LETTER

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Site-selective and versatile aromatic C–H functionalization by thianthrenation

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Direct C–H functionalization can quickly increase useful structural and functional molecular complexity[1–3]. Site selectivity can sometimes be achieved through appropriate directing groups or substitution patterns[1–4]—in the absence of such functionality, most aromatic C–H functionalization reactions provide more than one product isomer for most substrates[1,4,5]. Development of a C–H functionalization reaction that proceeds with high positional selectivity and installs a functional group that can serve as a synthetic linchpin for further functionalization would provide access to a large variety of well-defined arene derivatives. Here we report a highly selective aromatic C–H functionalization reaction that does not require a particular directing group or substitution pattern to achieve selectivity, and provides functionalized arenes that can participate in various transformations. We introduce a persistent sulfur-based radical to functionalize complex arenes with high selectivity and obtain thianthrenium salts that are ready to engage in different transformations, via both transition-metal and photoredox catalysis. This transformation differs fundamentally from all previous aromatic C–H functionalization reactions in that it provides direct access to a large number of derivatives of complex small molecules, quickly generating functional diversity with selectivity that is not achievable by other methods.

Bromo and boryl substituents are among the most useful linchpins in organic chemistry, but introducing those substituents selectively can be problematic when molecules lack appropriate functional groups or substitution patterns. We evaluated two of the most selective transformations for bromination[6] and borylation[7] to show their selectivity for functionalization of ethylbenzene (Fig. 1). Electrophilic bromination is mostly controlled electronically and, although some substrates can be brominated selectively, even the most selective bromination reactions developed so far[6,8–11] produce mixtures of isomers for most substrates (Fig. 1, Supplementary Table S6). Iridium-catalysed borylation reactions are mostly sterically controlled and can afford high selectivity for certain substitution patterns, such as for 1,3-disubstituted arenes[1]. Of the few highly selective aromatic C–H functionalization reactions that do not require particular directing groups or substitution patterns, including our *para*-selective TEDAylation reaction[12], none can introduce synthetic linchpins, and they are therefore not broadly useful for introducing a variety of substituents. The C–H functionalization reaction reported herein can proceed in >99% selectivity—not only for complex small molecules, but also for simple monosubstituted arenes such as ethylbenzene—to afford novel synthetically useful aryltetrafluorothianthrenium salts (Ar–TFT$^+$; Fig. 1).

Previously, we developed an aromatic C–H functionalization reaction that gives access to a large variety of constitutional isomers to generate structural diversity[13]. The design was based on achieving a highly exergonic radical addition with an early transition state that, in accord with Hammond's postulate, would elicit little discrimination between different positions of a given arene. Hammett analysis afforded a ρ value close to zero, as would be expected for a reaction with an early transition state. To achieve highly selective arene functionalization, we targeted a reaction with a large absolute Hammett value, which could result from an endergonic radical reaction with a late transition state. A large absolute Hammett value, by definition, would result in reaction rates spanning several orders of magnitude for a broad spectrum of electronically different arenes. A broad substrate scope, with resulting slow productive reaction rate for some arenes, requires that the reactive species not be consumed by other deleterious reaction pathways—such as hydrogen atom abstraction by a radical—even if the desired reaction with the substrate is slow. On the basis of this analysis, we evaluated electrophilic persistent sulfur-based radicals. A persistent radical does not engage in deleterious side reactions to the extent that most radicals do and could result in an endergonic radical reaction, and therefore a late transition state.

Thianthrene radical cations can be accessed in situ from the new thianthrene sulfoxide **1** (Fig. 2), which can be prepared on scale in two steps from 1,2-difluorobenzene and disulfur dichloride via tetrafluorothianthrene **2** (TFT). As part of an extended study on the reactivity of thianthrene in the 1970s, the reaction of isolated thianthrenium radical cations with simple electron-rich arenes—such as anisole—was evaluated, and the formation of arylthianthrenium cations was observed[14–16]. However, the selectivity of the reactions was not investigated, and the synthetic utility of arylthianthreniums was not recognized, possibly owing to the reported incompatibility of thianthrenium radical cations with many functional groups, such as pyridines[17], amines[18] and alcohols[19]. Instead of the moisture-sensitive, explosive thianthrenium perchlorate radical salt prepared separately, our new method uses the bench-stable, fluorinated sulfoxide-based thianthrene reagent **1** which—together with the modified reaction conditions—expands the substrate scope, probably owing to a higher reduction potential and functional-group tolerance (see Supplementary Tables S2, S3). Moreover, we discovered that addition of thianthrene proceeds with excellent selectivity and that thianthreniums can function as synthetically useful functional groups.

The tetrafluorothianthrene radical cation generated in situ by comproportionation of **1** and **2** reacts chemoselectively to functionalize arenes in preference to undergoing deleterious side reactions. The high degree of chemoselectivity enables a large substrate scope (Fig. 2). Thianthrenation can proceed on arenes as electron-rich as aniline derivatives to those as electron-poor as 1,2-dichlorobenzene. Arenes that are more electron-rich than anisole undergo unproductive oxidation with the TFT-reagent **1**, presumably through single-electron oxidation. Therefore, we used an analogous non-fluorinated thianthrene reagent for all arenes more electron-rich than anisole, such as meclofenamic acid (**30**) and famoxadone (**31**). Even more electron-rich arenes, such as indole, are not tolerated and undergo unproductive oxidation; hence, they cannot be functionalized. However, once an electron-withdrawing group is installed, the desired reaction pathway proceeds (for example, **32**). In addition, boronic acids are not tolerated in the reaction because they undergo *ipso*-substitution. The transformation is highly tolerant of many other functional groups, such as amines, amides, alcohols, ethers, esters, carboxylic acids and heterocycles.

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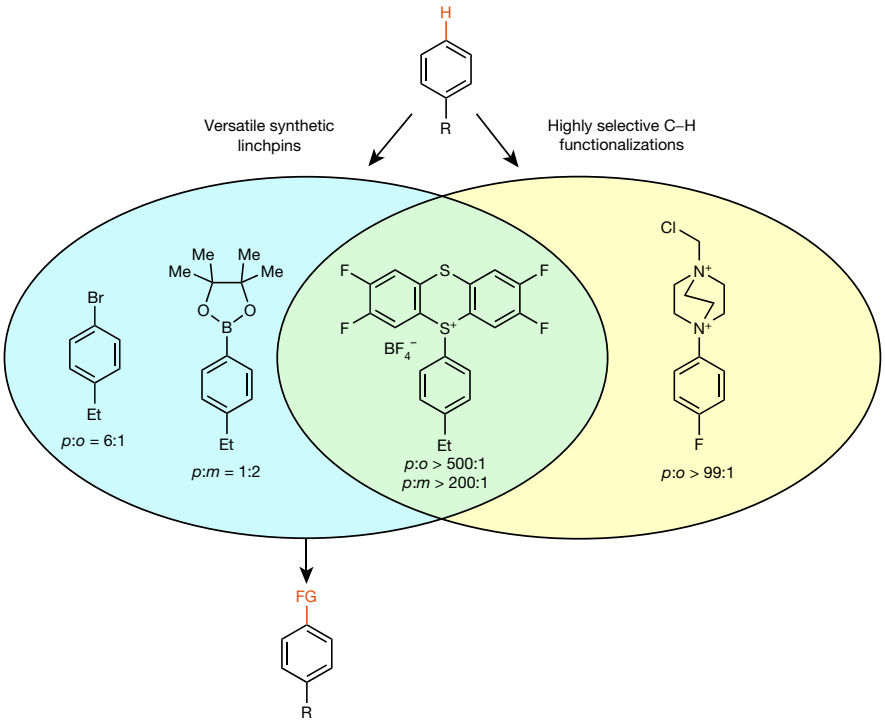
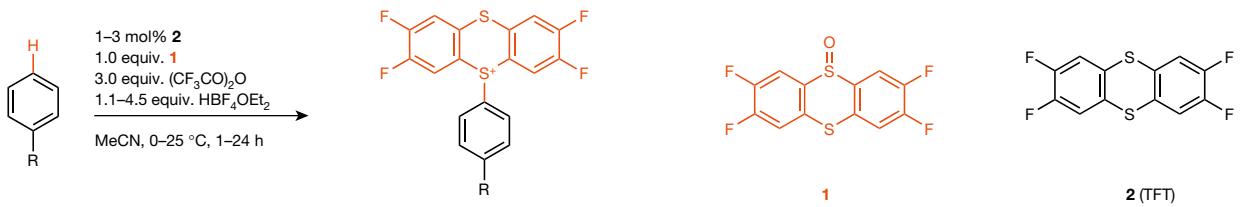


Fig. 1 | Selectivity of thianthrenation. Comparison of thianthrenation with halogenation[6], borylation[7] and TEDAylation[12]. FG, functional group (for example, CO_2Et, Cl, CN). Bromination[6] and borylation[7] produce synthetically useful arylbromides and arylboronic acids (blue area) as a 6:1 mixture of isomers for the bromination of ethylbenzene and a 1:2 mixture of isomers for the borylation of ethylbenzene. TEDAylation[12] is highly site-selective, giving a *para*:*ortho* ratio of *p*:*o* > 99:1 for fluorobenzene (yellow area); however, aryl-TEDAs are of low synthetic value. Thianthrenation produces synthetically versatile arylthianthrenium salts in high selectivity (*p*:*o* > 500:1, *para*:*meta* ratio of *p*:*m* > 200:1 for ethylbenzene; green area).

Alcohols are trifluoroacetylated under the reaction conditions but trifluoroacetate esters hydrolyse during aqueous workup. In the case of sufficiently electron-rich arenes, olefins can be tolerated (for example, strychnine, **22**). Basic functional groups are protonated under acidic reaction conditions and are thus protected from oxidation (for example, **12**, **21** and **27**). HBF_4OEt_2 must sometimes be replaced by Lewis acids—such as BF_3OEt_2 or TMSOTf—which enables successful functionalization of compounds that contain acid-sensitive functionality, such as salicin pentaacetate (**6**), or of compounds that would otherwise be protonated and therefore deactivated for functionalization, such as electron-rich pyridine derivatives (for example, **28**). The reaction is not sensitive to dioxygen or traces of water and can thus be carried out under an ambient atmosphere in most cases. The majority of the arylthianthrenium salts are soluble in organic solvents such as acetonitrile, dichloromethane, 1,4-dioxane, dimethylformamide and dimethyl sulfoxide, and can be stored as solids under ambient conditions for years (see Supplementary Table S4). Although these salts can usually be used without purification (see below), chromatography on silica gel provides analytically pure compounds, as shown in Fig. 2. High regioselectivity was observed in all cases, even for compounds containing several reactive positions in different aromatic rings, such as in 2-fluorobiphenyl (**5**), meclofenamic acid (**30**), famoxadone (**31**) and bifonazole (**7**). The only substrate for which we could identify more than one isomer was mizolastine (**27**), which produced a mixture of two products (ratio 16:1); the major isomer was obtained in pure form. The selectivity of the reaction is assumed to be mostly dependent on electronic effects, which can discriminate even between slightly different positions (for example, **7**) and can override steric biases (for example, **26**). Although thianthrenium is a large functional group, sterically hindered positions can be accessed—as exemplified by the thianthrenation of mesitylene (**13**)—presumably owing to the long C–S bond. The high selectivity for the most electron-rich position, combined with the positive charge of the sulfonium salt, enables selective monosubstitution, as illustrated by the selective functionalization of compound **29**. Some of the arenes shown in Fig. 2 have an intrinsic bias for regioselective electrophilic substitution reactions; for example, bromination of 1,2-dimethoxybenzene (**3**) and 2-methoxypyridine (**28**) proceed regioselectively[20,21]. However, regioselectivity is not achieved generally in arene C–H functionalizations, as shown in Fig. 1. In no instance out of 48 evaluated cases was bromination more selective for the position of thianthrenation, and in 46 of those cases bromination was substantially less selective or afforded no product at all (see Supplementary Table S6).

The thianthrenium salts can behave as versatile linchpin electrophiles in both palladium-catalysed cross-coupling chemistry and photoredox catalysis. We developed an initial set of 13 reactions, exemplified by the derivatization of the insecticide pyriproxyfen (**16**; Fig. 3a). Unlike alkylaryl sulfonium salts—which can engage in some cross-coupling reactions[22,23] but are strong alkylating reagents[23]—aryl thianthrenium salts are more resistant to nucleophiles such as cyanide, tertiary amines and organo zinc reagents, although treatment with strong bases can result in benzyne formation[24,25]. The increased stability of thianthrenium salts compared to alkylarylsulfonium salts towards side-reactions makes them useful cross-coupling partners in many palladium-catalysed reactions, such as Heck[26], Sonogashira[27], Negishi[28], Suzuki[29] and carbonylation[30] reactions. The thianthrenium substituent can engage in faster oxidative addition reactivity than observed with bromide and triflate, which enables chemoselective cross-coupling (Fig. 3b). Palladium is inserted selectively into the desired of the three C–S bonds of the triarylsulfonium group of the thianthrenium salts—possibly a result of steric hindrance and rigidity of the tricyclic thianthrene structure.

In addition to palladium-catalysed cross-coupling chemistry, photoredox catalysis[31] enables the coupling of thianthrenium salts with several different nucleophiles at ambient temperature. For example, with nucleophiles such as chloride, trifluoromethylthiolate and triphenylphosphite, various carbon–heteroatom bonds can be accessed. Photoredox functionalization of arylthianthrenium salts is also tolerant of arylhalides (for example, **51** and **52**) and can access reactivity that is not currently achievable with aryl bromides, such as a Minisci-type



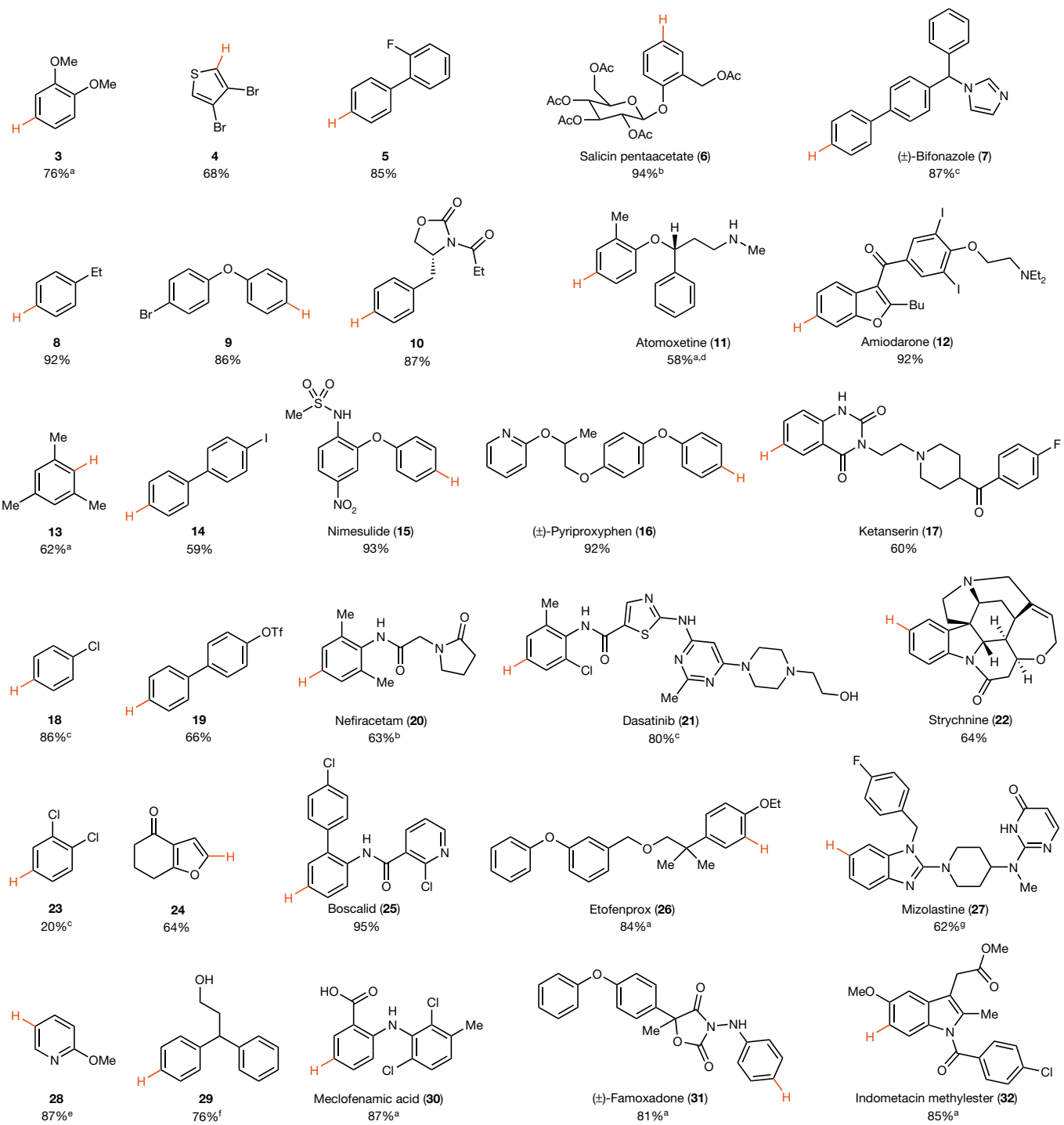


Fig. 2 | Substrate scope of thianthrenation. [a]Nonfluorinated thianthrene *S*-oxide and nonfluorinated thianthrene were used instead of **1** and **2**; no additional acid was used. The reaction was initiated at −78 °C. [b]BF_3OEt_2 was used instead of HBF_4OEt_2. [c]TfOH was used instead of HBF_4OEt_2. [d]The amino group was trifluoroacetylated. [e]TMSOTf was used instead of HBF_4OEt_2 and the reaction was carried out under an inert atmosphere with dry MeCN. [f]0.90 equiv. **1** was used. [g]Selectivity 16:1, isolated yield of major isomer. OTf, triflate; TMS, trimethylsilyl.

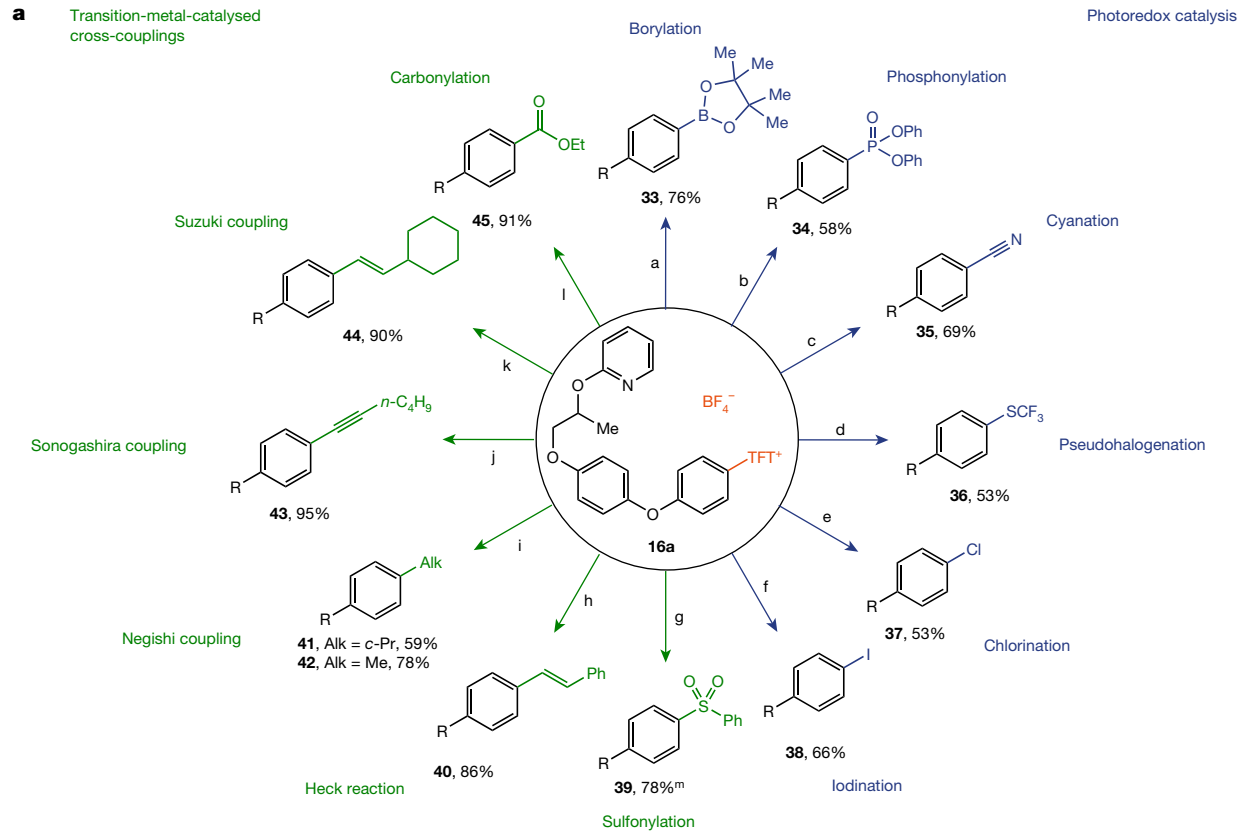


Fig. 3 | See next page for caption.

Fig. 3 | Application of thianthrenation for functionalizing complex arenes. a, Reaction scope of thianthrenium salts. Functionalization of the pyriproxyfen-derived thianthrenium salt **16a**. **b**, Compatibility of thianthrenium salt reactions with aryl electrophiles, functional-group tolerance, Minisci-type reaction and scalability. [a]B_2Pin_2 (2.5 equiv.), pyridine (5.0 equiv.), LED. [b]$P(OPh)_3$ (5.0 equiv.), pyridine (4.9 equiv.), NaI (20 mol%), LED. [c]NBu_4CN (2.5 equiv.), $Cu(MeCN)_4BF_4$ (1.2 equiv.), LED. [d]NMe_4SCF_3 (1.1 equiv.), $Cu(MeCN)_4BF_4$ (1.0 equiv.), LED. [e]CuCl (2.0 equiv.), NBu_4Cl (2.5 equiv.), LED. [f]LiI (10 equiv.), $Cu(MeCN)_4BF_4$ (1.0 equiv.), MeCN/DMSO (3/2), LED. [g]$PhSO_2Na$ (3.1 equiv.), $Pd_2(dba)_3$ (2.5 mol%), Xantphos (5 mol%), THF, 60 °C. [h]$Pd(OAc)_2$ (9.0 mol%), PPh_3 (15 mol%), styrene (2.0 equiv.), NEt_3 (3.0 equiv.), DMF, 100 °C. [i]*c*-PrZnBr or MeZnCl (3.0 equiv.), $Pd(PPh_3)_2Cl_2$, KOAc (6.0 equiv.), THF, 50 °C. [j]1-hexyne (2.0 equiv.), CuI (20 mol%), $Pd(dppf)Cl_2$, *N*-methylmorpholine (2.0 equiv.), dioxane, 40 °C. [k]Cyclohexylvinylboronic acid (2.0 equiv.), K_2CO_3 (4.0 equiv.), $Pd(dppf)Cl_2$, EtOH, 50 °C. [l]CO (1.0 bar), *N*-methylmorpholine (2.0 equiv.), $Pd(dppf)Cl_2$, EtOH/dioxane (1/1), 50 °C. [m]Non-fluorinated thianthrenium salt used. [n]*m*-methoxyphenylboronic acid (1.0–1.2 equiv.), K_3PO_4 (2.0–3.0 equiv.), $Pd(dppf)Cl_2$, *i*-PrOH/dioxane (1/1), 50 °C. [o]1) Thianthrenation, 2) CO (1.0 bar), *N*-methylmorpholine (2.0 equiv.), $Pd(dppf)Cl_2$, EtOH, 50 °C. [p]1) Thianthrenation (non-fluorinated thianthrene), 2) NBu_4CN (2.5 equiv.), $Cu(MeCN)_4BF_4$ (1.0 equiv.), MeCN/DMSO (2/1), LED. [q]K_2CO_3 (1.0 equiv.), $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (1 mol%), no $Ru(bpy)_3(PF_6)_2$, DMSO/pyrazine (1/2), LED. [r]NBu_4CN (3.3 equiv.), CuCN (2.3 equiv.), MeCN/DMSO (10/7), LED. [s]1) Thianthrenation, 2) $Cu(MeCN)_4BF_4$ (1.6 equiv.), LiCl (4.8 equiv.), CF_3CO_2H (1.2 equiv.), MeCN, LED. All photoredox processes: LED (450 nm, 60 W), 22 °C, $Ru(bpy)_3(PF_6)_2$ (2.0–4.0 mol%), MeCN, 3–18 h, unless stated otherwise. All Pd-catalysed reactions: Pd-source (2.0–5.0 mol%), 16–48 h, unless stated otherwise. Alk, alkyl; dba, dibenzylideneacetone; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; dppf, 1,1′-bis(diphenylphosphino)ferrocene; dtbpy, 4,4′-di-tert-butyl-2,2′-dipyridyl; pin, pinacolato; ppy, phenylpyridyl; THF, tetrahydrofuran.

pyrazine arylation reaction (Fig. 3b). We assume that the thianthrenium salt is cleaved into thianthrene and aryl radicals after single-electron reduction by a photosensitizer. The aryl radicals then abstract atoms or groups, react with copper complexes or add to arenes.

Complex small molecules such as **49**, **52** and **53** can be accessed directly from the parent C–H compounds in two steps, without purification of the intermediate sulfonium salts, and TFT can be recovered after the reaction; for example, 76% of thianthrene **2** was recovered mostly by precipitation after the two-step reaction sequence to **53** on a 25-g scale.

We propose that thianthrenation proceeds in three steps: generation of radical cations (**I**), formation of a dicationic adduct (**II**) and finally irreversible deprotonation to form the product (Fig. 4a). The generation of radical cations by comproportionation of TFT *S*-oxide **1** and TFT **2** under the reaction conditions, observed by electron paramagnetic resonance spectroscopy (Fig. 4b), supports the proposed mechanism.

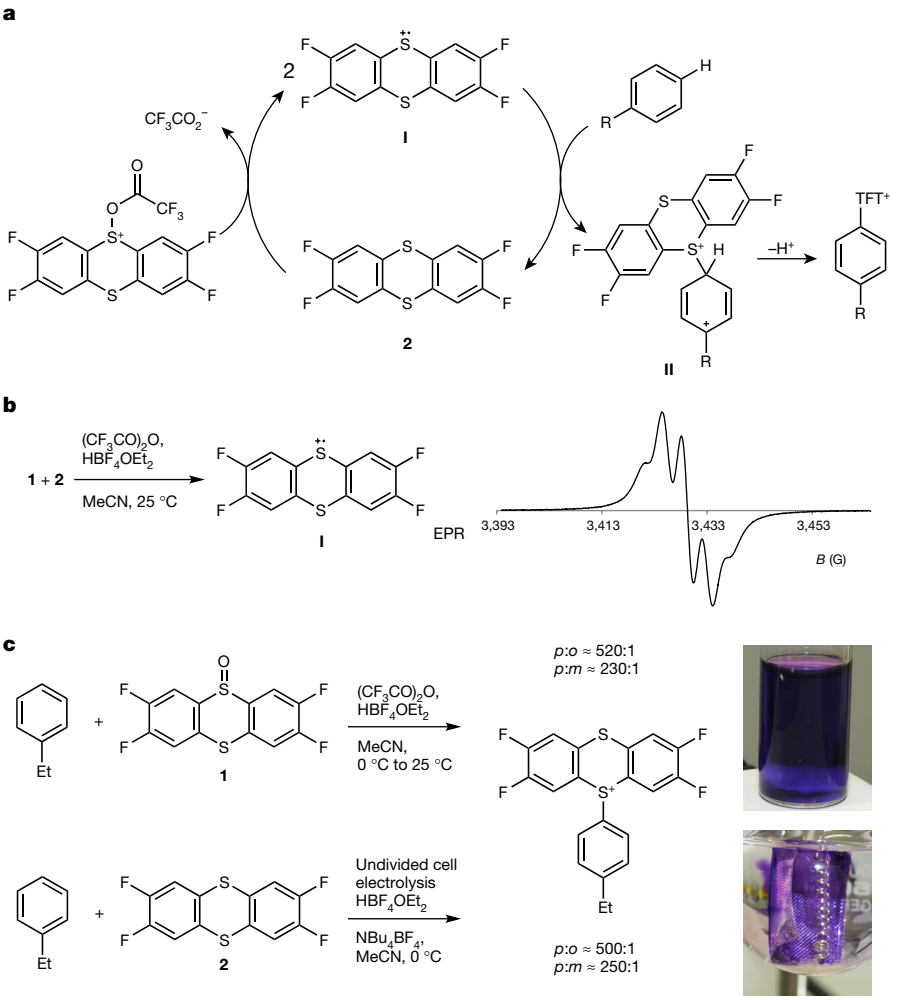


Fig. 4 | Proposed reaction mechanism and mechanistic experiments. **a**, Proposed mechanism involving chain transfer. **b**, Comproportionation of TFT *S*-oxide and TFT under the reaction conditions (left); electron paramagnetic resonance spectrum (right; *B*, magnetic flux density). **c**, Comparison of chemical and electrochemical thianthrenation. The photographs show the typical colour of the reaction mixture of TFT *S*-oxide with arenes (reaction almost complete; top) and the purple colour of TFT radical cations formed at the surface of the Pt anode during electrolysis of TFT in the presence of HBF_4OEt_2, NBu_4BF_4 and ethylbenzene in MeCN at 25 °C (bottom; the photograph was taken approximately 10 s after turning the current on).

Moreover, TFT radicals could also be generated and observed by anodic oxidation of TFT **2**, and in the presence of arene the formation of TFT salts was observed to have selectivities similar to those observed under standard reaction conditions, providing evidence that both reactions proceed via the same reactive species (Fig. 4c). Radical formation from **1** can also be induced by reductants other than **2**—for example, solvents or trace impurities—because radicals were also detected in the initial absence of **2**. Under typical reaction conditions, radical concentrations of more than 20% of the total TFT concentration were detected about one hour after combining the reagents, and the deep purple colour of such mixtures, which is indicative of **I**, did not fade away within one week at 25 °C. The inverse first-order dependence of the reaction rate of thianthrene radical cations with anisole on the concentration of thianthrene[15] rules out radical addition followed by hydrogen atom abstraction. A small primary kinetic hydrogen isotope effect of 1.7 and 1.9 for intra- and intermolecular competition experiments, respectively, together with this inverse first-order dependence, rules out radical addition followed by deprotonation and subsequent oxidation. A Hammett analysis indicated that positive charge is accumulated on the aromatic ring during the reaction, which supports a mechanism proceeding via a cationic intermediate such as **II**. The unusually steep slope of $\rho = -11$, obtained when using the σ^+ values reported in ref. [32], means that the rate of reaction varies by more than nine orders of magnitude between anisole and chlorobenzene. Dication **II** could be formed from arene and **I** by radical addition and subsequent oxidation, by single-electron oxidation of arene followed by recombination with radical **I**, or by addition of arene to a thianthrene dication, which could result from disproportionation of **I**. Detailed additional mechanistic investigations to distinguish between these three pathways for a better appreciation of the source of selectivity are currently under investigation in our laboratory.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability and associated accession codes are available at https://doi.org/10.1038/s41586-019-0982-0.

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Author Contributions F.B. designed reagent **1**, developed the reaction chemistry and investigated the mechanism. J.R., F.B. and M.H. explored the substrate scope. F.B., M.B.P., W.Y. and J.R. optimized the cross-coupling and photoredox reactions. M.B.P. investigated the selectivity of bromination. F.B., S.S., N.F. and J.R. developed the synthesis of reagent **1**. T.R. and F.B. wrote the manuscript. T.R. directed the project.

Competing interests A patent application (number EP18204755.5, Germany), dealing with the use of thianthrene and its derivatives for C–H functionalization and with reagent **1**, has been filed and F.B. and T.R. may benefit from royalty payments.

Additional information
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