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C–H Activation **Hot Paper**

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Radical C–H Functionalization of Heteroarenes under Electrochemical Control**

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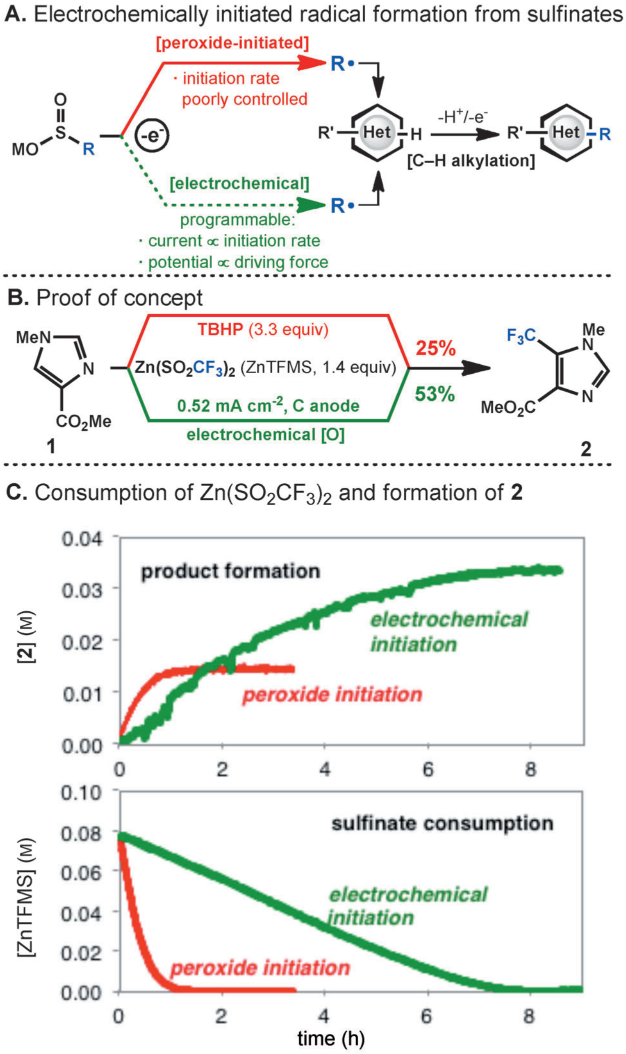
Abstract: *Electrochemical reactions are shown to be effective for the C–H functionalization of a number of heterocyclic substrates that are recalcitrant to conventional peroxide radical initiation conditions. Monitoring reaction progress under electrochemical conditions provides mechanistic insight into the C–H functionalization of a series of heterocycles of interest in medicinal chemistry.*

The C–H functionalization by sulfinate-derived radicals has emerged as a convenient method for late-stage functionalization of complex heterocycles (Scheme 1 A)[1] and has been shown to proceed cleanly in cases where other methods fail.[2] Sulfinate radical sources enable the synthesis of complex alkyl- and fluoroalkyl-substituted heterocycles that would be difficult or time-consuming to prepare de novo. The reaction exhibits high functional group tolerance with tunable and predictable regioselectivity.[3] However, despite the rapidly expanding scope of this transformation and its potential as a general method for late-stage C–H functionalization, low yields persist for a number of substrates, and the factors that lead to a successful reaction with a given heterocycle are not yet well understood. Herein, we report that electrochemical initiation results in significantly enhanced yields in the C–H functionalization of a number of complex substrates of pharmaceutical interest (Scheme 1B). Initial studies implicate the controlled generation of the free radical as a major factor in improving yield.

Our investigations of the functionalization of small heterocyclic pharmacophores as building blocks for fragment-based drug discovery showed that in the reaction initiated by peroxides (Scheme 1 A, red pathway) some substrates, in particular 1,2- and 1,3-azoles, give low yields even with high sulfinate loading. We undertook investigations of the factors influencing radical generation and consumption with the goal of enabling the C–H functionalization of recalcitrant substrates of interest in drug discovery with a reduction in sulfinate loading and to develop predictive models of the reactivity of heterocycle and radical pairs.



Scheme 1. Radical C–H functionalization of heteroarenes.

Prior reaction calorimetric studies[1a] revealed a high, unproductive heat output upon contact between sodium trifluoromethanesulfinate (NaTFMS) and *tert*-butyl hydroperoxide (TBHP). Together with the high sulfinate and

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TBHP loadings required to achieve good yields with most substrates, this suggests that a significant proportion of CF_3 radicals generated from the peroxide is lost to side reactions. Scattered reports on the electrochemical behavior of the $[CF_3SO_2]^-$ anion[4] suggested that initiation of the reaction by an anode, rather than TBHP, might provide a more controlled environment for the generation and subsequent reactions of sulfinate-derived radicals. Bulk electrolysis[5] allows either the driving force (potential) or the rate of electron transfer (current) to be explicitly and separately tuned (Scheme 1 A, green pathway).[6] We reasoned that electrolysis at constant current could provide direct control over the rate of sulfinate oxidation and hence allow the radical flux to be precisely defined.

Cyclic voltammetry of a series of zinc and sodium fluoroalkylsulfinates in DMSO–NEt_4ClO_4 solution at a carbon working electrode showed irreversible oxidation waves at potentials between 1.0 and 1.4 V (vs. Ag/AgCl).[7] For each sulfinate, a distinct peak corresponding to loss of SO_2 was observed at −0.7 V on the reverse scan, regardless of the oxidation potential observed in the forward scan. These data indicate, in accordance with previous reports,[4a] that rate-limiting electron transfer gives a sulfinate radical followed by rapid cleavage to generate the fluoroalkyl radical.

The combination of the low reactivity of imidazoles such as **1** towards fluoroalkylation in the TBHP-initiated reaction and the prevalence of the imidazole moiety in drug development prompted our choice of **1** as a substrate for detailed investigation of the reaction under electrochemical conditions.[8,9] Electrolysis of a solution of **1** and ZnTFMS was carried out in DMSO–NEt_4ClO_4 (0.1 M) at a carbon cloth anode at different constant current values.[7] Reaction progress was monitored by rapid circulation of the reaction mixture through a transmission FTIR cell.[7] The consumption of ZnTFMS and formation of product **2** were tracked by IR peaks at 1145 cm^{-1} and 1722 cm^{-1}, respectively. Scheme 1 C compares these processes under electrochemical and peroxide-initiated conditions. The TBHP-initiated reaction exhibits a faster initial production of **2**. Rapid total consumption of sulfinate accounts for the stalling characteristic of these reactions. By contrast, the electrochemical initiation causes much slower consumption of the sulfinate concomitant with a steady reaction proceeding to significantly higher conversion to product **2** (Scheme 1 B, 25 vs. 53 % yield of isolated product).

Reaction progress kinetics at different initial concentrations of **1** showed positive order in substrate concentration, and the productive reaction rate was not strongly influenced by the current (Figure 1, green). The rate of sulfinate consumption followed zero-order kinetics under electrochemical conditions and was controlled entirely by the cell current (Figure 1, blue). This allows prediction of the time for total consumption of the reagent, which in effect dictates the window of time for the productive reaction. The quantity of **2** formed per mole of sulfinate consumed is greater at lower current (Figure 1, red), implying a shift in favor of productive versus unproductive reactions when the radical is generated more slowly. Elevated temperature had no effect on the rate of sulfinate oxidation but resulted in slightly enhanced conversion. Good yields of **2** were obtained under electrochemical conditions using significantly lower ZnTFMS concentrations than in our previously reported conditions.[7]

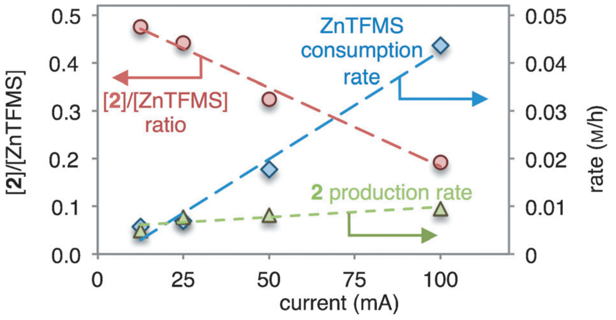


Figure 1. Initial rate of ZnTFMS consumption (blue, right axis), production of **2** (green, right axis), and moles of **2** produced per mole of ZnTFMS consumed (red, left axis), as a function of current in the reaction of Scheme 1 B.[7]

The magnitude of the observed redox potentials provides some insight into the privileged role of TBHP compared to other chemical oxidants that have been screened in previous work on these reactions. Reported reduction potentials for the *tert*-butoxy (*t*BuO) and *tert*-butylperoxy (*t*BuOO) radicals are −0.34[10] and 0.75 V[11] (vs. Ag/AgCl), respectively, below the oxidation potential of the sulfinate, whereas weaker single-electron oxidants, for example, ceric ammonium nitrate (CAN), possess much lower redox potentials.[12] The redox behavior of TBHP indicates that Fenton-type cleavage of the hydroperoxide O−O bond by adventitious trace metal, as previously suggested,[1a] is unnecessary for initiation of the reaction.[13]

If the increased yield observed under electrochemical conditions could be rationalized solely by differences in the rate of radical generation, then slow addition of TBHP should result in a yield similar to that observed under electrochemical conditions. Interestingly, however, whereas addition of TBHP over eight hours (Figure 2, red curves) showed slow consumption of ZnTFMS, no significant increase in yield was observed compared to standard protocol (Figure 2, gray curves). This implies further differences between the two protocols, possibly in the second oxidation process, which may also be the cause of slight differences in regioselectivity

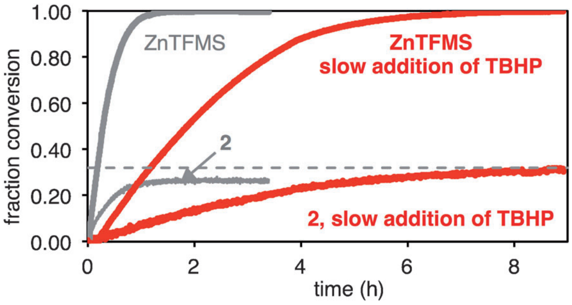
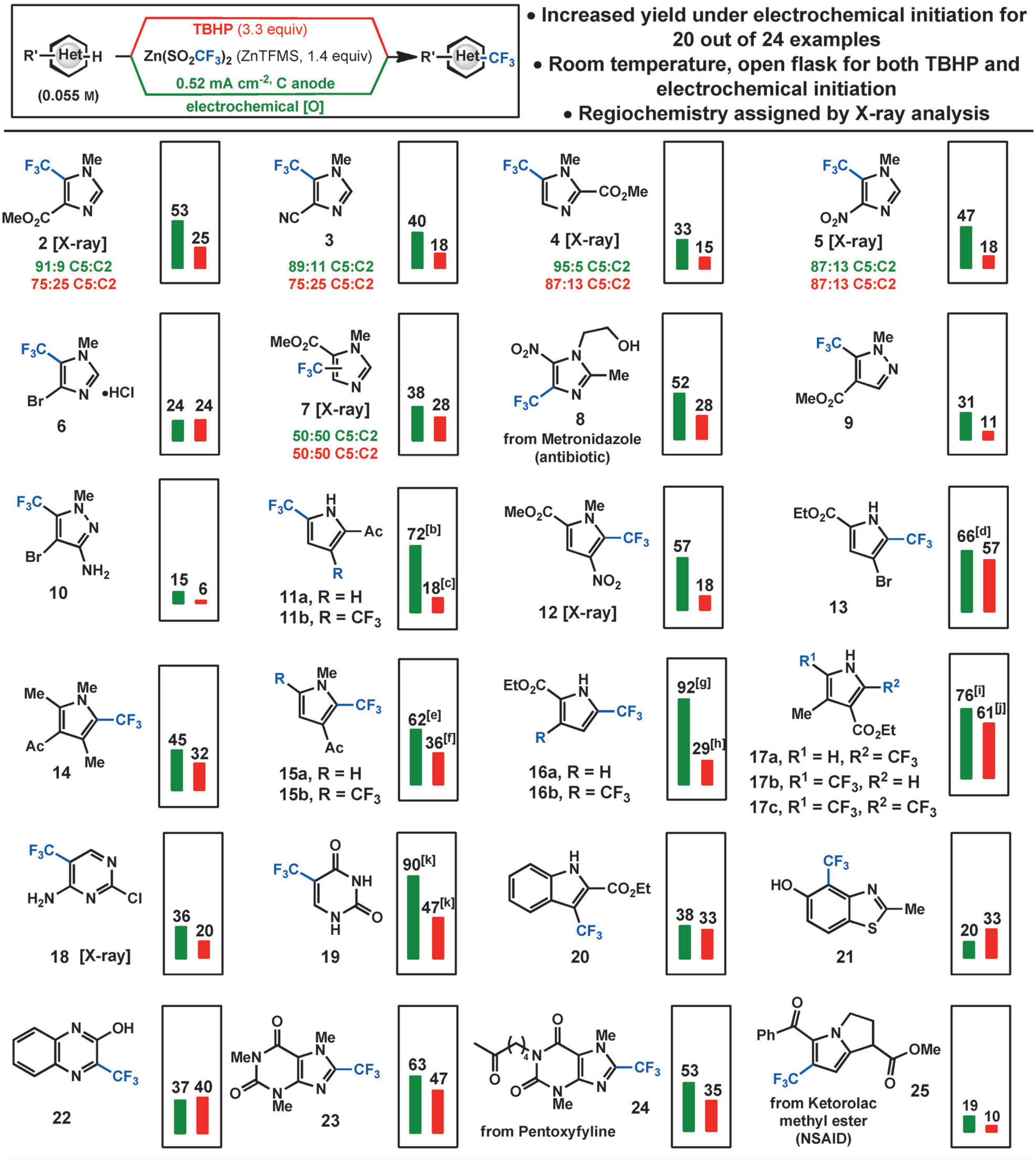


Figure 2. Consumption of ZnTFMS and production of **2** in the TBHP-initiated reaction of **1**. Comparison of reaction protocols: slow addition of TBHP over 8 h (red); standard protocol, TBHP added in one portion (gray).

between the two methods. The radical consumption/C–H functionalization step may also play an important role in the overall efficiency of these electrochemical reactions.

A broad range of substrates show enhanced reactivity under electrochemical initiation of trifluoromethylation (Scheme 2). The rate of sulfinate oxidation was found to be invariant with substrate, which suggests that the reported yields reflect intrinsic differences in the second oxidation step. The reactions are typically highly selective. Pyrroles unexpectedly showed disubstitution under electrochemical initiation in some cases. Pyrazoles were among the least reactive substrates. Where necessary, regiochemistry was assigned



Scheme 2. Comparison of trifluoromethylation under electrochemical and TBHP radical initiation.[7] [a] Typical conditions for electrochemical experiments: DMSO–NEt_4ClO_4 (0.15 M), carbon cloth anode, separated cell, 25 mA, 8 h. [b] **11a** (60%) and **11b** (12%). [c] **11a** only. [d] Accompanied by debrominated **16** (9%). [e] **15a** (55%) and **15b** (7%). [f] **15a** only. [g] **16a** (65%) and **16b** (27%). [h] **16a** only. [i] A 1:1 mixture of **17a** and **17b** (55%) and **17c** (21%). [j] A 1:1 mixture of **17a** and **17b** (34%) and **17c** (27%). [k] Conversion determined by HPLC analysis. Using MeCN/H_2O as the solvent gave **19** in 75% yield (electrochemical initiation).

using X-ray crystallography. X-ray structures of **5**, obtained as an amorphous solid, **7**, a highly volatile solid, and **12**, a brown oil, were obtained from less than 2 mg of material using the recently reported metal–organic framework method of Fujita[14] and co-workers (Figure 3). Difluoromethylation and trifluoroethylation were effective only for the most reactive substrates (Scheme 3). Although the sulfinate was oxidized in each case, products were obtained in low yield even at elevated temperature reflecting the poor reactivity of the CF_2H and CH_2CF_3 radical–heterocycle pairs.

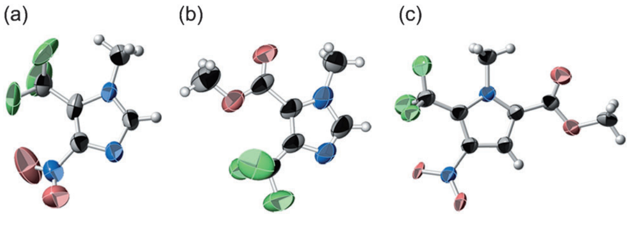
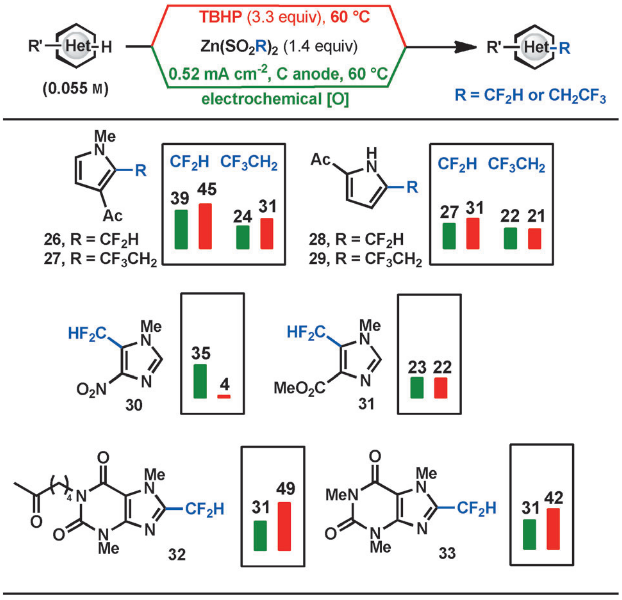


Figure 3. Structures of a) **5**, b) **7**, and c) **12**, determined by the crystalline sponge method. Thermal ellipsoids are drawn at 50% probability.[7,13]



Scheme 3. Comparison of electrochemical and TBHP radical initiation with DFMS and TFES.[7]

In summary, monitoring the reaction progress under electrochemical initiation allowed deconvolution of processes related to radical generation and radical consumption. Controlled radical formation mediates radical introduction into the system and increases the window of time for the productive reaction, leading to enhanced yields for recalcitrant substrates of pharmaceutical interest. These results demonstrate the successful radical C–H functionalization of a wide variety of heterocycles up to gram scale under electrochemical initiation using significantly less sulfinate reagent than peroxide radical initiation methods.

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