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*J. Am. Chem. Soc.*, **Just Accepted Manuscript** • DOI: 10.1021/jacs.9b13753 • Publication Date (Web): 22 Feb 2020

# Picolinate Directed Arene *meta*-C-H Amination via $FeCl_3$ Catalysis

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**ABSTRACT**: Direct C-H functionalization of aromatic compounds is a powerful tool for organic synthesis; however, differentiation amongst the ubiquitous and often chemically similar C-H bonds remains a significant challenge. Conflation with coordinating or directing groups incorporated into the intended substrate has helped address these limitations, although access to remote sites remains limited. Herein, we report an operationally simple and sustainable direct *meta*-selective $H_2N$-amination of benzylic and related aromatic picolinates under conditions mild enough to modify polyfunctional and late stage molecules.

## 1. INTRODUCTION

Arylamines are prominent structural motifs in a vast array of medically and economically important substances.[1] Traditionally, aminations of arenes utilized multi-step sequences and/or harsh reagents[2] (e.g., nitration/reduction), rearrangements (Beckmann, Curtius), reactive intermediates (benzynes[3]), or vicarious nucleophilic substitution (VNS) of strongly electron-deficient arenes.[4,5] These were largely superseded by aminations[6] via transition metal mediated cross-couplings with pre-functionalized substrates (e.g., Ullman-Goldberg,[7] Chan-Evans-Lam,[8] Hartwig/Buchwald[9]) or reactions of aryl anions with electrophilic amination reagents.[10,11] In more recent years, direct C-H functionalization procedures including aminations[12] have gained widespread acceptance and generally provide improved scope and efficiency. To address the challenge of differentiating amongst the various aromatic C-H bonds, which often have similar reactivities, C-H functionalization methodologies have been aided by embedded or introduced directing groups (DGs). This furnishes an additional level of regioselectivity, primarily proximal or ortho to the DGs, and in many cases can override the innate electronic and/or steric positional preferences of the aromatic substrate.[13] Extensions to *meta*-selective C-H functionalization, however, are more challenging due to spatial and/or geometric constraints.[14] The emergence of the Catellani[15] norbornene relay procedure,[16,17] purpose-designed U-shaped directing groups,[18-20] and other approaches,[21] have proven effective for *meta*-functionalization in many instances. Nevertheless, it was not until 2016 that Yu and colleagues[22] achieved the first and only directed *meta*-selective C-H arene amination (Fig. 1, Panel A). However, the Yu amination requires an elevated temperature and long reaction time (100 °C, 24 h); subsequent removal of the directing group utilizes hot hydrobromic acid (100 °C), conditions that can be anticipated to significantly limit synthetic applications. Based upon our prior investigations,[23,24] we envisioned a more practical aromatic electrophilic ($S_EAr$) amination procedure exploiting a weakly basic pyridyl directing group. Herein, we report[25] an operationally simple, direct *meta*-selective $H_2N$-amination of benzylic and related aromatic picolinates at rt-40 °C mediated by catalytic $FeCl_3$ under an inert atmosphere (Fig. 1, Panel B). This procedure contributes to the burgeoning list of iron-catalyzed C–H functionalizations[26a] while concurrently providing a high level of an otherwise elusive regioselectivity not observed in operationally similar aminations.[26b]

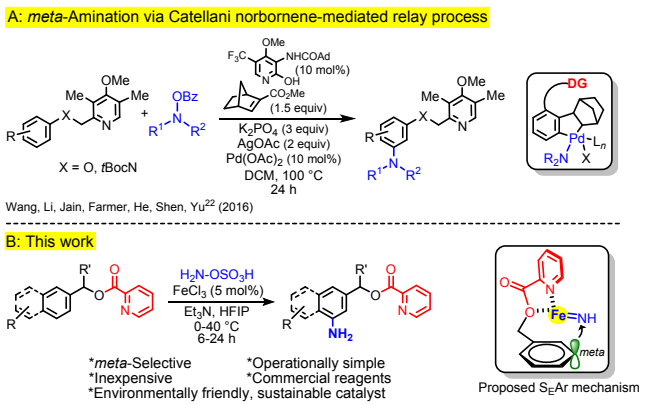


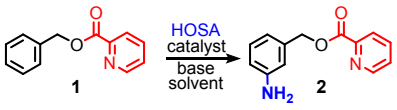

**Figure 1.** Directed Arene C-H *meta*-Amination Procedures. The *meta*-selective amination procedure reported by Yu and colleagues[22] (Panel A) is compared and contrasted with the method described herein (Panel B).

## 2. RESULTS AND DISCUSSION

Using benzyl picolinate (**1**) as a model system, a screen of common transition metal catalysts and known electrophilic aminating agents was used to identify the combination of $FeCl_3$ and commercial hydroxylamine-*O*-sulfonic acid[27] (HOSA) as optimum (Table 1). Most notably, spectral analyses of the crude reaction mixtures revealed that, of the three possible regioisomeric amination adducts, only *meta*-aminated **2** was present (≥99% by $^1H/^{13}C$ NMR, identified as the *N*-acetamide[28]); the structure of **2** was further confirmed by $^1H$ nOe after isolation. Using 1,1,1,3,3,3-hexafluoroisopropanol[29]

(HFIP) as solvent and HOSA/$Et_3N$ (2 equiv each) at rt, **2** was obtained in 72% isolated yield (entry 6) accompanied by unidentified, polar (baseline) material or 65% yield on a 5 mmol scale; in the former scale, **1** was completely consumed whereas 5% of **1** was recovered in the 5 mmol scale. In contrast with the Yu procedure,[22] no bis-aminated aryl picolinate was observed. Other organic and inorganic bases gave inferior results as did other solvents including 2,2,2-trifluoroethanol, MeOH, and $CH_2Cl_2$ as well as combinations with HFIP (see Supporting Information). Of several alternative commercial nitrogen-containing DGs, e. g., 1*H*-pyrrole-2-carboxylate, (*S*)-*N*-methylprolinate, 2-pyridineacetate, and 2-(dimethylamino) benzoate, only 1-isoquinolinecarboxylate was comparable to picolinate, although cost considerations excluded it from routine use. Removal of the picolinate directing group in **2** with $K_2CO_3$ in MeOH/$H_2O$ (10:1) at rt furnished 3-aminobenzyl alcohol in 81% yield.

**Table 1. Directed *meta*-Amination Optimization**[a]




| entry | catalyst (mol%) | solvent | base | temp (°C) | time (h) | yield (%) |
|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (10) | HFIP | $Et_3N$ | 40 | 24 | <5 |
| 2 | $Rh_2(esp)_2$ (10) | HFIP | $Et_3N$ | 40 | 24 | 0 |
| 3 | $Cu(OTf)_2$ (10) | HFIP | $Et_3N$ | 40 | 24 | <5 |
| 4 | $Ni(OAc)_2$ (10) | HFIP | $Et_3N$ | 40 | 24 | 0 |
| 5 | $FeBr_3$ (10) | HFIP | $Et_3N$ | 40 | 24 | 30 |
| 6 | $FeCl_3$ (5) | HFIP | $Et_3N$ | 23 | 10 | 72[b] |
| 7 | $FeCl_3$ (1) | HFIP | $Et_3N$ | 23 | 33 | 55 |
| 8 | $FeCl_3$ (0.1) | HFIP | $Et_3N$ | 23 | 33 | 42 |
| 9 | $FeCl_3$ (10) | TFE | $Et_3N$ | 40 | 24 | 20 |
| 10 | $FeCl_3$ (5) | THF | $Et_3N$ | 40 | 24 | 0 |
| 11 | $FeCl_3$ (5) | HFIP | CsOH | 23 | 26 | 30 |
| 12 | $FeCl_2$ (10) | HFIP | $Et_3N$ | 23 | 16 | 66 |

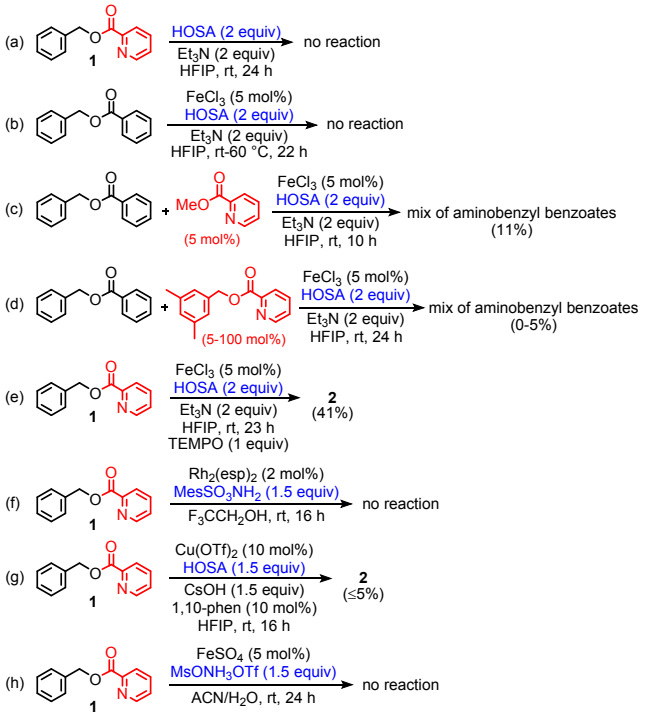
[a]See Supporting Information for additional details. [b]65% yield on 5 mmol scale, 5% of **1** recovered.

A selection of representative benzyl picolinates was explored to define the scope of the reaction (Table 2, Panel A) starting with 4-methyl-, 2-methyl- and 2,6-dimethylbenzyl picolinates that smoothly generated **3**, a regioisomeric mixture of **4a**,**b** (6:1), and **5**, respectively, overnight at rt. This series reveals picolinate-guided electrophilic aminations are comparatively unrestricted even if one or both *ortho*-positions bear substituents since it likely involves direct addition to the aromatic π-system (Fig. 1, Panel B). In contrast, methodology that operates through a Catellani norbornene-palladacycle,[15-17] templates,[18,20,30,31] or other protocols[32] to achieve *meta*-selectivity typically generate only the less hindered *meta*-isomer when one *ortho*-substituent is present, even if both *meta*-positions are available for functionalization; if both *ortho*-positions are occupied, their efficiencies suffer further and product yields are reduced. Generation of 4-methoxy-substituted adduct **6** in just 6 h is consistent with the influence of a powerful electron-donating substituent on a $S_EAr$ functionalization. Substitution at the benzylic position was well tolerated, e.g., **7** and **8a**,**b**, and had minimal influence on the distribution of regioisomers (cf., **4a**,**b** vs. **8a**,**b**). The picolinate of methyl *(R)*-mandelate, while more sluggish, still delivered a good yield of **9** whereas amination of benzaldehyde cyanohydrin to **10** was modest, but provided ready access to a useful masked aminated aldehyde. Arenes bearing electron-withdrawing substituents, *viz*., 3-trifluoromethyl **11**, 4-carbomethoxy **12**, 4-bromo **13**, and 2-chloro (**14a**,**b**), were warmed to 40 °C, except for 3,4-dichloro **15** that proceeded at rt. In this cohort, only 3-nitro-4-methoxy **16** was produced in poor yield, although most of the starting material was recovered.

Application to phenethyl picolinate led to a mixture of *meta*- and *para*-amines **17a,b** favoring the later by a factor of 2 (Table 2, Panel B). The appearance of this additional regioisomer is presumably due to the extended reach of the ethyl appendage. For phenpropyl picolinate, the distribution of *meta*-/*para*-regioisomers in **18a,b** moved closer to parity (1:1.2), but like its benzylic counterpart **9**, the reaction required 40 °C to reach completion. This might indicate some catalytically nonproductive bidentate binding of the $FeCl_3$ by the ester and picolinate.

To validate the utility of our methodology for applications to late stage molecules and pharmaceuticals, several polycyclic and multifunctional examples were examined (Table 2, Panel C). Interestingly, 1- and 2-naphthylmethanols showed a proclivity for functionalization of both rings giving rise to **19a**,**b** and **20a**,**b**, respectively. 2-Biphenylmethanol yielded **21a**,**b** as a 3:1 mixture. This regioselectivity likely reflects the orthogonal conformation of the two phenyl rings which brings the distal ring into closer proximity to the picolinate iron-nitrenoid chelate. The successful *meta*-selective aminations of dipeptide **22** and pyrazine **23** also bode well for applications with more complex systems.

**Scheme 1. Control Experiments**

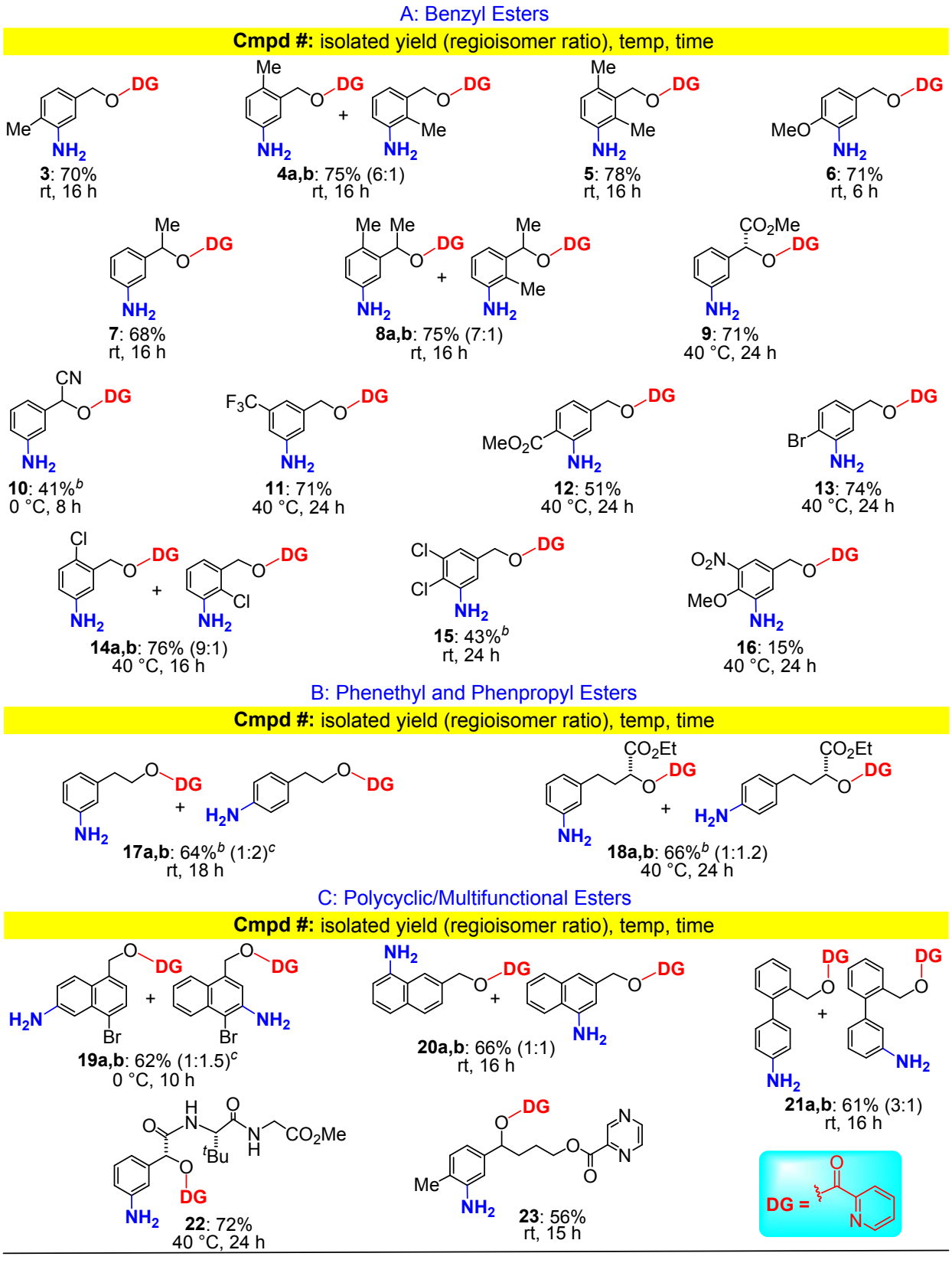



Mes = mesitylene, phen = phenanthroline

Control experiments proved instructive in understanding the requirements of the reaction. In the absence of $FeCl_3$ catalyst (Scheme 1a) or an attached picolinate directing group (Scheme 1b), the substrates, **1** and benzyl benzoate, were recovered unreacted even after prolonged reaction times. A mixture of regioisomeric aminobenzyl benzoates (11%) formed in the presence of added methyl picolinate (5 mol%) (Scheme 1c); however, there was no reaction in the presence of 1 equiv of

added methyl picolinate (see SI). To probe the possibility that the che-

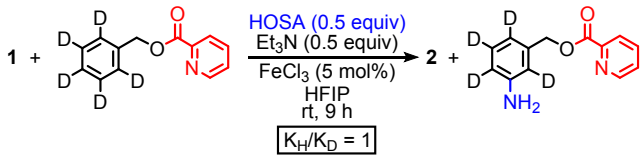
**Table 2. Directed C-H *meta*-Amination of Picolinates[a]**



[a]Reaction conditions: $FeCl_3$ (5 mol%), HOSA (2 equiv), $Et_3N$ (2 equiv), 0.1 M in HFIP. [b]4 equiv each of HOSA and $Et_3N$. [c]Ratio unchanged after 10-fold dilution which is consistent with intramolecularly directed amination.

lated active iron-nitrenoid species may need the extra stabilization provided by arene coordination, as suggested by a reviewer, 3,5-dimethylbenzyl picolinate was used as a ligand instead of methyl picolinate (Scheme 1d). A mixture of regioisomeric aminobenzyl benzoates (5%) formed in the presence of 5 mol% of 3,5-dimethylbenzyl picolinate; no reaction in the presence of 50 and 100 mol% of 3,5-dimethylbenzyl picolinate (see SI). We conclude from 1c and 1d that the picolinate directing group must be esterified to the substrate and that it plays a decisive role both in facilitating amination and as a *meta*-directing group. In the presence of TEMPO (1 equiv), the yield of **2** was reduced to 41% (Scheme 1e). Additional studies would be needed to determine if radicals have a role in the amination. An indication of the unique role of iron in these processes is highlighted by the failure or low conversion of **1** into **2** by other recently introduced transition metal C-H amination procedures including those mediated by $Rh_2(esp)_2$,[23] $Cu(OTf)_2$,[24] and $FeSO_4$[26b] (Schemes 1f,g,h, respectively).

**Scheme 2. Kinetic Isotope Effect Study**

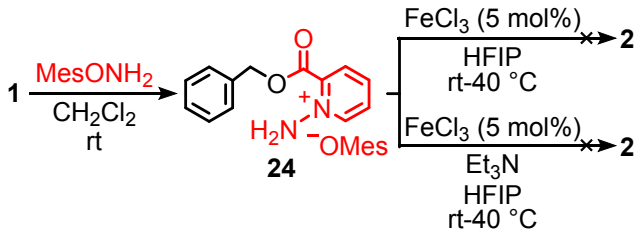



Competitive amination of an equimolar mixture of **1** and benzyl-2,3,4,5,6-$d_5$ picolinate using $FeCl_3$ (5 mol%) in HFIP (0.1 M) with a limiting amount of amination reagent [HOSA (0.5 equiv), $Et_3N$ (0.5 equiv)] at rt for 9 h. The ratio of **2** and 3-aminobenzyl-2,4,5,6-$d_4$ picolinate in the crude reaction product was measured by NMR.

To gain additional mechanistic insight, we measured the kinetic isotope effect (KIE) of the amination. Such studies have proven valuable for assessing mechanistic hypotheses in a wide variety of transition metal-catalyzed reactions.[33] An equimolar mixture of **1** and its deuterated analog, benzyl-2,3,4,5,6-$d_5$ picolinate, was subjected to competitive amination using $FeCl_3$ (5 mol%) in HFIP (0.1 M) with a limiting amount of amination reagent [HOSA (0.5 equiv) and $Et_3N$ (0.5 equiv)] at rt for 9 h (Scheme 2). $^1H/^{13}C$ NMR analyses of the crude showed a 1:1 mixture of *meta*-aminated products for a $K_H/K_D$ ratio of 1. Similar kinetic isotope effects (KIE) have been reported for related $Rh_2$-,[23] Cu(II)-,[24] and Fe(II/III)-mediated[26] reactions indicating C-H cleavage is not the rate-determining step, thus excluding organometallic C-H activation as a likely pathway. An alternative pathway invokes an *N*-aminopyridinium salt, generated *in situ* either directly from HOSA amination of the picolinate nitrogen or with the assistance of the iron catalyst, which serves as the actual amination intermediate. This was evaluated by independent preparation of **24** following literature procedure[34] and its exposure to $FeCl_3$, with and without $Et_3N$, in HFIP for 24 h with heating up to 40 °C (Scheme 3). No arene amination was observed.

Of the most plausible remaining C-H functionalization scenarios,[35] *viz*., (a) picolinate directed, iron-nitrenoid electrophilic aromatic substitution ($S_EAr$); (b) concerted metalation-deprotonation (CMD);[36] and (c) Heck-type carbometallation-elimination,[37] the electrophilic aromatic substitution ($S_EAr$) pathway [option (a)] is the most consistent with the regioselectivities in Table 2 and the above KIE measurements.

**Scheme 3. Preparation and Evaluation of 1-Amino-pyridinium 24 as a Potential Intermediate Leading to 2**




1-Amino-pyridinium 2,4,6-trimethylbenzenesulfonate (OMes) salt **24** was prepared according to literature procedure[34] and then heated with $FeCl_3$, with and without $Et_3N$, for 24 h. No *meta*-amino adduct **2** was observed.

## 3. CONCLUSIONS

Classical electrophilic aromatic functionalizations are associated with aggressive reagents and adherence to the Crum-Brown-Gibson Substitution Rule[38] (*ortho*/*para* vs *meta*). Consequently, *meta*-functionalizations of electron-rich and electron-neutral substrates are generally restricted or unavailable. The results presented above demonstrate picolinate directed C-H functionalizations can now be added to the options for remote arene functionalization strategies.[39] In light of its atom- and cost-efficiencies, we anticipate this methodology will find wide utility and encourage extensions to other C-H functionalization processes.

## 4. EXPERIMENTAL SECTION

General experimental considerations, procedures, analytical chromatograms, and spectral data are provided in the Supporting Information.

**General amination procedure.** To a stirring, 0 °C solution of HOSA (0.4 mmol, 2 equiv) in HFIP (1.5 mL) was added $Et_3N$ (0.4 mmol, 2 equiv). After 15 min, the picolinate ester (0.2 mmol, 1 equiv) in HFIP (0.5 mL) and anhydrous $FeCl_3$ (5 mol%; *n.b.*, deliquescent) were added sequentially. The reaction was conducted at the temperature indicated in Table 2. After complete consumption of the picolinate ester (6-24 h, monitored by TLC), the reaction mixture was diluted with $CH_2Cl_2$ (10 mL), washed with saturated aqueous $Na_2CO_3$ (10 mL), brine (10 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. The crude residue was purified on a commercial pre-packed $SiO_2$ column using a medium pressure, automated chromatograph equipped with a UV detector and eluted with MeOH/$CH_2Cl_2$ or EtOAc/hexanes to furnish aminated picolinate(s) in the indicated yield(s). Variations in reaction conditions are noted in the legend of Table 2 for select substrates.

## ASSOCIATED CONTENT

## SUPPORTING INFORMATION

The Supporting Information is available free of charge on the ACS Publications website at DOI:

General experimental considerations, procedures/characterization data, analytical chromatograms, and scanned spectra (PDF)

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### Notes

The authors declare no competing financial interests.

## ACKNOWLEDGMENT

Financial support provided by the Robert A. Welch Foundation (I-0011), Dr. Ralph and Marian Falk Medical Research Trust Bank of America, N.A., Trustee, and USPHS NIH (RO1 HL139793). Dr. Adeniyi Michael Adebesin is thanked for insightful advice and critical commentary.

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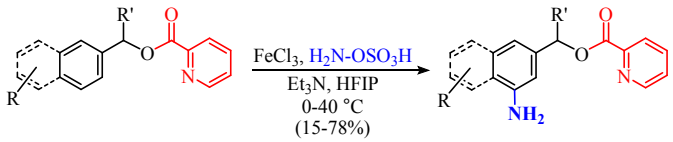


*meta*-selective • operationally simple • commercial reagents • inexpensive • sustainable