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Practical and Regioselective Synthesis of C4-Alkylated Pyridines

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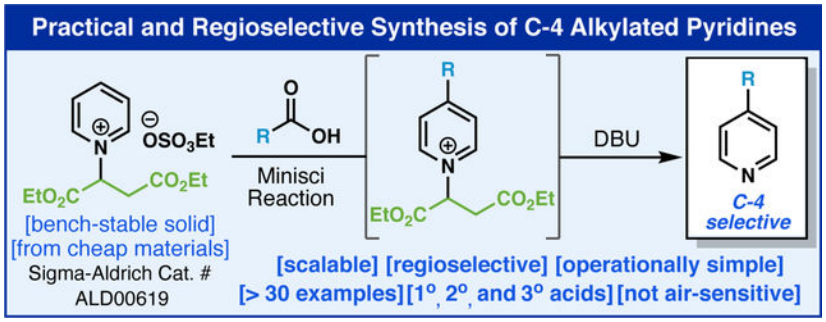
Abstract

The direct position-selective C–4 alkylation of pyridines has been a longstanding challenge in heterocyclic chemistry, particularly from pyridine itself. Historically this has been addressed using pre-functionalized materials to avoid overalkylation and mixtures of regioisomers. This study reports the invention of a simple maleate-derived blocking group for pyridines that enables exquisite control for Minisci-type decarboxylative alkylation at C–4 that allows for inexpensive access to these valuable building blocks. The method is employed on a variety of different pyridines and carboxylic acid alkyl donors, is operationally simple, scalable, and is applied to access known structures in a rapid and inexpensive fashion. Finally, this work points to an interesting strategic departure for the use of Minisci chemistry at the earliest possible stage (native pyridine) rather than current dogma that almost exclusively employs Minisci chemistry as a late-stage functionalization technique.

Graphical Abstract



The power of C–H functionalization logic in the context of synthesizing heteroaromatic structures is undeniable.[1] Its increasing utility in discovery and medicinal chemistry contexts is a testament to its utility in late-stage derivatization enabling structure activity relationships to be rapidly explored.[2] In particular, the venerable Minisci reaction and its many variants have long been recognized as a way to bypass pre-functionalized heterocycles

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at the carbon.[3] Just as the Friedel-Crafts reaction is commonplace for electron rich arene functionalization via electrophilic substitution, free radicals can react with electron deficient heterocycles by capitalizing on innate reactivity.[4] In cases where a heterocycle has multiple sites to intercept a free radical, mixtures often result which can be useful in a discovery setting but is problematic when a singular regiochemical outcome is desired (e.g. process scale).[5] For example, simple 4-alkylated pyridines (**1**, Figure 1A) are inaccessible using Minisci chemistry if a single regioisomer is desired. In such cases, C–4 prefunctionalization is necessary and the logical synthon is halopyridine **2**. This conundrum has rendered the early-stage application of Minisci chemistry on pyridine and mono-substituted pyridines rare in medicinal chemistry and, to our knowledge, non-existent on process scale. A recent collaborative program[6] within the agrochemical industry brought to our attention the need for a simple and inexpensive solution to this unmet challenge in pyridine alkylation for which available methods were not applicable. To be sure, several attempts to solve this problem from starting materials unfunctionalized at the carbon have appeared over the past decade (Figure 1B) mostly based on blocking competitive C–2 sites using transient or covalently linked species at the pyridine nitrogen.[7] Nakao's pioneering studies using bulky Al-based Lewis-acids in an elegant hydroarylation process is limited to olefin donors and must be performed in a glove box.[8] The Fier group at Merck invented clever oxime–based pyridinium species that could be employed in three examples of C–C bond formation with carbon-based nucleophiles.[9] Finally, the Hong group reported a radical-type addition using *N*-sulfonamidopyridinium species[10] using alkyl bromide donors requiring photochemical initiation and super stoichiometric amounts of an expensive silane [$(TMS)_3SiH$].[11] While this is an important precedent it could not be employed easily on process scale as three steps are needed to install the blocking group (1. *N*-amination using hydroxylamine-*O*-sulfonic acid, 2. tosylation, and 3. methylation with Meerwein's salt along with 1 column purification, 1 recrystallization). The Buchwald group reported a Cu-catalyzed, selective C–4 functionalization of pyridine with styrenes without a covalent blocking group, via a novel intramolecular rearrangement mechanism mediated by a pyridine coordinated copper species.[7e,7h] Herein we disclose a highly practical method featuring on a new blocking group based on a simple fumarate backbone (**6a**) enabling classic Minisci decarboxylative alkylations to take place with exquisite selectivity at C–4 (Figure 1C) under acid-free conditions. Emblematic of this advance is the preparation of 4-cyclohexylpyridine (**8**). Subjecting pyridine under four different Minisci-type conditions, the product cannot be accessed in a synthetically useful yield, and a mixture of isomers was observed.

Tactically, scalable access to valuable structures such as **8** (81% isolated yield from **6a**) can now be enabled with a dramatic reduction in cost. From a strategic perspective, this work opens a new dimension of retrosynthetic logic for use of the Minisci transform at an early rather than late stage.

Guided by colleague at Syngenta (E.G.) several criteria needed to be met for a practical blocking group (BG) design, such as: (1) derivation from feedstock materials (ca. $5/mole), (2) simple installation and removal, (3) high stability, ease of handling, and solubility in multiple solvents, and most critically, (4) complete regionchemical control to avoid the need for any chromatography. Towards this end, multiple BGs were explored with most falling

into one of two categories (Figure 2A): (1) simple BG installation with either modest or low reactivity under Minisci conditions (**BG1**, **2**, **4**, **6**) or (2) difficulty in forming a stable BG adduct. After extensive exploration, **BG10** emerged as an ideal candidate satisfying all of the criteria laid out above. **BG9** was the only other moderately successful one however it exhibited reduced reactivity towards Minisci addition. The preparation of pyridinium **6a** with **BG10** could be prepared through a simple, chromatography-free, two-step sequence starting from commodity materials (pyridine and maleic acid) followed by esterification. The structure of pyridinium **6a** was confirmed by X-ray crystallography and contained the ethyl sulfate as a counter-anion. This crystalline salt represents a straightforward gateway to a variety of C–4 alkylated pyridines (*vide infra*) and has been commercialized by Sigma-Aldrich (catalog # ALD00619).

The generalization of this fumarate-based BG approach is illustrated in Table 1 using acid-free Minisci conditions on a range of primary, secondary, and tertiary carboxylic acids. Although these C–4 alkylated pyridines appear simple, it is instructive to comment on the means by which such compounds were previously prepared. In nearly all cases the current method represents a more practical and cost-effective solution. In the case of primary carboxylic acid adducts, pyridine **11** was accessed from C–4 pre-functionalized 4-methylpyridine via lithiation-S_N2 with corresponding alkyl bromide (*ca.* \$105/g[13b]).[14] Pyridine **12** was obtained through an analogous sequence using an alkyl bromide containing a protected alcohol requiring subsequent deprotection and chlorination (*ca.* \$945/g[13b]).[15] Pyridine **13**, **14** and **17** were previously prepared via photochemical addition on 4-vinyl pyridine.[16] Pyridine **15** required a Pd-cross coupling on either 4-vinyl or 4-bromopyridine (Heck[17a] or Sonogashira,[17b] respectively) followed by reduction (*ca.* \$530/g[13c]). Similarly, pyridine **16** can be accessed via reduction of the Heck product of 4-vinylpyridine and an aryl iodide.[18]

Numerous secondary carboxylic acids were employed to access such pyridines with high simplicity when placed in context. For example, pyridine **8** has been prepared multiple times leading either to mixtures (e.g., Figure 2B) or requiring C–4 pre-functionalized pyridines (*ca.* \$584/g[13d]).[19] Similarly, pyridine **18** has been accessed from 4-bromopyridine through photochemical and electrochemical reductive couplings or by employing Hong's BG (Figure 1B) and a Hantzsch ester radical precursor[10b] (*ca.* \$150/g[13e]). Pyridine **21** has been accessed either via cross coupling/Hydrogenation[20a] or C4-selective Grignard addition using TBSOTf to generate a transient BG and reoxidation[20b] (*ca.* \$100/g[13b]). Cyclopropyl containing pyridine **23** was accessed either from 4-bromo or 4-Bpin pyridine via Suzuki or Grignard addition/rearomatization (*ca.* \$226/g[13a]).[21] The trivial cyclohexanone pyridine **25** has only been accessed in a controlled fashion using multistep routes with protecting groups and FG manipulations (*ca.* \$871/g[13f]).[22]

Many of the quaternary center containing C-4 alkylated pyridines (derived from tertiary carboxylic acids) prepared here are new (**29**-**33**) and are likely desirable starting materials for medicinal chemistry programs. Of the known alkylated pyridines in this series, two were prepared as mixtures of regioisomers using radical chemistry (**26** and **28**)[23,24] or via Minisci addition to 4-cyanopyridine.[25]

The chemistry outlined above is not limited to the parent pyridine **6a** but can also be employed on mono (**6b, 6d-i**) or bis (**6c**) substituted pyridines. Pyridines **35**, **39**, and **41** are new compounds and might be challenging to access controllably from the parent pyridines in other ways. Pyridines such as **37**, **38** (ca. $1620/g[13g]), and **40** have previously been synthesized either through Grignard addition/oxidation sequences[7c] or via Hong's HAT-based method[10d] employing BG's similar to that in Figure 1B.

It is worth noting that pyridines **8**, **12**, **27** and **28** have been prepared on a gram-scale with no significant reduction in yield. The limitations of this reaction (see SI for full disclosure) stem from the acidic conditions used to install the BG and a lack of tolerance for preexisting C–2 functionality.

Interestingly, when **6a** was used in borono-Minisci reaction involving aryl boronic acids as radical precursor,[28] lower regioselectivity was observed, leading to a mixture of C-2 and C-4 adducts. This outcome can be rationalized with the compact geometry of the Csp^2 radical, which allows the attack on the hindered C-2 position of **6a** (see SI for accurate description of the results).

Having facile access to pure C–4 alkylated pyridines open up a new opportunity for early-stage Minisci chemistry to be employed in the synthesis of 2,4-difunctionalized systems. Historically, such heterocycles are prepared by employing Minisci at the end of a sequence in order to obtain more regioselective outcomes. As shown in Figure 3A, a reversal of this traditional choreography is now feasible. Thus, adduct **8** can be submitted to known C–2 selective pyridine functionalizations such as carbamoylation[26], cyanation[9], and amidation[27] to afford pyridines **42**, **43**, and **44**, respectively. This sequence of events is general and can be utilized to obtain **46** (Minisci followed by borono-Minisci[28]), **47** and **48** (double Minisci), and **49** (Minisci followed by amidation). Conventional retrosynthesis of such compounds would likely involve pre-functionalized handles at the targeted carbon for controlling regiochemistry whereas in the present case innate reactivity and the fumarate-BG overcomes this challenge.

As mentioned above (Table 1), many of the pyridines reported herein have been prepared by less direct pathways and this is graphically depicted for pyridines **12**, **27**, and **25** in Figure 3B. The avoidance of C–4 pre-functionalized pyridines, pyrophoric reagents, and expensive transition metals are highlights of this method. Moreover, a proof of concept is shown for how the fungicide (oomycetes) candidate **54** could conceivably be accessed in a far more practical way from pyridine. Prior studies employed chemistry that was costprohibitive for the agrochemical industry commencing from **51** and employing expensive boronate ester **52**, N-oxide chemistry, toxic TMSCN, and a Pd catalyst to access 1,3-disubstituted **53** which required a subsequent hydrogenation to remove the 3,4-unsaturation.[29] In contrast, the two-stage Minisci approach from **6a** accesses a synthetically equivalent intermediate **50** directly without any of those drawbacks. Finally, as a demonstration of practicality in both medicinal and process scenarios pyridine **26** can be prepared and purified either through column chromatography or through a simple extraction/washing protocol (Figure 3C).

To summarize, a simple solution to the longstanding challenge of practical C–4 alkylation of pyridines has been presented using a simple blocking group derived from inexpensive maleic acid. The resulting pyridinium species is stable and, in many instances, crystalline. The resulting functionalization can be accomplished using classic Minisci conditions without the addition of any acid and proceeds to give a singular adduct at C–4. The scope of this reaction is broad and can be strategically used in concert with other functionalizations or as a stand-alone method to provide high value pyridines that despite their trivial appearance, have posed challenges for direct and inexpensive synthesis in a scalable way.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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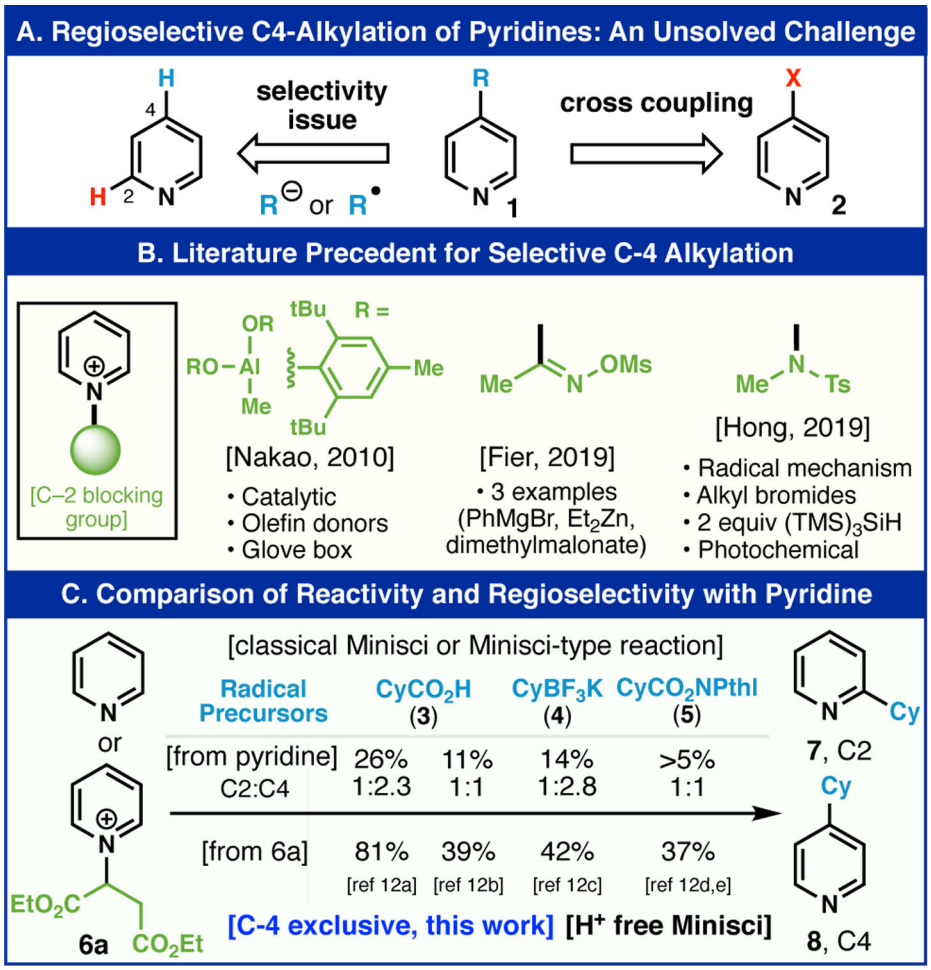
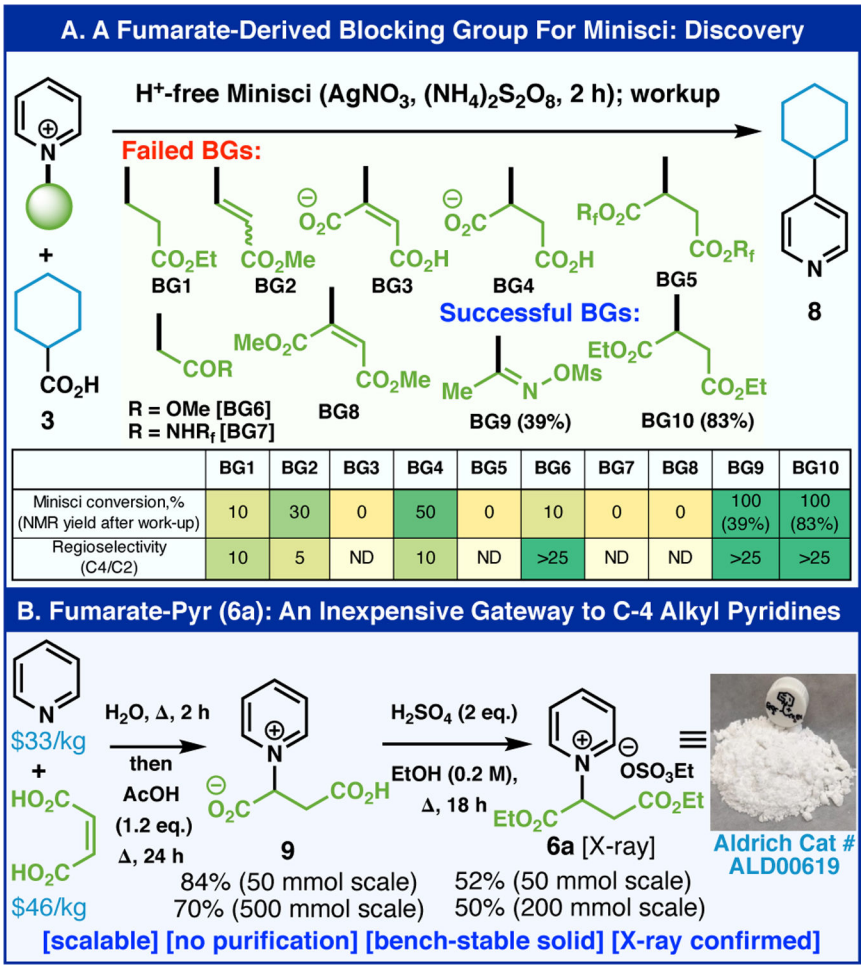


Figure 1.

(A) An unsolved challenge in the field of Minisci reaction. (B) Literature precedent. (C) Comparison experiment with pyridine



	BG1	BG2	BG3	BG4	BG5	BG6	BG7	BG8	BG9	BG10
Minisci conversion,% (NMR yield after work-up)	10	30	0	50	0	10	0	0	100 (39%)	100 (83%)
Regioselectivity (C4/C2)	10	5	ND	10	ND	>25	ND	ND	>25	>25

Figure 2.

(A) Fumarate-derived blocking group for Minisci reaction in discovery stage. (B) The pyridinium **6a** as an inexpensive gateway to C4 alkylated pyridine synthesis.

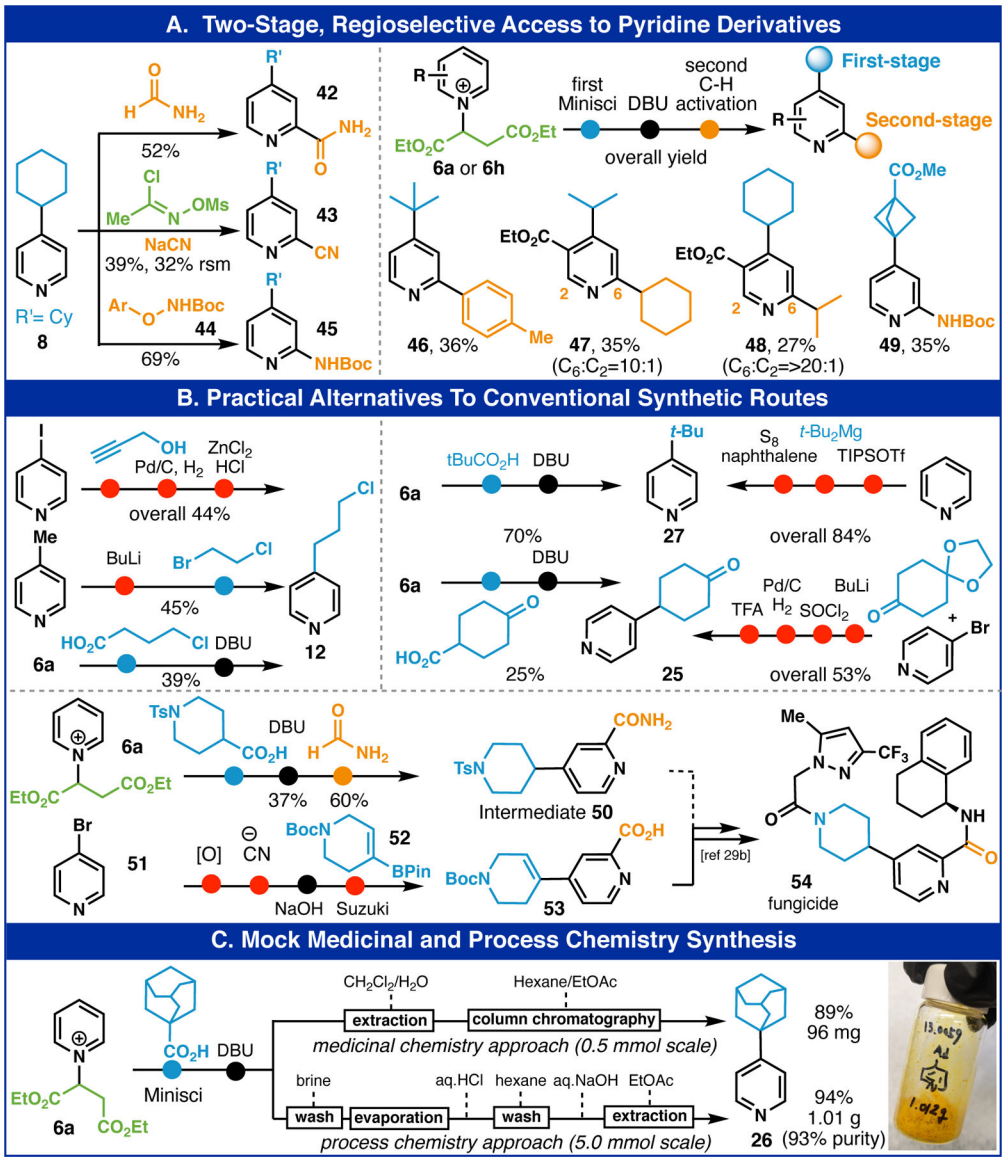


Figure 3.

(A) Two-stage derivatization. (B) Practical alternatives to conventional synthetic routes. (C) Mock medicinal and process chemistry synthesis. See Supporting Information for detailed experimental procedures.

Table 1.

Reaction scope: regioselective C–4 alkylation of pyridines via a BG approach. Yields of **6b**–**6l** are based on isolated yield from substituted pyiridines (two steps). a) **6a** (0.5 mmol), carboxylic acid (1.0 mmol), $AgNO_3$ (20 mol%), $(NH_4)_2S_2O_8$ (1.0 mmol), DCE: H_2O=1:1, 0.1 M, 50 °C, 2 h. The regioselectivity was determined by crude NMR after first step and confirmed again after final purification step. b) using carboxylic acid (2.0 mmol, 4

equiv) on the Minisci reaction step and DBU (3.0 mmol, 6 equiv) on the removal step. c) 5.0 mmol scale reaction. d) carboxylic acid was used as a limiting reagent. e) performed in 0.3 M. See Supporting Information for detailed experimental procedures.