2.1 Late-Stage Functionalization

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ABSTRACT: Late-stage functionalization reactions can chemo- and regioselectively functionalize complex molecules. Late-stage functionalization is desirable in areas such as pharmaceutical discovery to accelerate drug development and essential in other areas such as positron-emission tomography to avoid unproductive decay of short-lived isotopes before meaningful medically imaging. We have discovered a new reaction that can introduce a linchpin into complex small arene molecules with exquisite selectivity. Subsequently, the linchpin can be transformed into numerous groups that are important for medicinal and medical applications.

Late-stage functionalization has the potential to quickly access functional molecules of value in many areas, for example in pharmaceutical development or positron-emission tomography (PET). Late-stage functionalization is desirable because advanced, complex molecules can be used as suitable starting points, which avoids lengthy de novo syntheses from simple building blocks. However, the development of late-stage functionalization requires meeting the challenges for both, C-H functionalization reactions and functional-group-tolerant reactions. Large strides have been made in the past few decades in C-H functionalization chemistry, yet many of such reactions are not compatible with the functional complexity of complex small molecules. Likewise, important advances have been made in chemoselective functionalization of complex molecules, for example in the context of biorthogonal chemistry that can be applied to highly functionalized biomolecules, but specific functional groups must be introduced, typically at an early stage of the synthesis. Within the last reporting period we have succeeded in developing a remarkably selective C-H functionalization reaction that can function even on densely functionalized small-molecule arenes and some hetarenens. The method is unusual in the sense that for most arenes, independent of substitution pattern and directing groups, a single constitutional isomer, within the limits of conventional detection, of the functionalized product can be isolated. Subsequently, the sulfonium-based linchpin can be used as a useful synthetic handle in C–C, C–N, C–O, C–S, and C–F bond-forming reactions. We have shown for the first time that the specific arylsulfonium salts based on the heterocycle thianthrene are excellent substrates for conventional palladium-catalyzed cross-coupling chemistry, as well as provide conceptual advances in photoredox-catalyzed transformations when compared to other aryl (pseudo)halides.

As part of our ongoing program in site-selective C–H functionalization, we have attempted to identify persistent sulfur-based radicals that could add to arenes in an endergonic first step of the reaction; our design was motivated by a linear free energy relationship discovered by Brown and Stock in the 1950's that predicts reactions with a large absolute Hammett rho value to proceed inherently with high positional selectivity. A long, nascent C–S bond formed by radical addition to an arene may result in a high rho value, and we identified the thianthrene scaffold as promising heterocycle for C–H functionalization.

After reaction optimization, arene functionalization could be executed in high selectivity, in favor of the most electron-rich position, even for substrates that are otherwise only moderately directing, such as toluene or ethylbenzene.[1] While there are isolated examples of other selective reactions, they typically introduce substituents that are not themselves synthetic linchpins and therefore synthetically of lesser value.[2] Some of the most useful linchpins in organic synthesis such as bromides and boronic acid derivatives still cannot be introduced selectively into most arenes. *The most important research result in the past three years from my research group is the development of the thianthrenation reaction, which is the first example of a reaction that can do both, functionalize complex small molecule arenes in high selectivity, and provide a useful handle for subsequent follow-up transformations.*

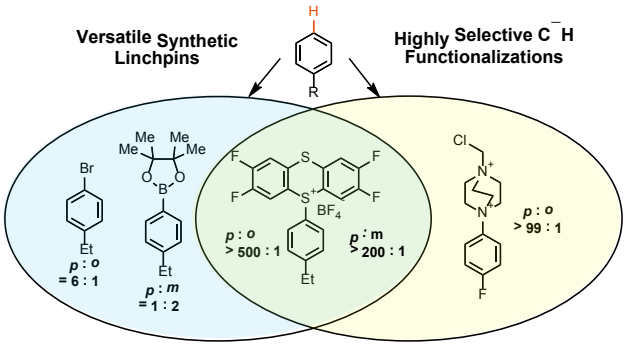
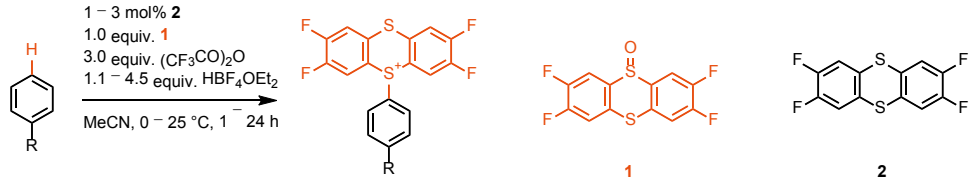
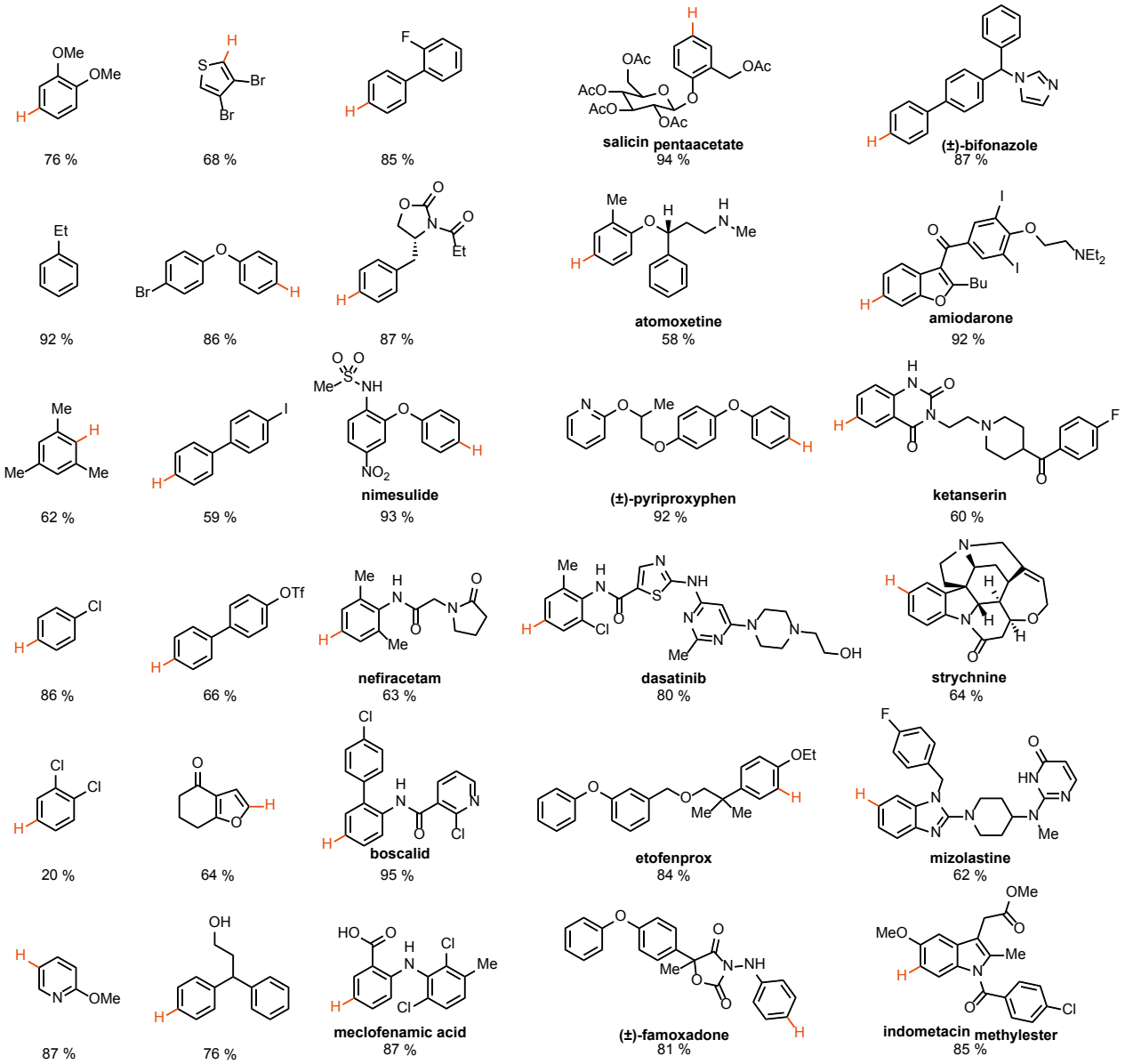


Figure 1. Highly regioselective C-H Thianthrenation.

Thianthrenation can proceed on a variety of small molecule-(hetarenes) as shown in table 1; in all cases a single constitutional isomer was observed. The reaction is successful on most electron-rich arenes but fails on arenes more electron-poor than dichlorobenzene. Only electron-rich heterocycles such as thiophene can be converted effectively, electron-poor heterocycles such as pyridine require strongly electron-donating substituents. A primary kinetic isotope effect of the transformation is consistent with rate-limiting

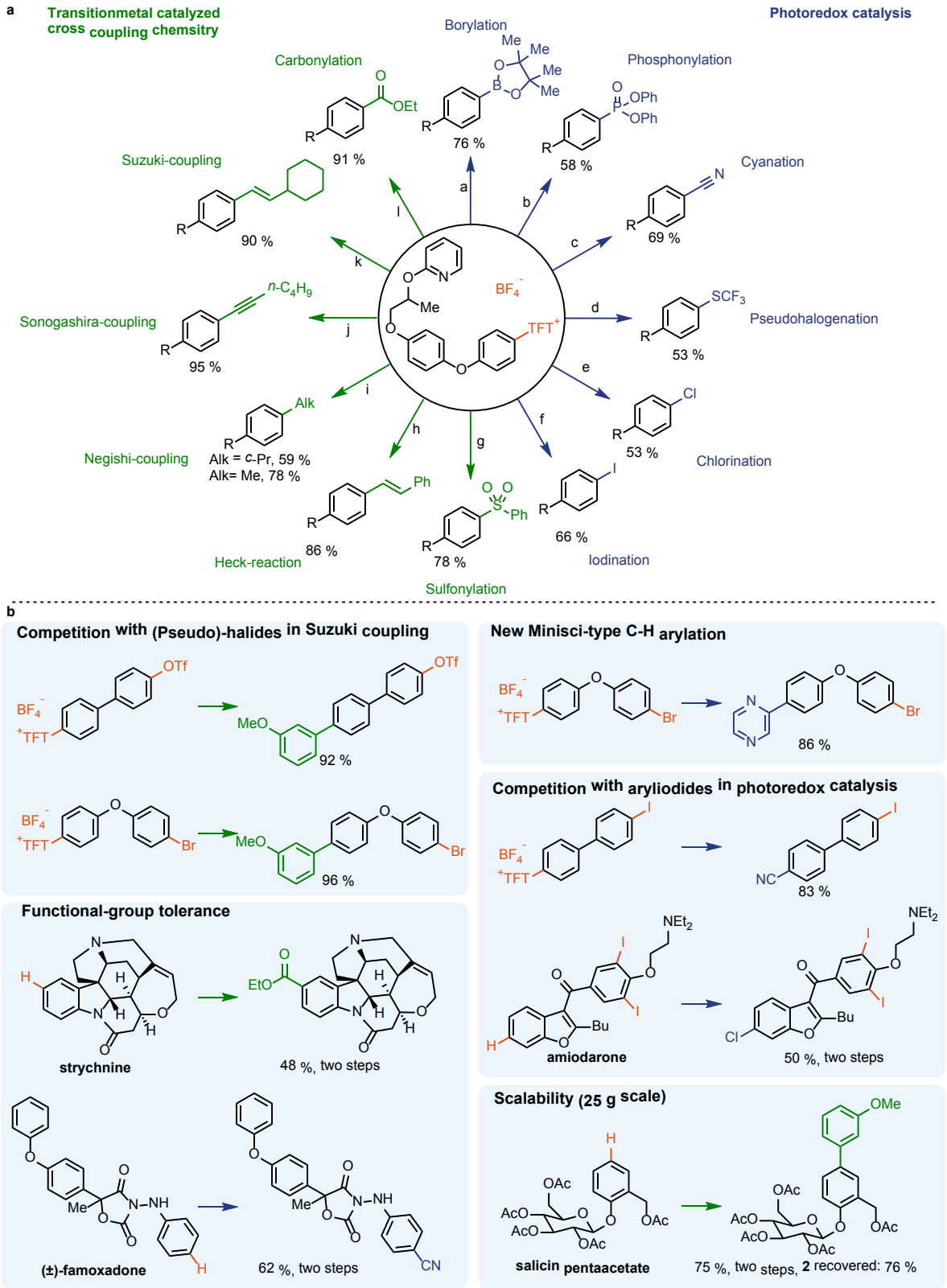
Table 1. Late-Stage Thianthrenation of (het)arenes.





deprotonation of a dicationic Wheland intermediate, and an unusually large rho value of –11 establishes the electrophilic nature of the transformation. Given the current mechanism data, the source of selectivity seems more subtle than what was originally designed. Radical addition is not necessarily relevant; a dicationic thianthrenium intermediate may add to the arene reversibly before rate-limiting deprotonation, which is subject of current investigations, but the current hypothesis favors an electrophilic aromatic substitution mechanism in which the aromatic thianthrenium dication reacts with the arene directly. Selectivity in this case would be determined by the relative energies of the different Wheland intermediates, assuming that the transition states of the subsequent rate-limiting deprotonations of the different Wheland intermediates are of similar magnitude. The different energies of the Wheland intermediates can be rationalized by maximization of charge separation. Equipped with this analysis, we predicted that other dicationic electrophiles should elicit similarly selective substitution reactions, which, preliminarily, seems to be the case.

Scheme 1. Cross-Coupling Reactions and Photoredox Reactions of Arylthianthrenium salts.



The thianthrenium group is useful as a leaving group in palladium-catalyzed cross coupling reactions, as well as in photoredox-mediated reactions (Scheme 1). All evaluated conventional carbon-carbon cross coupling reactions proceed well. Remarkably, the thianthrene group outcompetes bromide and triflate leaving groups, with catalysts under reaction conditions originally developed for halides and triflate. Such reactivity enables chemoselective cross coupling even in the presence of other halides.

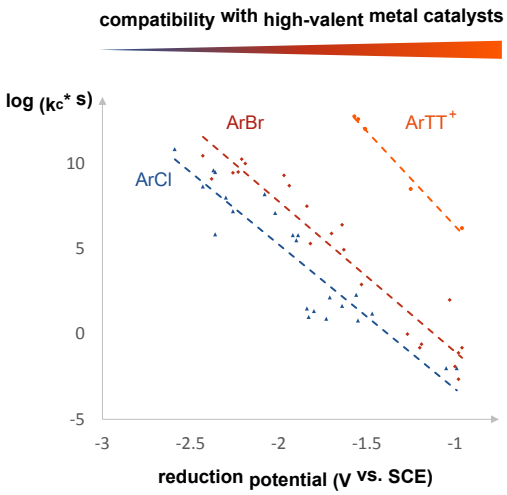
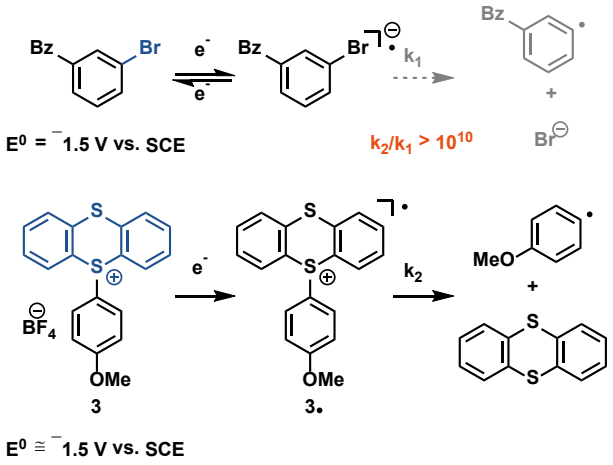


Figure 2. Conceptual Advantage of Arylthianthrenium salts of aryl halides in photoredox catalysis.

In palladium-catalyzed cross coupling, the thianthrene group behaves as an excellent, but conceptually identical, leaving group when compared to halides or other pseudohalides. For photoredox catalysis, the thianthrene group displays a fundamental advantage when compared to other (pseudo)halides. Figure 2 shows a linear relationship between the reduction potential and the log of the rate constant for mesolytic cleavage, and rationalizes that arylthianthreniums are better suited to engage in aryl radical formation through photoredox catalysis.

Scheme 2. Mesolytic Cleavage after single Electron Reduction.



It is intuitive why the reduction potential of aryl thianthreniums is lower when compared to aryl halides with identical aryl substituents owing to the positive charge. Therefore, reduction of all investigated arylthianthrenium salts is accessible to conventional photoredox catalysts (≥ 1.7 V), whereas reduction of aryl halides is often plagued by fast back electron transfer. It is less obvious why mesolytic cleavage of the radical anions, which forms the synthetically useful aryl radicals, generated by single electron reduction of arylthianthrenium salts, proceeds at least ten billion times faster for aryl thianthreniums than for aryl bromides with similar reduction potential, and thereby successfully avoids unproductive back electron-transfer that is observed in aryl halides (Scheme 2).

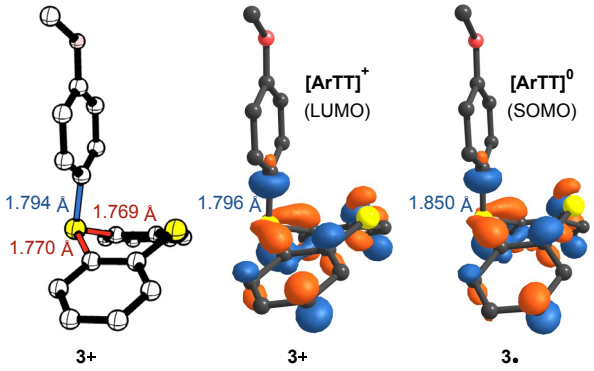


Figure 3. X-ray structure of **3** with 50% elipsoids; H atoms and counteranion not shown for clarity, as well as computed LUMO and SOMO of **3** and **3·**, respectively.

An orbital analysis reveals that the SOMO of radical **3·**, the compound obtained following single electron reduction of **3+**, as well as the LUMO of **3+**, have an antibonding interaction along the carbon sulfur bond that must break for arene radical synthesis (Figure 3). Due to the π system of the thianthrene heterocycle, as well as the flagpole conformation of the aryl substituent, the appropriate population of the σ* orbital is energetically more favorable than in arenes with monoatomic leaving groups such as aryl halides, which results in a substantial rate increase for mesolytic cleavage.

The ability to more effectively access aryl radicals through photoredox catalysis enabled the combination with copper-based redox catalysis in a way that has not been possible with other electrophiles, and resulted in the successful development of C–CF_3,[3] C–N,[4] C–O,[5] and C–F[6] bond forming reactions. Analysis of the reaction mechanism and further development based on the lessons learned enabled us to develop a selective C–H to C–^{18}F fluorination reaction that shows promise due to its reliable and simple reaction setup for PET tracer synthesis in hospital settings. Attempts to translate our new fluorination technology to human imaging are currently underway.

Funding Sources

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