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Radical-Based Regioselective C–H Functionalization of Electron-Deficient Heteroarenes: Scope, Tunability, and Predictability

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ABSTRACT: Radical addition processes can be ideally suited for the direct functionalization of heteroaromatic bases, yet these processes are only sparsely used due to the perception of poor or unreliable control of regiochemistry. A systematic investigation of factors affecting the regiochemistry of radical functionalization of heterocycles using alkylsulfonate salts revealed that certain types of substituents exert consistent and additive effects on the regioselectivity of substitution. This allowed us to establish guidelines for predicting regioselectivity on complex π -deficient heteroarenes, including pyridines, pyrimidines, pyridazines and pyrazines. Since the relative contribution from opposing directing factors was dependent on solvent and pH, it was sometimes possible to tune the regiochemistry to a desired result by modifying reaction conditions. This methodology was applied to the direct, regioselective introduction of isopropyl groups into complex, biologically active molecules, such as diflufenican (**44**) and nevirapine (**45**).

Introduction

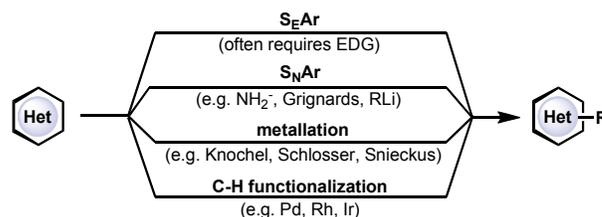
Aromatic heterocycles are essential structures in a large proportion of small molecule drugs. Structural optimization of bioactive leads through systematic chemical alteration is essential for selecting a clinical candidate, and methods to synthesize or elaborate key pharmacophores hold particular significance in the drug discovery process. However, the production of such libraries of compounds can be very challenging, as electron-deficient heteroaromatic bases such as pyrimidines, pyrazines, pyridazines and pyrimidines are often difficult to derivatize directly with standard reactions (Figure 1A).^{1–4} As a result, the development of mild, direct functionalization methods for the selective late-stage modification of complex heteroarene structures remains an important practical goal.

A universal, but perhaps underappreciated, tendency of a heteroarene (electron-rich or electron-poor) is to react with radical species. Functionalization methods that proceed via radical addition would therefore be expected to be a convenient method for elaborating aromatic heterocycles, yet methodology exploiting this innate reactivity is seldom employed.⁵ There is a perception that direct radical functionalization processes are frequently low yielding, have unpredictable regioselectivity, and give intractable mixtures of products. Although this reputation is sometimes justified, the problem is compounded because the factors governing the reactivity and selectivity of radical addition to heteroarenes are not widely known or understood.

In our ongoing studies into the functionalization of heteroarenes using alkylsulfonate-derived radicals,⁶ we have begun to observe certain trends pertaining to regiocontrol that – based upon the similarity to patterns observed in various other radical-mediated functionalization reactions – could be useful in a more general manner. In this full report, an extensive study of the reactivity trends of heteroarene functionalizations employing alkylsulfonate-derived radicals is presented. This work further defines the scope of these reactions, demonstrates

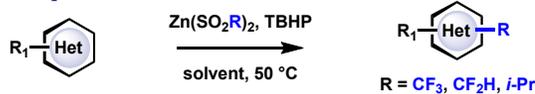
that regioselectivity can be tuned according to solvent and pH, and establishes useful, substituent-based reactivity patterns. These studies culminate in the presentation of a hierarchical set of empirically derived, practical guidelines allowing for both prediction and tunability of regioselectivity (Figure 1B). These guidelines provide the framework for further mechanistic studies that promise to increase fundamental understanding of radical-mediated heteroarene functionalization.⁷

A. Regioselective direct functionalization of electron-deficient heterocycles



B. Predictable, regioselective radical functionalization of heterocycles

[this work]



- predictable based on functional groups
- tunable based on solvent
- may be applied to simple and complex systems

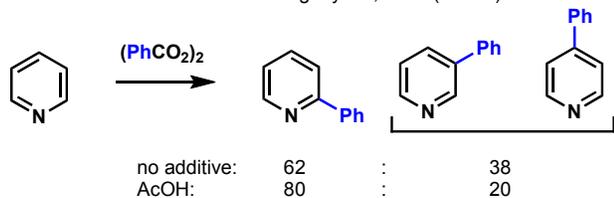
Figure 1. Regioselective radical functionalization of heteroarenes.

Background

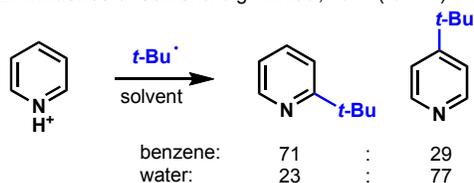
A major objective at the outset of our studies was to understand the reasons behind seemingly diverse regiochemical results, both in our own work and in studies reported in the literature, with the goal of establishing trends that would allow the prediction of results. One broad conclusion that can be drawn from a variety of different radical-mediated heteroarene functionalization studies⁸ dating back thirty years or more is

that regioselectivity is dominated by the inherent reactivity of the substrate,⁹ for example the strong preference for pyridines to react at the α and γ positions. Regulating regioselectivity is therefore challenging, but as summarized in Figure 2, there is precedent for innate regiochemical preferences to be influenced by acid (Figure 2A), solvent (Figure 2B), substituents on the heterocycle (Figure 2C), and nature of the radical (Figure 2D).¹⁰⁻¹⁸

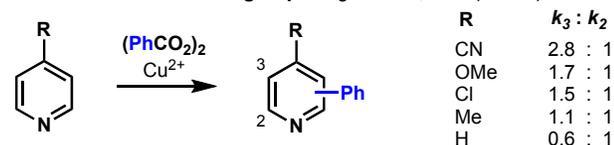
A. Influence of acid additives: e.g. Lynch, 1964 (ref. 10)



B. Influence of solvent: e.g. Minisci, 1974 (ref. 11)



C. Influence of functional groups: e.g. Minisci, 1986 (ref. 13)



D. Influence of nature of radical: e.g. Minisci, 1974 (ref. 11)

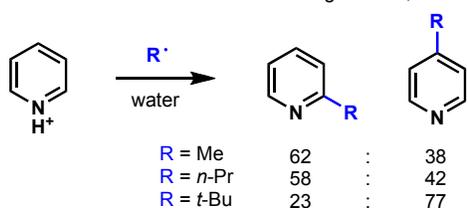
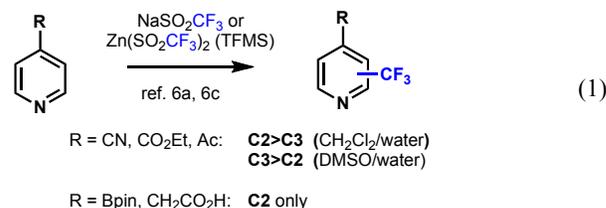


Figure 2. Factors influencing regioselectivity in reports of homolytic substitution reactions of heteroarenes (Refs. 10-18).

Comparison of these literature results with regiochemical preferences observed in our previous studies using radicals derived from alkylsulfinate salts⁶ revealed some of the same trends as well as some contrasting observations (Equation 1). Substitution at the α and γ positions of pyridine is generally preferred, although some C3 substitution was observed on pyridines with CN, CO₂Et or Ac groups at C4. Intriguingly, however, the ratio of products for these substrates could be altered to favor either C2 or C3 substitution simply by changing the solvent.^{12b, 15b, 19} Pyridines substituted with CH₂COOH or Bpin groups at C4 were fully selective for C2,^{6c} an observation that could not be explained by steric effects, and is in contrast to Minisci's proposal that both electron-donating and electron-withdrawing groups at C4 stabilize the radical adduct arising from attack at C3.^{14a}

Our analysis of the literature underlined the similarity of the trends in regioselectivity observed in a number of different radical functionalization systems, but also revealed examples that were difficult to explain using established knowledge. These considerations led us to undertake further systematic

investigations of the factors regulating regiochemical outcomes with the aim to delineate generalizable effects leading to a practical approach to predicting regioselectivity in the radical functionalization of heteroarenes.



Results and Discussion

Experimental Design. In-depth study of the regioselectivity of the direct alkylation and fluoroalkylation of heteroarenes using radicals derived from alkylsulfinate salts was initiated, with ¹H NMR spectroscopy employed as the primary tool for both product identification and analysis. The ¹H NMR spectra of the crude reaction mixtures were exceptionally clean and the aromatic region typically contained only peaks corresponding to starting material and the different product regioisomers. As a result, it was possible to identify products and determine the regioisomeric ratio from these spectra (Figure 3A). Product regiochemistry derived from these spectra was supported by structural assignment after isolation.

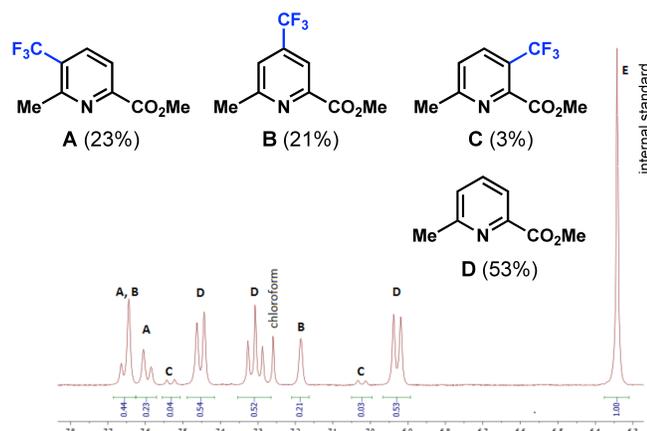
Preliminary studies identified reaction conditions optimal for regiochemical studies. This entailed limiting the occurrence of multiple substitution, which was responsible for the most significant side products observed at higher conversions, and which could alter conclusions about primary reactivity and selectivity. The yields reported below therefore represent intentionally limited values, and not optimized reaction conditions. Temporal profiles of conversion and regioselectivity were monitored in a number of cases, and regioselectivity was found to be constant over the course of the reaction (Figures 3B and 3C). A reasonable mass balance was observed in most cases (Figure 3C). This confirms that selective product degradation that could alter regioselectivity was not significant and that the experimental protocol provides results that accurately reflect the regiochemical preferences in each reaction. (Further experimental details are given in the Supporting Information.)

Reactivity patterns for alkylsulfinate-derived radicals. As a first example, we studied the alkylation of 4-substituted pyridines by radicals derived from alkylsulfinate salts. Figure 4A shows the results of examination of the effect of solvent and pH on the substitution ratio in the isopropylation of 4-cyanopyridine, revealing a pattern reminiscent of that previously observed in Gomberg-Bachmann¹⁰ and Minisci^{8,11-14} chemistry: (i) addition of acid strongly favors reaction at the α position;²⁰ (ii) changing solvent could affect the regioselectivity.

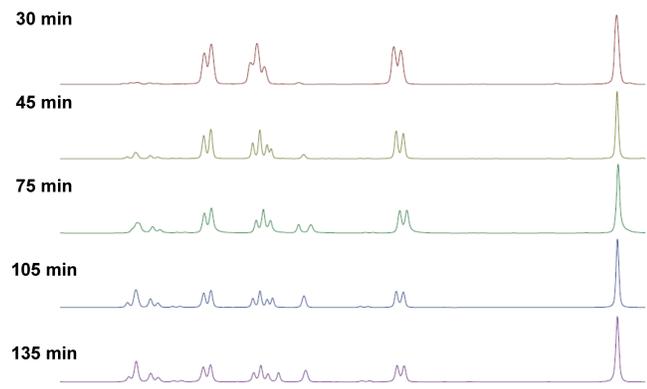
The influence of functional group on regioselectivity was probed by determining the C3:C2 ratio in the isopropylation of C4-substituted pyridines in DMSO (Figure 4B). C3 substituted products were observed only when a C4 π -conjugating, electron-withdrawing group was present, with the C3:C2 ratio roughly corresponding to the electron-withdrawing power of the functionality, as indicated by σ -values²¹ for these substituents.²² The importance of π -conjugation of the electron-withdrawing group is underlined by the fact that while C3 substitution was observed for the CONH₂ derivative, only C2 substitution occurred for the sterically hindered CON(*i*-Pr)₂ group, which cannot act as a *conjugating* electron-

withdrawing group, as it must adopt a conformation orthogonal to the pyridine ring. Non-conjugating groups – such as phenyl, *t*-butyl, or strongly σ -withdrawing CF_3 – did not give C3 products, nor did the conjugating π -donating OMe group.

A. ^1H NMR allows conversion to individual isomers to be quantified



B. Reactions can be monitored to determine rates



C. The regioisomeric ratio remains constant throughout the reaction

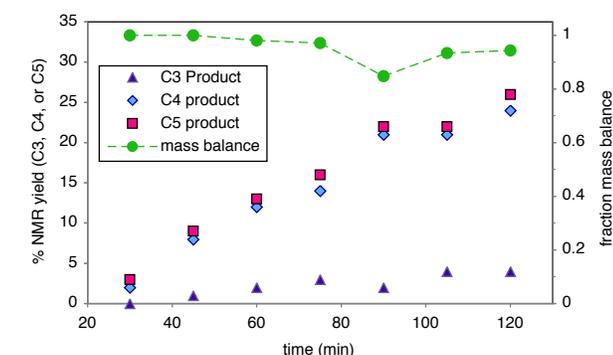
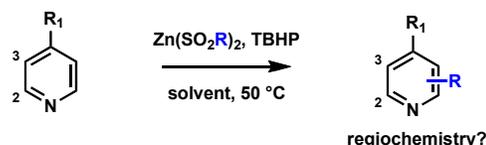


Figure 3. ^1H NMR analysis of the crude reaction mixture allowed ratios of regioisomeric products and starting material to be quantified (A) and tracked as the reaction progressed (B). The regioisomeric ratio remained constant throughout the reaction (C).

Figure 4 reveals an *ortho* directing effect of π -conjugating electron-withdrawing groups at C4, reminiscent of *ortho-para* effects suggested by other systems,¹⁵ and this pattern was supported by further screening. For brevity, in Figure 4 and elsewhere, this *ortho-para* directed reactivity induced by π -

conjugating electron-withdrawing groups is referred to as “conjugate reactivity” because of the similarity of favored regiochemistry to that which would be obtained by a formal “conjugate” or Michael addition at the pyridine ring.

The electronic reasons for the directing effect is under further investigation, but presumably it is due to the ability of the π -conjugating electron-withdrawing group to stabilize the radical intermediate arising from attack at the *ortho* and *para* positions. The strong directing effect of π -conjugating electron-withdrawing groups contrasts with the weak or negligible directing effect of π -conjugating electron-donating groups such as OMe, which might also be expected to stabilize the intermediate radical adduct. This may be attributed to the additional captodative stabilization of radicals that can be stabilized by both an electron accepting (such as CN), and an electron donating (the pyridyl nitrogen) group.²³



(A) solvent/pH effect: ($R = i\text{-Pr}$, $R_1 = \text{CN}$)

solvent	C-3 : C-2	
DMSO	4.3 : 1	addition of acid reduces influence of conjugate reactivity
DMF	2.7 : 1	
MeCN	1 : 2.3	
$\text{CHCl}_3/\text{H}_2\text{O}$	1 : 3.0	
DMSO/1 eq. H_2SO_4	1 : 3.9	
$\text{CHCl}_3/\text{H}_2\text{O}/\text{excess TFA}$	1 : 5.0	
DMSO/excess H_2SO_4	1 : 6.6	

(B) nature of substituent R_1 : ($R = i\text{-Pr}$, solvent = DMSO)

R_1	σ	C-3 : C-2	
π-conjugating EWG			
CN	0.66	4.3 : 1	influence of conjugate reactivity decreases with decreasing electrophilicity of π -conjugating EWG
Ac	0.50	1.4 : 1	
CO_2Me	0.45	1.3 : 1	
Bz	0.43	1.3 : 1	
CONH_2	0.36	1 : 4.3	
non π-conjugating EWG and other groups			
CF_3	0.54	C2 only	no C3 products observed in the absence of a π -conjugating EWG
$\text{CON}(i\text{-Pr})_2$	-	C2 only	
H	0.0	C2 only	
Ph	-0.01	C2 only	
<i>t</i> -Bu	-0.20	C2 only	
OMe	-0.27	C2 only	

(C) nature of radical R : ($R_1 = \text{CN}$, solvent = DMSO)

R	C-3 : C-2	
<i>i</i> -Pr	4.3 : 1	effect of protonation increases with radical nucleophilicity
CF_2H	3.2 : 1	
CF_3	2.5 : 1	
CF_3 (+ 1 eq. H_2SO_4)	2.4 : 1	
CF_2H (+ 1 eq. H_2SO_4)	1 : 1.8	
<i>i</i> -Pr (+ 1 eq. H_2SO_4)	1 : 3.9	

Figure 4. Factors controlling the regiochemistry of radical addition to pyridines. Reagent and conditions: pyridine (0.125 mmol), zinc sulfinate reagent (1 eq.), TBHP (1.5 eq.), 50 °C, 1.5–2 h. See Supporting Information for more details.

As the nucleophilicity of the radical species decreases²⁴ on moving from *i*-Pr to CF_2H to CF_3 , the influence of “conjugate reactivity” also decreases, as indicated by the C3:C2 ratio (Figure 4C). This effect also correlates with a decreasing influence of protonation; isopropylation in DMSO showed a complete reversal of selectivity when acid was added, whereas the results with CF_3 were virtually unchanged. The more nu-

dines (Figure 4B) illustrates this trend: (i) the π -donating OMe group induces δ^- charge at C3, and the pyridine is reactive with CF_3 (behaving as an electrophile) at this position; (ii) the π -withdrawing CN group induces δ^+ charge at C3, and the pyridine is reactive with *i*-Pr and CF_3 (behaving as a nucleophile) at this position; (iii) the σ -withdrawing CF_3 group does not induce significant charge at C3 and the pyridine is effectively unreactive at this position, despite the CF_3 group presumably being able to stabilize the radical adduct arising from attack at C3. The consequences of the electrophilicity of trifluoromethyl radical will be revisited later when the regioselectivity of complex structures containing a number of aromatic and heteroaromatic rings are considered, but in general, for the vast majority of small heterocyclic substrates described in this paper, both CF_3 and *i*-Pr radicals show similar regioselectivity trends. The main difference that is observed is that CF_3 is more reactive than *i*-Pr with electron-rich pyridines and that *i*-Pr radical is more reactive than CF_3 radical with the very electron-deficient diazines.

Solvent and acid effects. Attack on a pyridine by a nucleophilic radical may occur at any of the identified δ^+ "reactive" sites. If there are no π -conjugating electron-withdrawing groups, only the pyridine α and γ positions will be activated. If there are π -conjugating electron-withdrawing groups present, the relative strengths of innate and conjugate reactivity will determine the ratios of products obtained. In chlorinated solvent/water mixtures, the innate reactivity is typically the dominant factor, and reaction primarily occurs at the α and γ positions, which have higher δ^+ charge than the β positions. In DMSO, the balance between conjugate and innate reactivity is altered, such that the "effective" δ^+ activation felt by the incoming radical is greatest at the positions *ortho* and *para* to the π -conjugating electron-withdrawing group; thus reaction primarily occurs at these sites. In either solvent system, the addition of acid emphasizes the influence of innate reactivity to the extent that it exceeds the influence of conjugate reactivity, even in DMSO (Figure 6A).

Using these concepts, the regioselectivity outcomes from our previous work in alkylsulfinate-derived radical addition to C4 substituted pyridines (Equation 1)^{6a-6c} that were not initially straightforward to explain are now easily rationalized. Pyridines with a C4 π -conjugating electron-withdrawing group, such as Ac, CO_2Et or CN, are activated to attack by nucleophilic radicals (δ^+ charge) at both the C2 and C3 positions, thereby yielding a regioisomeric mixture. In contrast, the Bpin or $\text{CH}_2\text{CO}_2\text{H}$ group do not induce either δ^+ or δ^- charge at C3, so the pyridine is unreactive at this position; as a result exclusive C2 substitution is observed.

The lower susceptibility of CF_3 radical to regioselectivity change induced by π -conjugating electron-withdrawing groups or protonation can also be rationalized using this model. The reactivity of the more nucleophilic *i*-Pr radical can be considered strongly dependent on the δ^+ charge of the reactive site, so there is high regioselectivity for the most activated site, whereas the CF_3 radical is less dependent on the δ^+ charge for reactivity, and therefore retains more reactivity with the less δ^+ activated site (Figure 6B). A possible electronic rationale for this preference may be extended from a frontier molecular orbital argument for the increased selectivity of *t*-butyl radical relative to methyl radical for reaction with electron-poor 4-cyanopyridine compared with electron-rich 4-methoxy-pyridine. The SOMO of the trifluoromethyl radical is lower in energy than the SOMO of the isopropyl radical, so the SOMO-LUMO distance is larger for CF_3 than *i*-Pr. As a result, the *i*-Pr

radical is more strongly affected than the CF_3 radical by electronic differences between regioisomeric sites.²⁸

The reason for the change in influence of innate and conjugate reactivity with solvent is unclear. Although it is possible that some component of the solvent dependence is related to the differing pKa of a protonated pyridine in different solvents (pyridine protonation is typically less favorable in DMSO than in water, for example),²⁹ it is likely that a solvent effect unrelated to pKa alters the balance between innate and conjugate reactivity. Minisci observed that the ratio of C2:C4 substitution of *protonated* pyridines showed a distinct solvent effect,^{11, 30} and it is known that many other radical reactions exhibit large solvent effects.³¹ Calculations have also shown that the nucleophilicity and chemical hardness of a radical can vary depending on solvent, either of which could impact the balance between innate and conjugate reactivity.³²

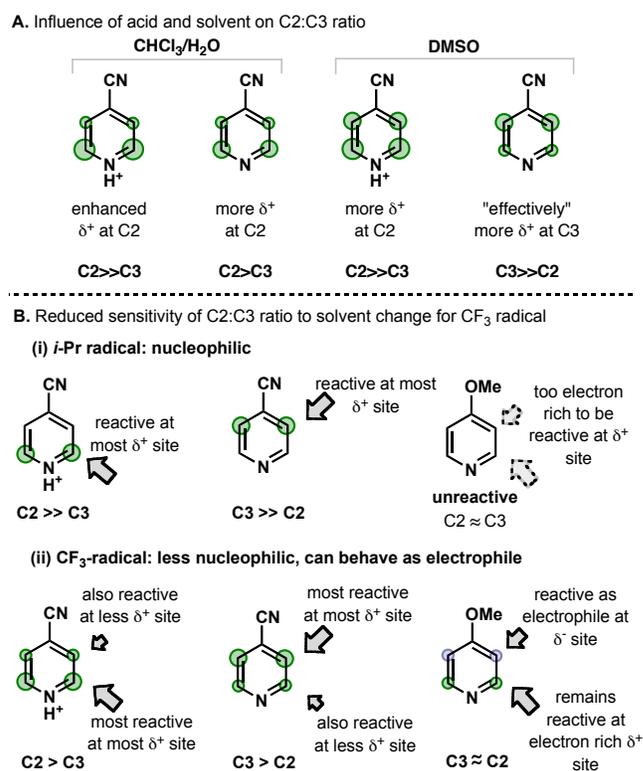


Figure 6. Regioselectivity modifying effect of solvent and radical electrophilicity. Green circles highlight positions activated to attack by nucleophilic radicals; blue circles highlight positions activated to attack by electrophilic radicals. The size of the circle represents relative degree of activation within the same molecule.

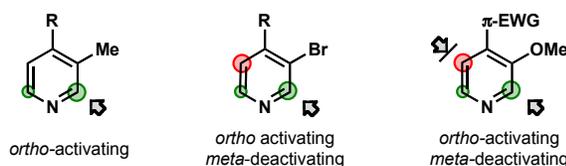
Reactivity-modifying factors. While the previous section focused on identifying which sites were capable of reacting, an important factor in predicting regioselectivity is accurately assessing the relative reactivity of multiple "activated" sites. The factors illustrated in Figure 7 and discussed below are termed "reactivity-modifying" because although they can discriminate between *activated* (δ^+) sites, they cannot in general give rise to useful levels of reactivity at a position that is not already activated.

The influence of a variety of functional groups on the reactivity of already activated sites was tested by measuring substitution patterns in otherwise symmetrical (C4-substituted) pyridines. C4 substituted pyridines are reactive at C2 under

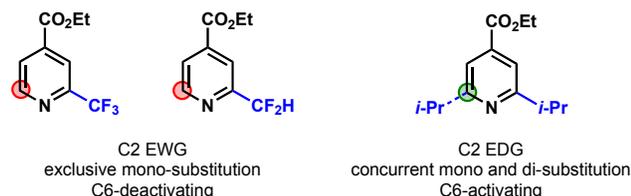
CHCl₃/water conditions that promote innate reactivity. Introducing a C3 group allows the effect of this group on the C2:C6 substitution ratio to be determined. Accordingly, methyl, halogen and methoxy groups were found to function as *ortho*-activators (Figure 7A). The reason for this is unclear, but possibly relates to a neighboring functional group being able to help stabilize a radical intermediate or transition state. Halogen and methoxy also function as *meta*-deactivators (highlighted in red), with the effect being particularly strong at the pyridine β and γ positions. Again, the reason for this is unclear but may be due to the π-donor capabilities of these groups.

Substitution at C2 has a particularly strong effect on the reactivity at C6. Electron-withdrawing functionality at C2 typically shut down reaction at C6, a fact that is well illustrated by the exclusive production of mono-substituted products in the trifluoromethylation or difluoromethylation of symmetrical C4-substituted pyridines (Figure 7B).^{6c} In contrast, attempted C2 isopropylation in CHCl₃/water/TFA resulted in mono-alkylation being accompanied by concurrent dialkylation; as a result electron-donating functionality at C2 is proposed to be activating at C6.³³

A. Me, X, OMe groups: affects reactivity of *ortho* and *meta* positions



B. C2 substitution: affects reactivity at C6



C. Sterics: a fairly minor effect for the radicals studied

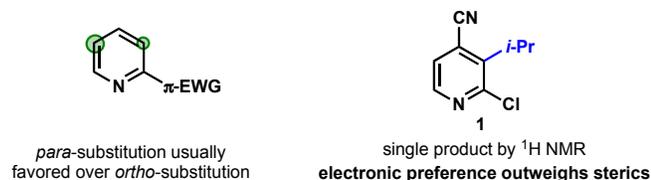


Figure 7. Regioselectivity-modifying effects of functional groups. Green circles highlight sites activated to nucleophilic attack, red circles represent a site with a functional group induced deactivating effect. The size of the circle represents relative degree of activation/deactivation within the same molecule.

Sterics are known to be a significant factor in Minisci reactions³⁴ but appeared to be a secondary consideration in determining regiochemistry for the alkylsulfinate-derived radicals employed in our studies. The preference for *para* over *ortho* substitution in “conjugate reactivity” is attributed to steric effects, and the bulky *i*-Pr radical usually had a stronger preference for *para*-substitution than CF₃ radical. Nevertheless, as shown in Figure 7C, steric effects did not overturn the regioselectivity preference set by functional groups, even when this required substitution in a position with steric crowding.

Predicting the site of radical addition to pyridines. The regioselectivity trends described above operated consistently and reliably across pyridines bearing numerous different functional groups and substitution patterns. Furthermore, the relative importance of each factor followed a consistent hierarchy for each solvent system. Consequently, it is possible to assess whether a pyridine is likely to be reactive at a desired position by considering each of the factors above in turn and combining the activating or deactivating factors. To simplify the thought process for predicting regioselectivity by consideration of the above factors we have designed a flowchart (Figure 8A, with an example³⁵ illustrated in Figure 8B) which guides the reader through the relevant factors in order of importance.

In **Step 1**, the innate sites of the heterocycle are identified. **Step 2** considers those sites that are reactive because of their orientation relative to a π-conjugating electron withdrawing group. The sites identified in these two steps may be considered “activated” and are highlighted in green. A further level of analysis (**Step 3**) considers other factors that may modify the reactivity of these “activated sites” but will not usually alter the regioselectivity preferences of an unactivated site. These modifying factors may reinforce an existing preference, or exert a deactivating effect (highlighted in red) on an otherwise activated site – in this case the “activated” site will have reduced or negligible reactivity (highlighted in yellow).

The final level of prediction (**Step 4**) considers the solvent system being used for the reaction, and how this affects the relative importance of innate reactivity (**Step 1**) and conjugate reactivity (**Step 2**). In general, in CHCl₃/water or CH₂Cl₂/water solvent systems (with or without acid), or in DMSO/acid the significantly reactive sites are the innate sites identified in **Step 1**, and in DMSO (neutral) the significantly reactive sites are the “conjugate” sites identified in **Step 2**.

An example of how this analysis might be used to predict the regioselectivity is illustrated for the case of methyl 3-methylpicolinate as shown in Figure 8B (further details of the regioisomeric ratio of this reaction are given in Figure 10).³⁵ Proceeding through the steps of our model, we find that the analysis correctly predicts the trend of the C4 product being preferred in CHCl₃/water, and increased preference for C5 reactivity in DMSO.

These guidelines are based upon regioselectivity ratios obtained in reactions with the set of commercially available pyridines tested, but the trends observed have proven to be applicable to unfamiliar substrates and functional groups (*vide infra*, for example, **43-46** in Figure 12). In general, the predictions of regioselectivity obtained by this method closely matched the experimental results, although there are some cases where the predicted values fit less closely, reflecting the fact that guidelines seeking to be general will necessarily simplify information concerning the relative contributions of different factors. For example, the result shown in Figure 8B shows that the increased preference for conjugate reactivity in DMSO for isopropyl radical is not sufficient to fully outweigh the innate reactivity in the case of this substrate. It is interesting to compare this result with that for the nitrile analog **16** (see Figure 9B). The CN group is a more strongly electron-withdrawing π-conjugating group than is CO₂Me, which enhances the influence of conjugate reactivity (see Figure 4B). Isopropylation of 3-methylpicolinonitrile in DMSO gave an enhanced preference for the C5 product compared to methyl 3-methylpicolinate (C5:C4 = 2.6:1 for **16** compared to 1:1 for **3**).

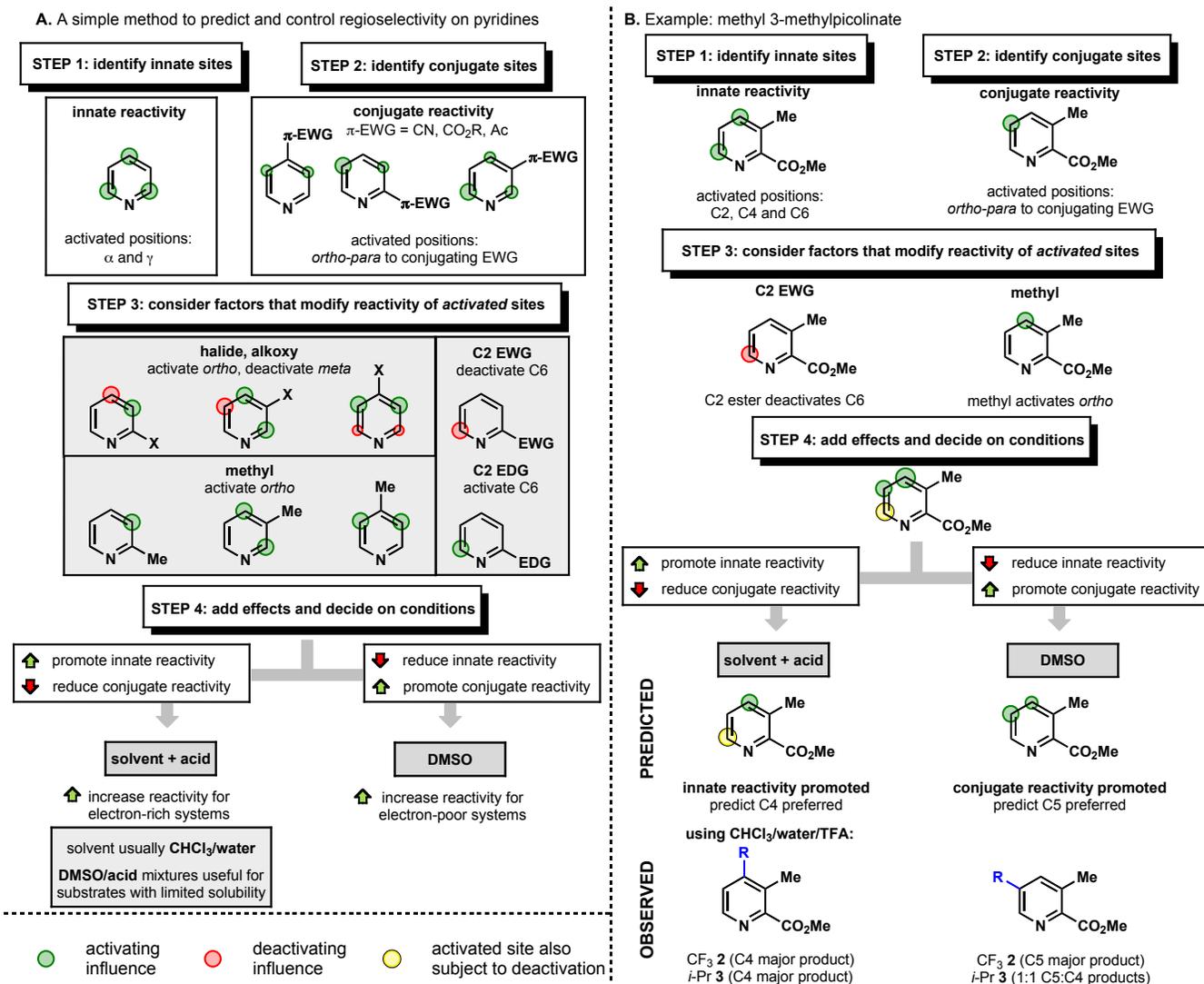


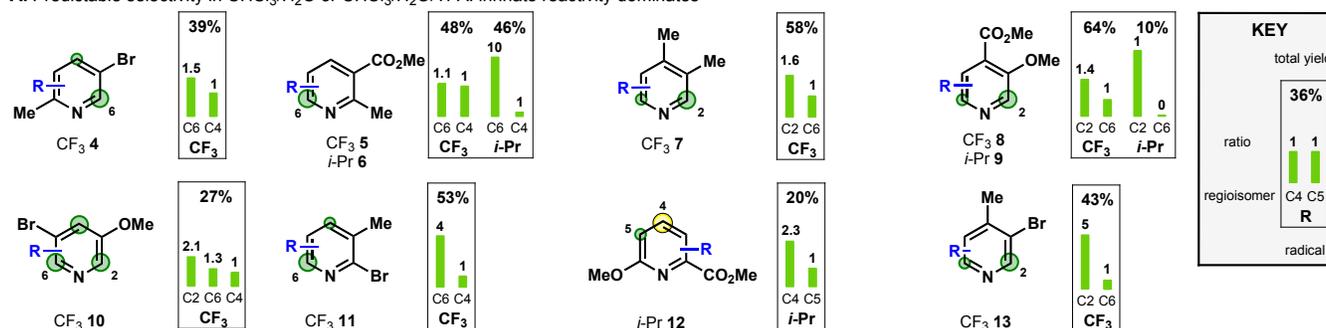
Figure 8. Flowchart for the prediction of regioselectivity of alkylsulfinate-derived radical functionalization of pyridines. Color code: green circles, sites activated to nucleophilic attack; red circles, sites subject to a functional group induced deactivating influence; yellow circles, otherwise activated sites that have reduced or negligible activity due to substituent-induced deactivation. The size of the circle represents relative degree of activation within the same molecule. Further examples of regioselectivity prediction are in the Supporting Information.

Testing the model. A selection of substrates used to develop and test these guidelines is shown in Figure 9. Regioselectivity was examined with both IPS (*i*-Pr radical) and TFMS (CF₃ radical) to represent both the most nucleophilic and the most electrophilic from our alkylsulfinate salts. Where a result is listed for only one radical species or solvent, this usually reflects a lack of reactivity, or product instability.³⁶ This study focused on two different reaction conditions: (i) CHCl₃/water (with the addition of TFA to enhance reactivity for the *i*-Pr examples), and (ii) DMSO without addition of acid.³⁷ Typically CHCl₃/water³⁸ solvent gave higher yields for electron-rich pyridines, and DMSO gave higher yields for electron-poor pyridines.

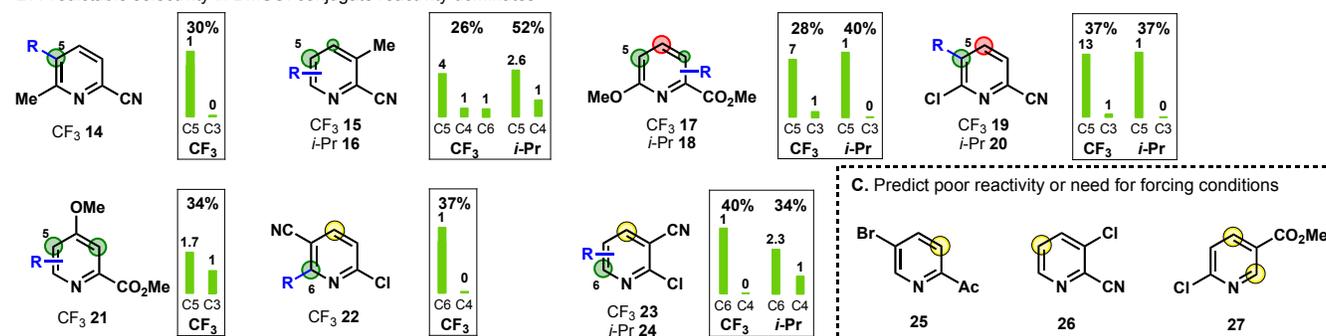
Particular points of note include: (i) an interesting example of the *meta*-deactivating effect of chlorides may be seen by comparing the unreactive **26** (Fig 9C) with the successful functionalization of the methyl analogue (**15** and **16**, Fig 9B); (ii) methoxy proved to be a stronger *ortho*-activator than bromide on **10** (Fig 9A), in keeping with the high electronegativity of oxygen relative to bromine;¹⁷ (iii) *i*-Pr gave very low

yields (albeit with the same general regioselectivity pattern) on the most electron-rich pyridines (**7–9** and **13**, Fig 9A) as expected for a nucleophilic radical; (iv) neither position in **12** (Fig 9B) is very activated under the reaction conditions, resulting in low yield and selectivity – the C5 position has little reactivity when not in DMSO solvent, and the C4 position has limited reactivity due to the *meta*-deactivating methoxy group, even under acidic conditions. Importantly, these results show that it is possible to predict which substrates are likely to fail or be reluctant to react.

As described previously, the relative contribution of innate and conjugate reactivity is dependent on solvent and pH. As a consequence, in examples where the innate and conjugate reactivities activate different sites, it is sometimes possible to tune the reactivity to favor a specific site, simply by changing solvent, as shown in Figure 10. Note the slightly lower selectivity for C5 over C4 substitution in **29** relative to **18** and **20**, reflecting the absence of a group that *meta*-deactivates the C4 position.

A. Predictable selectivity in CHCl₃/H₂O or CHCl₃/H₂O/TFA: innate reactivity dominates

B. Predictable selectivity in DMSO: conjugate reactivity dominates



C. Predict poor reactivity or need for forcing conditions

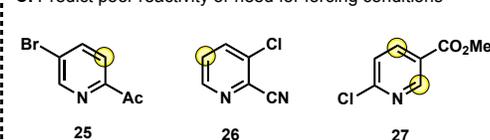


Figure 9. Substrates tested to assess combined directing effects on complex pyridines. (For key to highlighting circles see Figures 6 and 7.) Reagents and conditions: pyridine (0.125 mmol), zinc sulfinate reagent (TFMS or IPS) (2 eq.), TBHP (3 eq.), 50 °C, 12–16 h. See Supporting Information for more details.

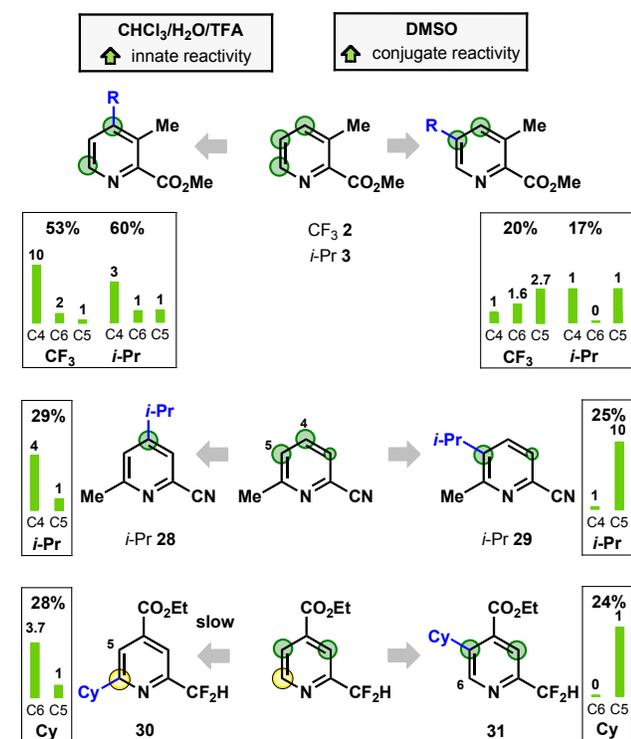


Figure 10. Tuning regioselectivity with solvent choice. (For key to highlighting circles see Figures 6 and 7.) Reagents and conditions: standard conditions as previously described. Forcing conditions for compound 30.^{6c} See Supporting Information for details.

Extension of regioselectivity trends to diazines. The regioselectivity of radical isopropylation of various functionalized and unfunctionalized diazines was examined to assess whether the functional group-dependent regioselectivity observed in pyridines could be extended to other heteroarene systems (Figure 11).³⁹ DMSO was used as solvent to achieve synthetically useful conversions of products on these substrates. The pattern observed with the diazines was similar to that for pyridines: (i) the parent heterocycle had an innate regioselectivity preference for a particular position; (ii) π -conjugating, electron-withdrawing groups induced a preference for reaction at the *ortho* and *para*-positions, and could allow functionalization at otherwise unreactive sites; (iii) halides and methyl groups did not activate the *para* position, but did exert an *ortho*-directing effect. The influence of conjugate reactivity on the innate preference is weaker compared with the pyridines, and the preference of the functional group typically influenced, but did not override, the innate preference.

2-Acylpyridazine derivatives gave the *para*-substituted products as a single regioisomer both for isopropyl (33), and the trifluoromethyl^{6a} and difluoroethyl^{6d} examples reported previously. Similar regioselectivity effects have also been seen in Minisci alkylations and acylations of 2-acyl pyridazines.⁴⁰ Pyridazines had an innate reactivity at the C4/C5 (β) positions. One of these two activated positions could be favored over the other with an *ortho*-directing functional group in the α position. The innate reactivity preference was by far the dominant factor, with even a strongly electron withdrawing nitrile group (37) having a limited capability to activate the *para* C6 position. Pyrimidines had an innate reactivity for C4, which could be partially overridden to give significant quantities of the C2 or C5 products with a π -conjugating electron-withdrawing group in the *para*-position (cf. 39 with 40; 41 with 42).

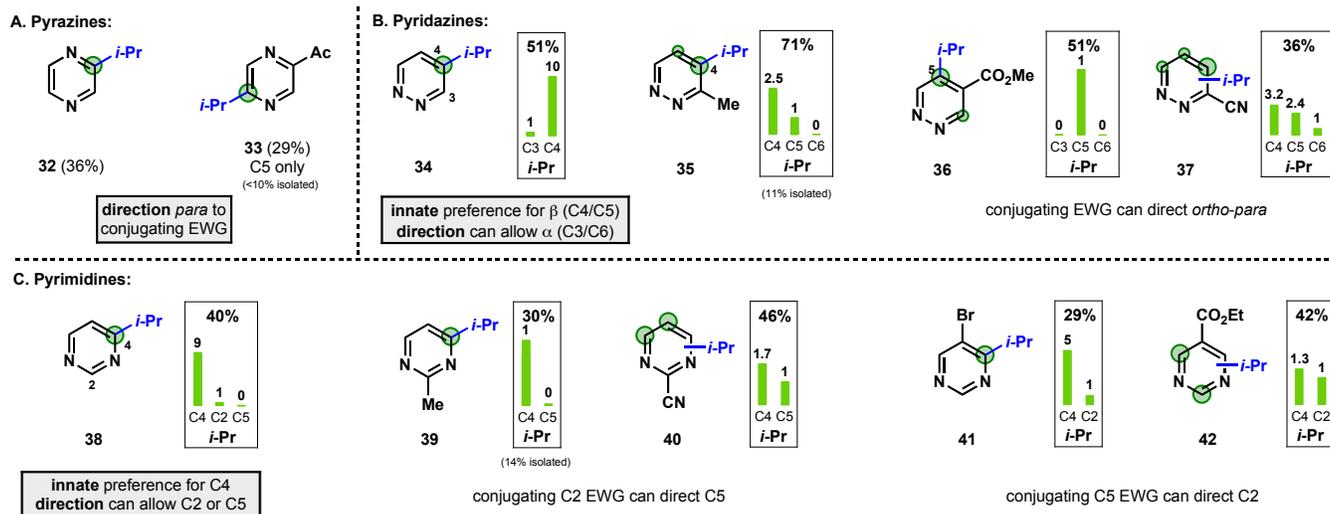


Figure 11. Extension of regioselectivity study to diazines: the same general principles apply, although the innate preference of the parent heterocycle is harder to overcome. (For key to highlighting circles, see Figures 6 and 7.) Reagents and conditions: heterocycle (0.125 mmol), IPS (2 eq.), TBHP (3 eq.), DMSO, 50 °C, 12–16 h. See Supporting Information for more details.

The innate sites of reactivity to radical functionalization for pyrimidines and pyridazines identified here are not unique to the alkylsulfonate-derived radical system; the same preferences have been observed in Minisci-type alkylations and acylations of diazine substrates.^{40a, 41}

Testing on complex biologically active substrates. An important goal of our predictive model is to demonstrate generality for more complex heteroarenes such as those that might be encountered in pharmaceutical or agrochemical research. These compounds are often difficult to elaborate due to problems of solubility, the presence of other reactive functional groups, or steric crowding. Several small heterocyclic drugs, herbicides, pesticides, and natural products were identified as substrates likely to give good reactivity and regiocontrol based upon the previously described guidelines. It was intended that these would provide a simulation of the size and complexity of the kind of molecules that the alkylsulfonate reagents might be used to functionalize.

Figure 12 shows that isopropylation of these compounds in DMSO solvent gave products that very closely followed the expected results. In all cases the predicted product was the major regioisomer obtained, with a ratio of at least 9:1; in most cases the reaction was fully selective for the predicted product.

The pesticide picolinafen (**43**) isopropylates exclusively at C5, closely following the precedent set by simple pyridines **18** and **20**. The elucidation of the regioselectivity guidelines focused on a limited selection of functional groups such as esters, nitriles and methoxy for which a wide variety of disubstituted pyridines are commercially available, but the trends observed are generalizable to other functional groups in the same class. Thus the π -conjugating electron-withdrawing amide group functions as an *ortho-para* director, and the aryl ether behaves as an *ortho-activator*. The exclusive regioselectivity of radical isopropylation of the herbicide diflufenican (**44**) is also explained in this manner, bearing in mind that like the methoxy group, an aryl ether can function as a *meta*-deactivator.

Nevirapine (**45**), an anti-retroviral drug, shows 9:1 selectivity for substitution at C9 on the nicotinamide ring, rather than

at C2 on the electron-rich pyridine. This illustrates two important points: (i) the strong preference of the nucleophilic *i*-Pr radical to react with the polar, electron-deficient pyridine ring, instead of the electron-rich pyridine; (ii) the ability to predict regioselectivity for a molecule bearing the previously unaminated amine group, based on the reasoning that this σ -withdrawing, π -donating functionality should function as an *ortho-activator* and *meta*-deactivator, as do methoxy and halide functionalities.

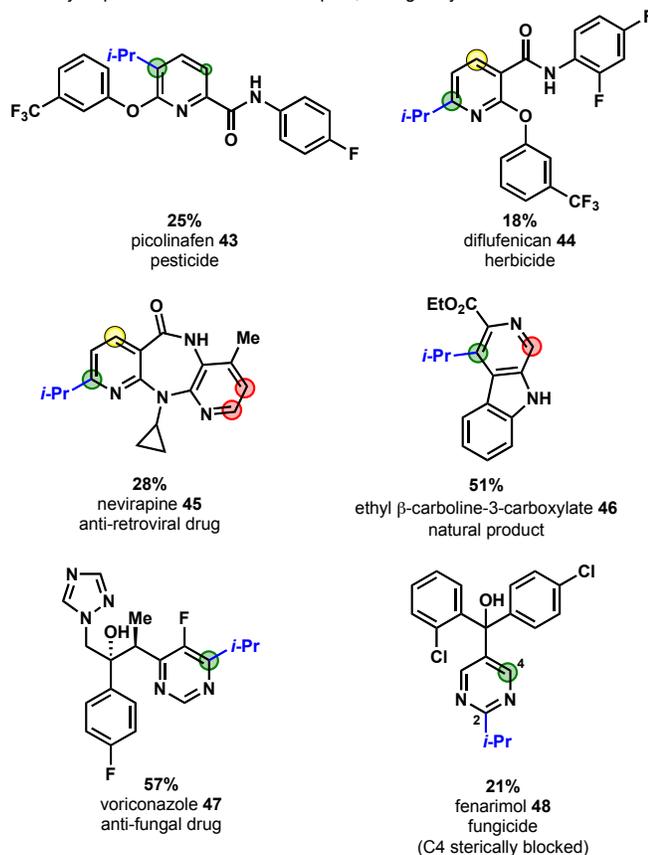
The exclusive regioselectivity of substitution of ethyl β -carboline-3-carboxylate (**46**) shows the very strong deactivation of a pyridine C2 position by a strongly electron-withdrawing group at C6. The reason for the amine failing to act as a *meta*-deactivator, as predicted in this case, is under further investigation. It is likely that the *meta* deactivation effect is dependent on the π -donor capability of the functional group, and that this is reduced by participation of the nitrogen lone-pair in the indole system.

Voriconazole (**47**), an anti-fungal medicine, is isopropylated exclusively at the pyrimidine C4 position. One position is selected over three other open heterocyclic sites α to nitrogen. The sensitivity of regiocontrol that is possible in radical functionalization processes is underlined by the fact that the C2 position of a pyrimidine is also reactive to radicals. Indeed, C2 substitution occurred exclusively for fenarimol (**47**), where the C4 position is too sterically crowded to react.

Influence of the electrophilic character of CF_3 radical. Our guidelines for predicting regioselectivity identify the sites on heteroarenes that are most reactive towards attack by radicals acting as nucleophiles. This works well for simple heteroarenes because despite their different electronic properties, both trifluoromethyl and isopropyl radicals primarily behave as nucleophiles when attacking electron-deficient substrates such as pyridines and diazines. A limitation of this prediction method may arise when considering more complex structures with several potentially reactive arenes and heteroarenes. In these cases, the site of reaction may be dependent on the properties of both the radical and (hetero)arene. In the examples shown in Figure 12, the nucleophilic *i*-Pr radical invariably reacted with the most electron-deficient ring, whereas regiose-

lectivity for the more electrophilic trifluoromethyl radical was more subtly controlled.

A. Ability to predict is retained on complex, biologically active substrates^a



B. In the absence of a reactive heterocycle, CF₃ may substitute on arenes

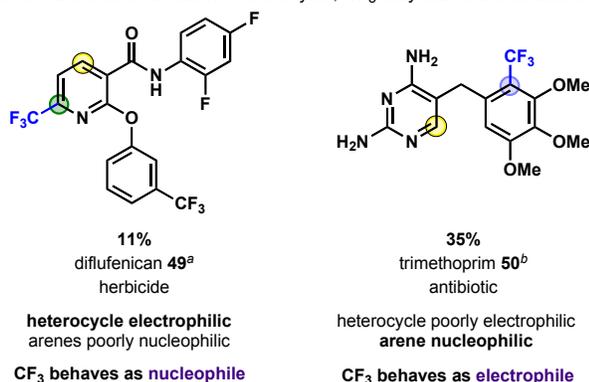


Figure 12. Regioselectivity remains predictable on complex substrates. (For key to highlighting circles see Figures 6-8.) Reagents and conditions: standard conditions as previously described. All examples gave >9:1 selectivity for the regioisomer shown. ^aDMSO solvent. ^bCHCl₃/H₂O solvent mixture.

In diflufenican (49) there is a reactive pyridine that competes with the relatively unreactive arenes bearing electron-withdrawing groups. Thus, trifluoromethylation occurred exclusively at the pyridine C6 position, analogously to the *i*-Pr radical. On the other hand, trimethoprim (50), which has an unreactive, electron-deficient heterocycle (neither amine can donate electron density to the unsubstituted position) compet-

ing with a very reactive trimethoxybenzene, is trifluoromethylated almost exclusively on the arene. The previously reported results on differing sites of reactivity for difluoromethylation and trifluoromethylation of varenicline and dihydroquinine can be explained by using a similar argument.^{6b}

Further investigations aim towards predicting the point at which trifluoromethyl radical will switch from nucleophilic to electrophilic behavior, but our investigations so far suggest that the analysis described in Figure 8 generally provides a good model for predicting the regioselectivity of alkylsulfinate-mediated radical addition to electron-deficient heteroarenes. Nevertheless, an important caveat is that when considering trifluoromethylation of molecules containing electron-rich arenes, or electron-deficient heterocycles that are fused to benzenoid or five-membered heteroaromatic rings, the possibility of the trifluoromethyl radical behaving as an electrophile to attack nucleophilic sites should also be considered.

Generalization to the borono-Minisci radical arylation. Examination of substitution patterns in literature examples of homolytic substitution of heteroarenes suggested that the principles of predicting and controlling regiochemistry for alkylsulfinate-derived radicals might be generalizable to other radical-mediated C–H functionalizations. A preliminary study was undertaken to assess the extent to which the findings in this report could be generalized to direct arylation of heteroarenes.

Arylboronic acids or alkyltrifluoroborates can be used for the direct functionalization of electron-deficient heteroarenes via a radical substitution process.⁴² The observed regiochemistry is broadly in line with that for typical for Minisci-type reactions (i.e., an overwhelming preference for the α and γ positions). However, in the “borono-Minisci” arylation^{42a} of heterocycles there were unexplained regiochemical results. The direct arylation of C4-substituted pyridines gave mixtures of C2 and C3 products for the 4-cyano and 4-chloro derivatives, yet the 4-trifluoromethyl and 4-(1,3-dioxolan-2-yl) derivatives were substituted only at the C2 position (Figure 13A). These results are understandable based upon the model described earlier (Figures 5 and 6), noting that aryl radicals are slightly more nucleophilic than trifluoromethyl radicals, and may also react as weakly electrophilic or nonpolar species.²⁴

The original reaction conditions^{42a} used a 1:1 CH₂Cl₂:H₂O solvent in the presence of TFA. By increasing the reaction temperature from room temperature to 50 °C, we were able to get appreciable conversions without the presence of acid. NMR studies of the regioselectivity of direct arylation of 4-cyanopyridine showed a familiar trend: (i) using DMSO rather than a chlorinated solvent³⁸ increased the proportion of “conjugate reactivity” to give the C3 product; (ii) as seen with CF₃, addition of acid showed only a slight increase in production of the “innate” C2 product (Figure 13B). The regioselectivity of arylation of a selection of more complex pyridines were assessed and similar regioselectivity patterns to those found for alkylsulfinate-derived radicals were observed (Figure 13C).

These preliminary results provide a precedent that the regioselectivity guidelines that we developed may be generally useful for other radical-mediated direct functionalization processes, and they show that it may be possible to apply information from the solvent dependence of regioselectivity in the alkylsulfinate system to tune regioselectivity in the functionalization of heteroarenes by other types of radicals.

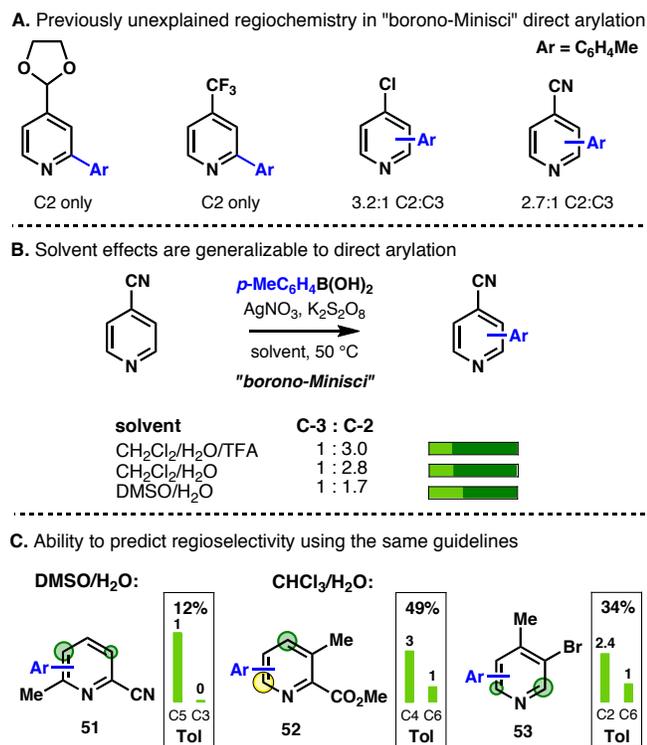


Figure 13. Extension of regioselectivity prediction to "borono-Minisci" direct arylation. Reagents and conditions: heterocycle (0.125 mmol), *p*-tolylboronic acid (1.5 eq.), AgNO₃ (20 mol%), K₂S₂O₈ (3 eq.), 50 °C, 3–16 h.

Conclusions

Factors affecting the regioselectivity of radical functionalization of pyridines were investigated systematically from a view to understanding, predicting and tuning the regiochemical outcome. A hierarchical model to rationalize the observed regioselectivity is proposed based upon experimental results and literature reports of related reactions. The principles of this model for regiocontrol have been distilled into a set of guidelines that summarize the stepwise process for predicting the regioselectivity of direct C–H functionalization of electron-deficient heteroarenes using radicals derived from alkylsulfinate salts. An advantage of alkylsulfinate salts as a means for radical generation compared with more traditional techniques is the facile ability to modify solvent and pH to influence the regioselectivity of substitution. This empirical model provides a method of explaining and predicting regiochemistry that closely fits with experimental observations.

The regioselectivity trends observed for pyridines were replicated for other heteroarenes, including pyrimidines and pyridazines. The results obtained with alkylsulfinate salts correspond with published data describing other radical direct functionalizations of heterocycles, such as Minisci chemistry. The potential general applicability of these observations was illustrated by similar regioselectivity effects with the "borono-Minisci" radical arylation. The guidelines established for simple pyridines proved to be equally valid for more complex heterocyclic drugs and agrochemicals.

Further studies to investigate the regioselectivity principles described in this report are ongoing and will be reported in due course. Application of the guidelines described here should aid in the increased application of radical-mediated direct func-

tionization processes in modern pharmaceutical and agricultural chemistry.

Supporting Information. Experimental procedures and analytical data for all new compounds, including ¹H, ¹³C, and ¹⁹F NMR files. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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ABBREVIATIONS

Bpin, 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl; DFMS, bis(((difluoromethyl)sulfinyl)oxy)zinc; DMSO, dimethylsulfoxide; EDG, electron-donating group; EWG, electron-withdrawing group; IPS, bis(((isopropyl)sulfinyl)oxy)zinc; TBHP, tert-butyl hydroperoxide; TFA, trifluoroacetic acid; TFMS, bis(((trifluoromethyl)sulfinyl)oxy)zinc.

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(27) It is important to note that the δ^+ sites identified in this manner indicate only that the position *may* be capable of reacting with a nucleophilic radical, not that it must do so. Furthermore, the magnitude of the δ^+ charge on a position does not generally relate to relative reactivity in any straightforward manner. Simple calculations of Hückel charges failed to adequately predict regioselectivity, as did examination of the proton and carbon NMR spectra of substrates. Although more sophisticated calculations may be able to better model the reaction, our aim was to provide a method of predicting regioselectivity and reaction outcome in a quick and simple manner.

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(33) This does not address the overwhelming preference for production of 2,5-dialkylated products in DMSO, or the similar pattern observed under non-protonative conditions by Tiecco and Testaferri.

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(35) Further examples of the prediction and explanation of regiochemistry for **1**, **11**, **12**, **15**, **16**, **17**, **18**, **28** and **29** may be found in the Supporting Information.

(36) NMR analysis of the reaction mixture for the 2-chloro derivatives **1** and **22** both showed only starting material and products for *i*-Pr substitution, but when purification was attempted after workup, numerous products were obtained. It is possible that the 2-chloro functionality is unstable on silica with electron-rich alkyl pyridine derivatives.

(37) Although DMSO/H₂SO₄ had given a promising C2:C3 ratio in early testing (Figure 3), there was a reduction in yield associated with removal of DMSO by aqueous washing from small, water soluble pyridine products. As a result the use of DMSO was limited to cases where "conjugate reactivity" was specifically needed. The use of DMSO/acid solvent mixtures may, however, be useful if the molecule under consideration has poor solubility in chlorinated solvent/water mixtures.

(38) Chloroform was substituted for dichloromethane to accommodate the increase in reaction temperature and facilitate NMR studies. This substitution did not make a significant difference in the results obtained.

(39) Trifluoromethyl radical did not show synthetically useful reactivity with many of these electron-poor diazines; therefore, although the same regioselectivity trends as described for *i*-Pr radical were observed, these results were not reported in this study. Electrophilic radicals were generally less regioselective for the most polar (C4) site on pyridazines and pyrimidines, although the same preference was still followed. Examination of the literature also showed that, for the limited range of examples showing substitution of a diazine with a somewhat electrophilic radical, a similar pattern to that observed with pyridines was seen.

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Insert Table of Contents artwork here

