A Predictive Model for Additions to *N*-Alkyl Pyridiniums

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ABSTRACT: Disclosed in this communication is a thorough study on the dearomative addition of organomagnesium nucleophiles to *N*-alkyl pyridinium electrophiles. The regiochemical outcomes have observable and predictable trends associated with the substituent patterns on the pyridinium electrophile. Often, the substituent effects can be either additive, giving high selectivities, or ablative, giving competing outcomes. Additionally, the nature of the organometallic nucleophilic component was also investigated for its role in the regioselective outcome. The effects of either reactive component are important to both the overall reactivity and site of nucleophilic addition. The utility of these observed trends is demonstrated in a concise, dearomative synthesis of a tricyclic compound shown to have insecticidal activity.

Heterocyclic compounds containing nitrogen atoms are ubiquitous in the realms of natural product isolation, materials chemistry, and drug discovery.[1-5] In particular, as 59% of all marketed small molecule drugs contain a nitrogen heterocycle,[6] direct and concise synthetic access to diverse libraries of these important moieties remains an outstanding challenge.[7] Furthermore, being that the most common nitrogen heterocycles in marketed drugs are piperidine and pyridine (ranked first and second, respectively), easily functionalizing and modifying their structures is of the utmost importance to expediting therapeutic campaigns.[8-10]

Shown in Figure 1A are a selection of medicinally important natural products and rationally designed therapeutic agents that all contain variously substituted piperidines or tetrahydropyridines. While manzamine A (**1**)[11] and morphine (**2**)[12] contain stereochemically dense patterns within and contiguous to their piperidine rings, compounds like **3**[13] and Paroxetine (**4**),[14] while arguably less complex, still pose several synthetic questions regarding their construction. The control of relative and absolute stereochemistry is a consideration for all of these targets (**1**–**4**). Furthermore, the regiochemical control of desired unsaturation (e.g. **3**) poses an issue,[15] especially when the final product has sensitive functionality.[16]

Many strategies exist for the construction of piperidines, some of which are highlighted in Figure 1B.[17,18] Certainly, utilizing nitrogen's innate nucleophilicity dominates most disconnection strategies where substitution or reductive amination tactics are common. Additionally, hydroamination tactics that encourage N-C2 disconnections are also employed, but these approaches are often beset by arduous construction and prefunctionalization of linear precursors.[19] The reduction of lactams and imides in higher oxidation levels also remains a popular avenue for achieving the desired saturation, but controlled reduction of these carbonyls can be challenging in a complex setting, lending need for protecting groups or circuitous redox adjustments.[20,21] Thus, dearomative functionalization arose as an attractive tactic for the conversion of parent pyridine heterocycles to their reduced piperidine analogs.[22-26] This type of disconnection is not without its challenges, however, as derivatization of
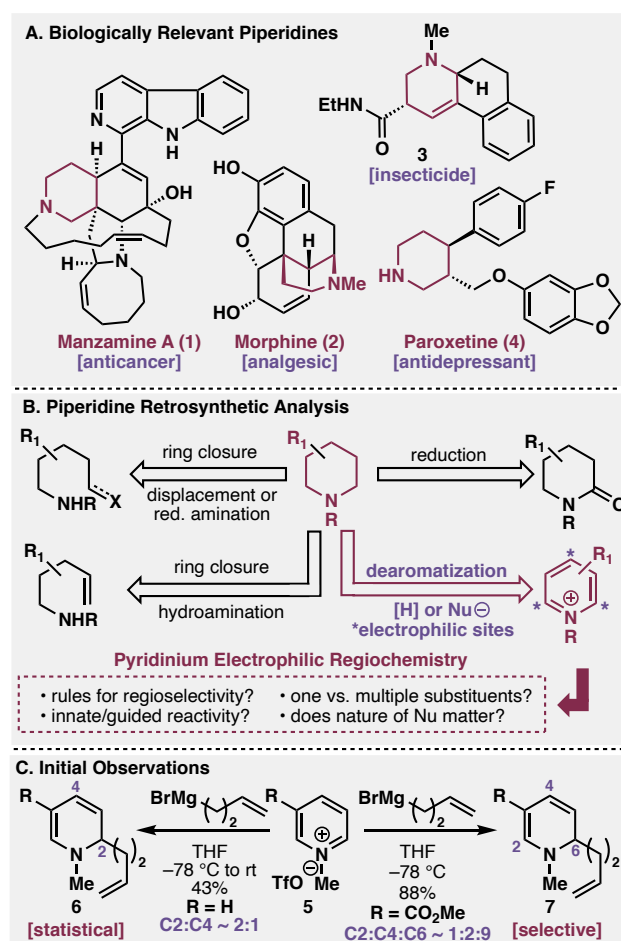

Figure 1. (A) Representative and important piperidines and tetrahydropyridines. (B) Common strategies for assembling piperidines. (C) Substituent biasing of innate regiochemical preference of pyridiniums. Yields were determined by ^{1}H NMR with an internal standard.

pyridines requires initial activation to a pyridinium[27] followed by a predictable nucleophilic addition. Prior to this study, organometallic additions to some monosubstituted pyridiniums have been established, but the innate selectivity of addition to
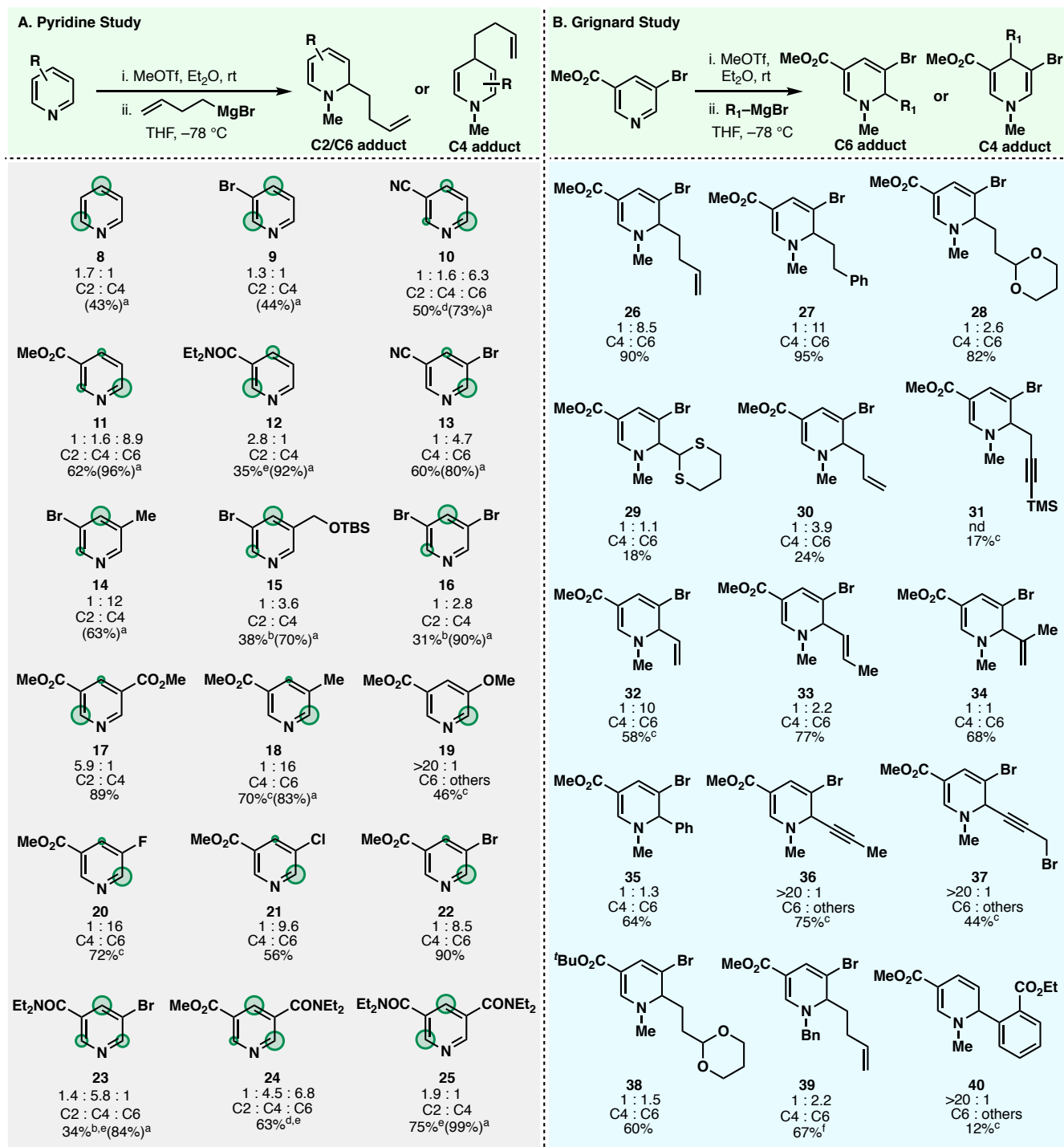
multiply-substituted substrates has not been well understood.[28] Notable contributions made by Comins,[29-31] Yamaguchi,[32,33] and Donohoe[34] have laid some basic groundwork in this area. Nevertheless, understanding the innate electrophilic regioselectivity of substituted pyridiniums stands as a significant problem towards practitioners harnessing dearomative strategies. In considering factors such as steric, electronic, and chelation effects, this study aims to identify rules and guidelines understanding the regiochemical outcomes of additions to *N*-alkyl pyridiniums, enabling practitioners to more accurately predict the site of nucleophilic addition to these valuable heterocyclic synthons.

Activation of pyridines via acylation or alkylation of the nitrogen has been a realm of research for several decades.[15] The study of acyl pyridinium reactivity and regioselectivity has dwarfed the studies of their *N*-alkyl counterparts, largely due to product stability and/or enhanced reactivity. Many have invoked the acyl/iminoyl group as a non-innocent activating group capable of guiding[35-37] and/or sterically controlling[38-40] reactivity upon the event of dearomatization. In these examples, the innate reactivity of the pyridinium intermediate is perturbed, giving a more engineered and programmatic outcome. Conversely, with an interest in pursuing targets such as **1–4**, exploiting and controlling alkylated pyridiniums would provide a more direct and ideal route for their preparation. Initially, the activation of unsubstituted pyridine and methyl nicotinate, via activation with methyl triflate, was investigated (for ease and solubility purposes) followed by subsequent treatment with 3-butenylmagnesium bromide. By crude ^{1}H NMR, Grignard addition to the methylated pyridinium gave a near statistical mixture of possible products with a C2:C4 ratio of roughly 2:1. By contrast, executing the same reaction with methyl nicotinate gave the C6 adduct with much higher selectivity of 1:1.6:8.9 of C2:C4:C6 (see Figure 1C). Clearly, the effect of the ester substituent greatly biased the addition and served as a starting point for our study to evaluate the various effects of pyridine substituents on the regioselective preference of nucleophilic addition.

In Scheme 1A, the results of nucleophilic additions to various pyridiniums are outlined. The general reaction employs first the treatment of a parent pyridine with methyl triflate at rt, followed by the subsequent addition of 3-butenylmagnesium bromide solution at –78 °C (for optimization of conditions, see SI). For simplicity, methyl was chosen as the *N*-alkyl substituent so that the innate reactivity of the pyridinium was observed with the least steric perturbation, but rationally, many other alkyl substituents can be employed, with similar reactivity trends (e.g. **39**, *vide infra*). It is worth noting that the only observed electrophilic sites for addition are the 2, 4, and 6 positions of the pyridine. For monosubstituted pyridiniums **9–12**, various substituent directing effects were observed. Esters and nitriles induced a *para*-directing effect (see **10** and **11**), while the diethyl amide and bromide directed addition to the *ortho* positions. It is hypothesized that the amide's observed selectivity arises from chelation, while the bromide's effect is electronic in nature. The combined effects of these substituents on regioselective addition were then evaluated. First, bromides **14** and **15** showed preference for C4 owing to an additive directing effect of the C5 alkyl group. Dibromide **16** also showed the same contrasteric preference for C4 addition, albeit with reduced selectivity (C4:C2 = 2.8:1). For 5-bromonicotinitrile (**13**) and methyl 5-bromonicotinate (**22**), the combined directing effect resulted

in preferential addition at C6. When other nicotinates were evaluated (**18–21**), the same selectivity was observed as with **22** (C6 preferred). However, the substituent at the 5 position had a drastic effect on the C4/C6 regiomeric ratio. Selectivity was enhanced with more inductively withdrawing substituents (OMe, F, Cl), and, similarly, alkyl substitution (Me, e.g. **18**) also served to enhance preference for C6. Diester **17** also displayed reasonable selectivity for C6, despite lacking an *ortho* directing substituent (*vide supra*). With regard to nicotinamides, the original *ortho* directing effect was hypothesized to be a result of organometallic chelation. When evaluated further, 5-bromonicotinamide **23** showed preference for C4 as ester-amide **24** showed marginal selectivity for C6. Diamide **25** showed preference for C2 similar to the observed selectivity for monoamide **12**.

The scope of Grignard addition was largely evaluated using pyridine **22** as a model substrate (see Scheme 1B). Notably, this substrate only gives addition at C4 and C6, but the degree of selectivity is reliant on the Grignard reagent. Initially with 3-butenylmagnesium bromide, an exceptional yield (90%) and regiomeric ratio were observed favoring C6 with 8.5:1 selectivity giving **26**.[41] A similar reactivity profile was observed when using phenethylmagnesium bromide (see **27**). Surprisingly, acetal **28** was produced with a much lower C6 selectivity (2.6:1), which was hypothesized to be a result of internal chelation of the acetal oxygen to the Mg atom in the nucleophile. This cyclic nature of the nucleophile is thought to make it more sterically hindered than the simpler alkyl Grignard reagents used to forge **26** and **27**. This steric effect was exacerbated when employing dithianylmagnesium bromide to deliver **29** with nearly equal amounts of the C4:C6 isomers observed. This indiscriminate selectivity was also coupled with poor yield due to the its low reactivity. Decreased yields were also observed using allyl and propargylic[42] nucleophiles (**30** and **31**), albeit with modest selectivity for C6 in **30** (3.9:1). With sp[2] hybridized Grignard reagents, varying regioselectivities were also observed based on size or substitution pattern. While vinylmagnesium bromide had a high C6 preference (10:1), simply incorporating a methyl group into the nucleophile decreased selectivity substantially. Utilizing 1-Propenylmagnesium bromide gave **33** with 2.2:1 C6:C4 selectivity and the addition of 2-propenylmagnsium bromide gave an even lower selectivity of 1:1. Addition of phenylmagnesium chloride gave a similar ratio of 1.3:1 slightly in favor of C6 (see **35**). Again, larger nucleophiles, albeit sp[2] hybridized, gave poorer C6:C4 selectivity. In stark contrast, sp hybridized Grignard reagents gave high selectivities (>20:1) for C6 (**36** and **37**), which aligns with previously observed reactivity with acylated pyridiniums.[32,33] Small modifications to the electrophilic partner were also evaluated for comparison. Combination of the *tert*-butyl bromonicotinate and acetal Grignard reagent delivered **38** slightly favoring C6 in 60% yield, with slightly diminished selectivity compared with **28**. Activation of pyridine **22** with benzyl triflate led to adduct **39** in 67% yield and a C6:C4 ratio of 2.4:1. This decrease in selectivity for C6 compared to the analogous methylated product **26** was expected due to the increased size of the benzyl substituent.[43] Finally, the Grignard reagent of ethyl 2-iodobenzoate was added in to the methylated pyridinium of methyl nicotinate (**11**) with exclusive regioselectivity for C6 (>20:1). This substrate was important as it had been previously studied, however, no explanation was giving for the observed regioselectivity trends.[44]

Scheme 1.

A. Pyridine Study

i. MeOTf, Et₂O, rt
ii. 3-butenyl–MgBr
THF, −78 °C

C2/C6 adduct or C4 adduct

B. Grignard Study

i. MeOTf, Et₂O, rt
ii. R₁–MgBr
THF, −78 °C

C6 adduct or C4 adduct

A. Pyridine Study compounds

8
1.7 : 1
C2 : C4
(43%)[a]

9
1.3 : 1
C2 : C4
(44%)[a]

10
1 : 1.6 : 6.3
C2 : C4 : C6
50%[d](73%)[a]

11
1 : 1.6 : 8.9
C2 : C4 : C6
62%(96%)[a]

12
2.8 : 1
C2 : C4
35%[e](92%)[a]

13
1 : 4.7
C4 : C6
60%(80%)[a]

14
1 : 12
C2 : C4
(63%)[a]

15
1 : 3.6
C2 : C4
38%[b](70%)[a]

16
1 : 2.8
C2 : C4
31%[b](90%)[a]

17
5.9 : 1
C2 : C4
89%

18
1 : 16
C4 : C6
70%[c](83%)[a]

19
>20 : 1
C6 : others
46%[c]

20
1 : 16
C4 : C6
72%[c]

21
1 : 9.6
C4 : C6
56%

22
1 : 8.5
C4 : C6
90%

23
1.4 : 5.8 : 1
C2 : C4 : C6
34%[b,e](84%)[a]

24
1 : 4.5 : 6.8
C2 : C4 : C6
63%[d,e]

25
1.9 : 1
C2 : C4
75%[e](99%)[a]

B. Grignard Study compounds

26
1 : 8.5
C4 : C6
90%

27
1 : 11
C4 : C6
95%

28
1 : 2.6
C4 : C6
82%

29
1 : 1.1
C4 : C6
18%

30
1 : 3.9
C4 : C6
24%

31
nd
17%[c]

32
1 : 10
C4 : C6
58%[c]

33
1 : 2.2
C4 : C6
77%

34
1 : 1
C4 : C6
68%

35
1 : 1.3
C4 : C6
64%

36
>20 : 1
C6 : others
75%[c]

37
>20 : 1
C6 : others
44%[c]

38
1 : 1.5
C4 : C6
60%

39
1 : 2.2
C4 : C6
67%[f]

40
>20 : 1
C6 : others
12%[c]

(A) Regioselectivity study for addition of 3-butenylmagnesium bromide to substituted pyridiniums. Unless specified otherwise, the isolated yield is of all respective isomers (C2, C4 and C6). B) Regioselectivity study for the addition of Grignard reagents to alkylpyridiniums of pyridine **22**. Reaction conditions: MeOTf (1.0 equiv), Et₂O, rt; Grignard reagent (1.0 equiv), THF, −78 °C. The regiomeric ratio was determined by ¹H NMR of the crude material. (a) Spectroscopic yield with trimethoxybenzene as an internal standard. (b) Isolated yield of the C4 isomer. (c) Isolated yield of C6 isomer. (d) Isolated yield of C4 and C6 isomers. (e) Methylation of substrate was performed in CH₂Cl₂. (f) BnOTf was used as an activating agent (See Supporting Information).

In order to aid practitioners in effectively harnessing pyridinium-based retrosynthetic analysis, a directing group guide and user's roadmap has been delineated in Figure 2 deduced from this study of 3 and 3,5-disubstituted pyridiniums. First, understanding the various directing group effects is paramount to employing a predictive reactivity model (Figure 2A). As unveiled in this study, chelating groups such as amides have an *ortho* directing effect presumably due to chelation of the organomagnesium nucleophile.[45] Secondly, resonance electron-withdrawing groups like nitriles and esters primarily promote conjugate reactivity to the *para* position and secondarily to the ortho positions.[28] Lastly, alkyl groups, halides, and heteroatoms (e.g. N,O) promote *ortho* addition to the pyridinium.[46] It should be noted that the use of other

organometallic species (e.g. RCu, R₂Zn) are not expected to necessarily follow the above trends as this study concerns the use of Grignard reagents as nucleophiles (See Supporting Information for details).

An example of how to utilize these additive effects in a stepwise fashion is depicted in Figure 2B. Given bromonicotinamide **23**, step 1 involves the identification of C2, C4, and C6 as innate electrophilic sites. Next, step 2 involves identifying chelating directing groups that promote proximal addition to *ortho* sites. Third, conjugate sites are then determined by the presence of resonance electron-withdrawing groups. Relative to **23**, this preferential reactivity trend is not applicable. Lastly, the *ortho* directors are evaluated, which in this case, the bromine promotes addition at C4 and C6. Adding these effects together reveals a predicted selectivity for C4 being the highest preference with C2 and C6 being minor products of dearomative addition. Indeed, the experimental results indicate this trend in which the *N*-methylpyridinium of bromoamide **23** gives a 1.4:5.8:1 selectivity for C2:C4:C6. In general, these reactivity trends hold true in the present study, with regard to preferential addition. Variability is seen based on nucleophile identity, where larger nucleophiles seem to be less selective in terms of the product ratios (see **28**, **29**, and **38**). Importantly, while selectivity can be variable in this sense, the major product observed still adheres to the guidelines depicted in Figure 2B.
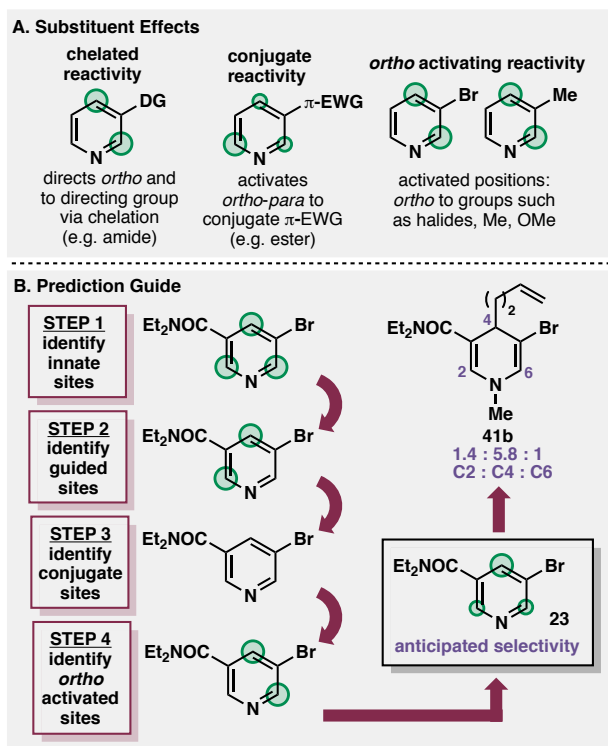

Figure 2. (A) Directing Group Effects. (B) User's guide to regioselective addition.

In order to evaluate the synthetic utility of this reactivity study, the construction of **3** was investigated.[13] This compound has shown notable insecticidal activity and has shown affinity towards binding the 5HT₇ serotonin receptor. First, methylation of **22** and addition of phenethylmagnesium bromide delivered the dearomatized addition product. This compound was then subsequently reduced with LiAlH₄ to give **42**

on gram scale in 69% yield over 2 steps. A radical annulation utilizing Bu₃SnH and AIBN afforded despyrrole methyl lysergate (**43**) in 21% yield (43% based on recovered starting material). This 3-step procedure compares favorably to the prior synthesis, which required 7 steps to synthesize this target.[47-50] Ester saponification with aqueous HCl followed by an amidation protocol with CDI gave **3** in 30% yield over 2 steps and in 5 total steps (previously 13 steps). It is worth noting that the bromide serves both as a directing group for the innate selectivity of the dearomatization and as a handle for C–H annulation. The selectivity of the hydride reduction step is also remarkable, giving dihydropyridine **42**, in that very little ester reduction is observed and the reduction regiochemistry is absolute.
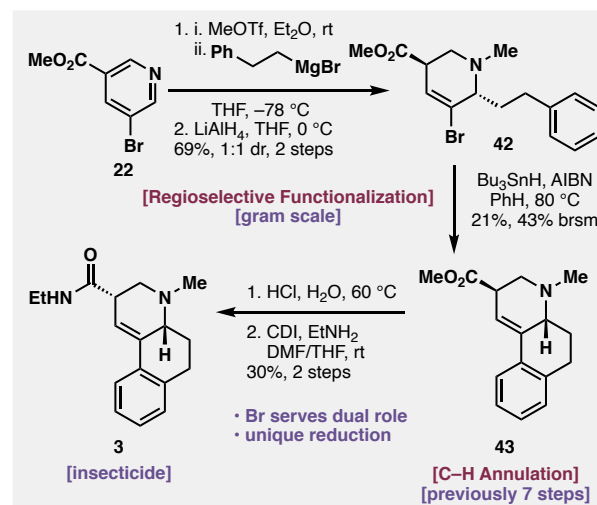
Scheme 2. Concise synthesis of insecticide **3**.

In conclusion, this study has shown the innate reactivity trends associated with *N*-alkyl pyridinium electrophiles. The effects of substitution patterns have revealed outcomes in organometallic additions that are systematic and easily employed in first-pass retrosynthetic analyses. These data serve to delineate reactivity that, prior to this study, were limited and not conclusively understood. In some instances of the current work, the selectivity proved quite high, and could be easily utilized in multistep synthesis, as shown by the concise construction of **3**. It is hoped that the lessons learned will be broadly helpful to practitioners ambitious to utilize the inherent advantages of dearomative synthetic approaches. The expansion upon these findings and their application to future synthetic targets is anticipated to be reported by our group in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

> Experimental Procedures and analytical data (1H, 13C NMR, MS) for all new compounds (PDF)
> Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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