approach for meta-selective functionalization of heteroarenes should be widely applicable in the pharmaceutical and agrochemical research arenas.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Supplementary Text
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