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Communication

Site-Selective C−H alkylation of Complex Arenes by a Two-Step Aryl Thianthrenation-Reductive Alkylation Sequence

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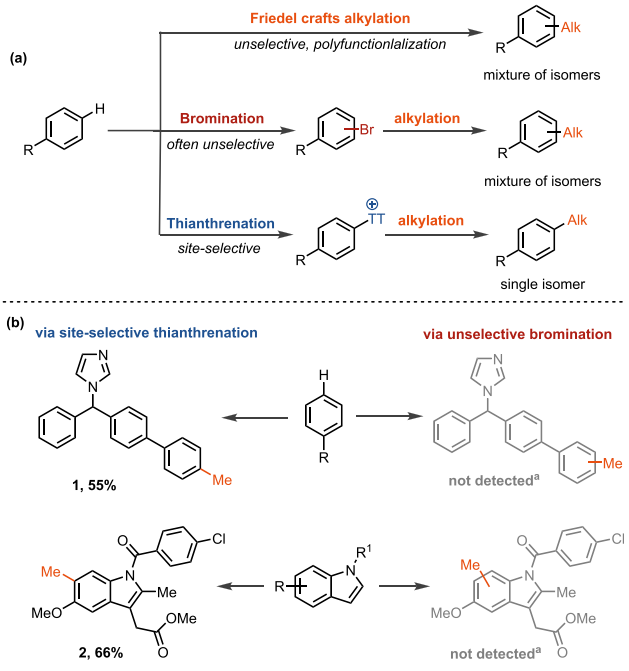
ABSTRACT: Herein, we present an undirected *para*-selective two-step C−H alkylation of complex arenes useful for late-stage functionalization. The combination of a site-selective C−H thianthrenation with palladium-catalyzed reductive electrophile cross-coupling grants access to a diverse range of synthetically useful alkylated arenes which cannot be accessed otherwise with comparable selectivity, diversity, and practicality. The robustness of this transformation is further demonstrated by thianthrenium-based reductive coupling of two complex fragments.

The Csp^2−Csp^3 coupling, particularly direct aryl C−H alkylation, has gained considerable attention as an attractive strategy for alkylation of arenes. While Csp^2−Csp^2 cross-coupling reactions have been common, Csp^2−Csp^3 cross-coupling reactions are less frequently used due to unresolved shortfalls in available methodologies.[1] A significant challenge is the regioselective functionalization of structurally complex molecules at a late stage (Scheme 1). Though several methods exist to install alkyl groups via C−H functionalization,[2] regioselective alkylations in the absence of directing groups remain problematic.[3] The alkylation of arenes via aryl halides is efficient[4] but lacks applicability to a wide class of aryl substrates due to the challenging site-selective synthesis of complex aryl halide starting materials.[5] Simply put, there is currently no reaction chemistry available to introduce, in high positional selectivity, a diverse set of alkyl groups into complex small molecules.[6] Herein, we present a solution to this problem by a Csp^2−Csp^3 reductive cross-coupling between complex aryl thianthrenium salts and readily available alkyl iodides, bromides, and triflates via a two-step undirected regioselective C−H functionalization/reductive alkylation sequence. We show that it is now possible to rapidly access a wide range of alkylated complex arenes, which cannot be accessed by other undirected C−H alkylation methods with the same selectivity, practicality, and diversity of substrates (Scheme 1b). The reactivity of this transformation is robust and can even be applied to two complex fragments. The reaction is thought to proceed via the *in situ* formation of an alkylzinc species. Compared to many other related Negishi-type aryl alkylations, thianthrene-based reductive couplings do not require the organometallic zinc to be preformed prior to the cross-coupling event.[4a,6a,7] The ability to engage structurally complex arenes at a late stage, a broad selection of alkyl iodides, and excellent functional group tolerance distinguish this protocol to quickly access new value-added chemical entities.

Selective direct aryl C−H alkylation reactions are difficult. Classical Friedel−Crafts C−H alkylations are limited by harsh conditions, low regioselectivity, and overalkylation (Scheme 1a).[8] Synthetically useful regioselective C−H alkylations via

Scheme 1. Strategies for Undirected C−H Alkylation of Arenes[a]



[a](a) Conceptual representation of various strategies for undirected C−H alkylation of arenes. (b) Experimental results for palladium-catalyzed aryl C−H alkylation via bromination versus thianthrenation. Two-step yield given for compounds **1** and **2**. [a]Product not detected by LCMS, GCMS, ^{1}H NMR spectroscopy, and ^{13}C NMR spectroscopy (see the Supporting Information for details).

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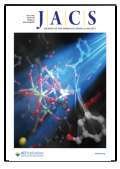

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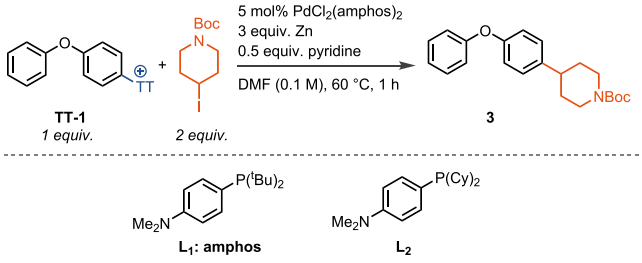
transition-metal-catalyzed approaches are restricted to arenes that bear coordinating groups.[2b] The Negishi reaction is one of the most efficient methods to alkylate aryl (pseudo)halides; however, a long-standing challenge is competitive ß-hydride elimination.[4a,9] In addition, the required (pseudo)halides are often not available and can generally not be accessed in high selectivity from complex arenes (Scheme 1).[5] Furthermore, the Negishi reaction and many other traditional transition-metal-catalyzed reactions remain constrained by the availability, stability, and reactivity of the organometallic nucleophiles that must be prepared separately from the electrophile prior to the cross-coupling event and may limit the substrates that can be employed. In view of these limitations, Weix,[10] Molander,[11] Gong,[12] MacMillan,[13] and others[14] independently have achieved considerable progress in the field of reductive electrophile cross-coupling reactions and have successfully demonstrated the possibility of directly engaging two readily available halides for Csp^2-Csp^3 bond formation in the presence of a sacrificial reductant.[15] Nonetheless, current reductive electrophile aryl alkylation reactions utilizing alkyl halides often require the use of an aryl (pseudo)halide, and progress toward complex small molecules has not been widely explored. Because general site-selective halogenation is difficult, the substrate scope consists mainly of simple arenes. Thianthrenium salts are promising electrophilic coupling partners for the late-stage site-selective introduction of alkyl motifs on structurally complex arenes to forge products that are currently challenging to access. Owning in part to their positive charge, they can be easier to reduce than aryl halides, which could present a further advantage.[6c] We rationalized that the use of aryl thianthrenium salts in reductive alkylation reactions with alkyl halides would provide an unrealized opportunity for a two-step undirected *para*-selective C–H alkylation of complex arenes which, to date, has not been reported.

We investigated the reaction of aryl thianthrenium salt **TT-1** with 1-boc-4-iodopiperidine in the presence of a palladium catalyst and a reducing agent (Table 1). Zinc was found to be crucial for the reaction, and other reducing agents such as manganese and tetrakis(dimethylamino)ethylene did not produce any cross-coupled product, which is consistent with the involvement of an intermediate organozinc species. A preference for polar solvents such as DMF was observed as larger amounts of unreacted alkyl iodide remained when the reaction was conducted in less polar solvents, such as toluene, which could be explained by the faster rate of oxidative addition of zinc into alkyl iodides in polar solvents.[16] While nickel is the preferred transition metal for reductive aryl–alkyl bond formations,[10a,b,11–13] we identified palladium to be the metal of choice for the reductive alkylation of aryl thianthrenium salts. A series of bulky phosphine ligands were tested including those that have been successful in previous aryl alkylation reactions to suppress competing ß-hydride elimination (see the Supporting Information, Table S1, entries 8 and 17).[7d,14d,17] $PdCl_2(amphos)_2$ (Table 1) was found to be pivotal for efficient cross-coupling, and all other catalyst systems resulted in significantly lower yields. Simply replacing the ^{t}Bu groups in amphos with cyclohexyl groups (L_2) decreases the yield to 5%. A general challenge in transition-metal-catalyzed alkylation chemistry is control over regioselectivity due to reversible ß-hydride elimination, which often results in constitutional isomers.[4a,9] We investigated the selectivity for the branched versus linear product in the cross-coupling of *i*-PrI with pyriproxyphen thianthrenium salt **TT-3** and found superior selectivities when amphos was used as a ligand (>20:1 of *i*-Pr product over *n*-Pr product).[7a,d,e,18] $PdCl_2$(tri*o*-tolyphosphine) and $PdCl_2$(dppf), for example, only yielded the products in 4.2:1 and 0.84:1 selectivity, respectively (see Supporting Information, Table S2). The high selectivities for the branched product with $PdCl_2(amphos)_2$ are worth mentioning as competitive ß-hydride elimination is a reoccurring problem in palladium-catalyzed reactions.[7e,14k] The importance of steric effects of the ligand on the extent of competing ß-hydride elimination can also be observed in Negishi-type aryl alkylations, which require specialized catalysts in order to minimize undesired ß-hydride elimination.[7a,d,e,18,19] Noteworthy is also that the preformed $PdCl_2(amphos)_2$ complex was more efficient than the complex generated *in situ* from $PdCl_2$ and amphos (L_1) even when higher quantities of both $PdCl_2$ and amphos were used. The presence of pyridine could potentially interfere with complex generation *in situ*. Nonetheless, pyridine was found to improve the overall yield of the reaction, possibly due to ligation to palladium after oxidative addition or to stabilize the organozinc reagent.[14d]

The alkylation of aryl thianthrenium salts occurred efficiently with primary and both cyclic and acylic secondary alkyl iodides; tertiary alkyl iodides could not be engaged (Scheme 3). Arenes as electron-rich as anisole to electron-poor as chlorobenzene were tolerated (see the Supporting Information, compound **S5**). The ability to employ a wide variety of alkyl substrates in a practical way presents an advantage to our previously published selective aryl C–H alkylations that only engage selected alkylzinc reagents and cannot operate on many complex small molecules.[6a,7g] We targeted both alkyl and aryl substrates, which contain various functional groups, as high functional group tolerance is relevant for the application of this transformation late stage. Unprotected basic amines, acidic NH groups, strained

Table 1. Optimization of the Reaction Conditions[a]



change in reaction conditions	yield[b]
none	75%
Mn instead of Zn	n.o.
TDAE instead of Zn	n.o.
toluene instead of DMF	20%
no catalyst	n.o.
$NiBr_2$ + phen instead of $PdCl_2(amphos)_2$	n.o.
$PdCl_2$ instead of $PdCl_2(amphos)_2$	<5%
$PdCl_2$(dppf) instead of $PdCl_2(amphos)_2$	20%
10 mol % $PdCl_2$ + 30 mol % L_2 instead of $PdCl_2(amphos)_2$	5%
no pyridine	66%

[a]Reactions were carried out on a 0.1 mmol scale. [b]Yields were determined by ^{1}H NMR spectroscopy with mesitylene as the internal standard. TDAE = tetrakis(dimethylamino)ethylene. n.o. = not observed.

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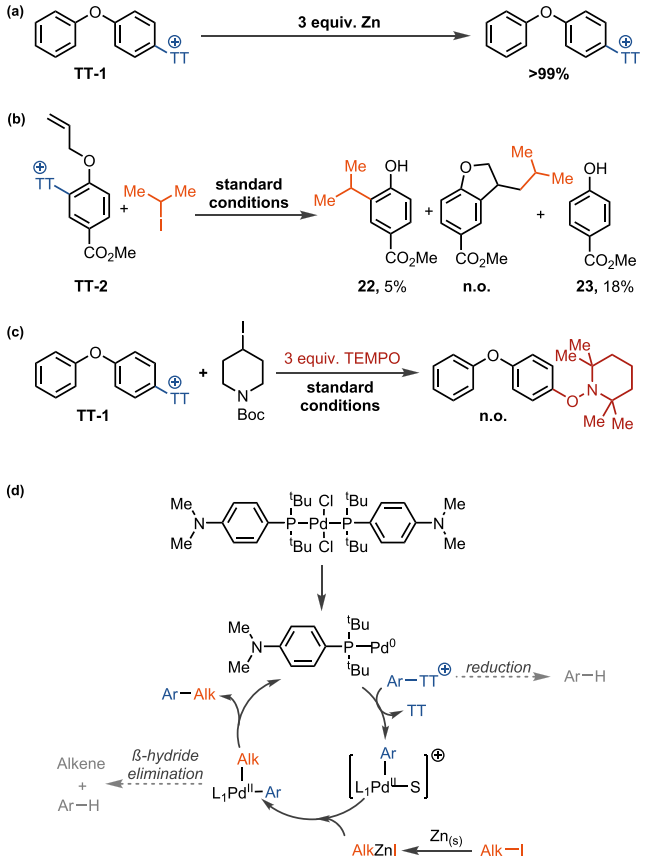
Scheme 2. Mechanistic Investigation[a]



[a](a) Zinc insertion experiment. (b) Radical clock cyclization of allyl ether thianthrenium salt **TT-2** under standard conditions. (c) Radical trapping experiment with TEMPO under standard conditions. (d) Mechanistic hypothesis. S = solvent or pyridine. L_1 = amphos. n.o. = not observed.

heterocyclic ring systems (e.g., ß-lactam rings), and a range of basic heterocycles, often considered problematic in transition-metal-catalyzed reactions, did not hamper the reactivity. Despite being under reducing conditions, sulfones could be tolerated and were not reduced. Our catalytic system is also tolerant to sulfonamides, which is noteworthy as organozinc reagents are typically reactive toward such acidic functional groups.[20] Alcohols, sulfides, and bromides were not compatible. Furthermore, the efficiency of the cross-coupling was not impeded by *ortho*-substituents (**2**, **5**, **15**, **16**, and **20**). Also the presence of a ketone on the alkyl halide was compatible with the cross-coupling, which requires protection as acetals in other, related protocols.[14k] Other organometallic groups such as silyl and boron groups are not activated for transmetalation and can be held intact for potential further functionalization (**7** and **8**). As exemplified by **1**, **2**, and **15**, undirected selective methylations of aryl thianthrenium salts with methyl iodide instead of methylzinc chloride are now possible, which may have potential for isotopic labeling protocols.[6a,7g] Alkyl substrates containing ß-σ acceptor substituents, which are difficult to engage by other methods such as S_N2-type substitutions, could be coupled efficiently (e.g., **5**, **6**, **9**, **10**, **11**, **12**). Because the introduction of saturated heterocyclic motifs is often challenging, they are typically introduced via a more viable sp^2–sp^2 coupling followed by hydrogenation.[21] In this transformation, a variety of saturated heterocyclic motifs could be successfully engaged such as oxetane, azetidine, piperidine, and oxaspiro[3.3]heptane (**5**, **10**, **11**, **12**, **14**, **17**). Radical ring-opening reactions such as observed for compound **13** can give rise to otherwise challenging to access structures. We also show that the thianthrene-based reductive cross-coupling can be successfully employed for the linkage of two complex building blocks (**18**, **19**, **20**, **21**), as exemplified by the coupling of a sulbactam iodide derivative, a privileged motif in drug discovery, which is found in 30% of the approved ß-lactam antibiotics,[22] with nefiractam, a nootropic drug (**19**). In addition to alkyl iodides, primary alkyl bromides and triflates can be used successfully for the reductive cross-coupling. Secondary alkyl bromides are reactive as well, albeit in lower yields; for example, pyriproxyfen thianthrenium salt **TT-3** with 3-bromooxetane and 3-iodooxetane gave product **10** at 26% and 72% yields, respectively (see the Supporting Information, pp S41−S44 for details).

A plausible mechanism hypothesis for this transformation is depicted in Scheme 2d. Though most reductive electrophile cross-coupling reactions with alkyl halides proceed via a radical chain process,[4d,10a,15b,23] we believe an oxidative addition-transmetalation-reductive elimination sequence is operative in this transformation. Control experiments showed that, in the presence of zinc and absence of a palladium-catalyst, no cleavage of aryl thianthrenium salts occurred on a time scale compatible with the reductive cross-coupling (Scheme 2a). Instead, the alkyl iodide was hydrodehalogenated with 90% conversion in <5 min (see the Supporting Information). On the basis of redox potentials, aryl thianthrenium salts ($E(PhTT^+/PhTT^\bullet)$ = −1.5 V vs SCE)[6c] cannot be reduced by zinc ($E(Zn^{2+}/Zn_{(s)})$ = −0.76 V vs SCE). Though unactivated alkyl iodides ($E(n\text{-BuI}/BuI^\bullet)$ = −2.5 V vs SCE)[24] are even more difficult to reduce then aryl thianthrenium salts, oxidative addition of zinc is known to proceed via an inner sphere electron transfer involving a bridging ligand.[25] Because such a process is more feasible on the alkyl iodide than on the aryl thianthrenium salt,[25] selective radical mediated oxidative addition of zinc into the alkyl iodide could take place. Furthermore, since zinc cannot be replaced by an organic reductant, tetrakis(dimethylamino)ethylene (see Table 1), we postulate the intermediacy of an alkylzinc species under our reaction conditions. A radical clock experiment was conducted with **TT-2** as a mechanistic probe to distinguish between a concerted oxidative addition and a pathway which involves single electron transfer.[6c,26] The observation of noncyclized product **22** in the aryl alkylation of allyl ether thianthrenium salt **TT-2** under standard conditions is consistent with a concerted oxidative addition mechanism (Scheme 2b). The aryl 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) adduct was not observed for the aryl alkylation upon addition of TEMPO, which is consistent with the absence of aryl radicals (Scheme 2c). By using amphos, the rate of ß-hydride elimination is slower relative to the rate of reductive elimination, which is consistent with the different product distributions of *n*-PrAr:*i*-PrAr when different catalysts are used (see discussion above). The faster reductive elimination from complexes with bulky monodentate ligands instead of bidentate ligands is in agreement with a T-shaped intermediate from which reductive elimination is faster than from a four-coordinate square planar intermediate.[27] Though the preliminary mechanistic data presented above is consistent with an oxidative addition−transmetalation−reductive elimi-

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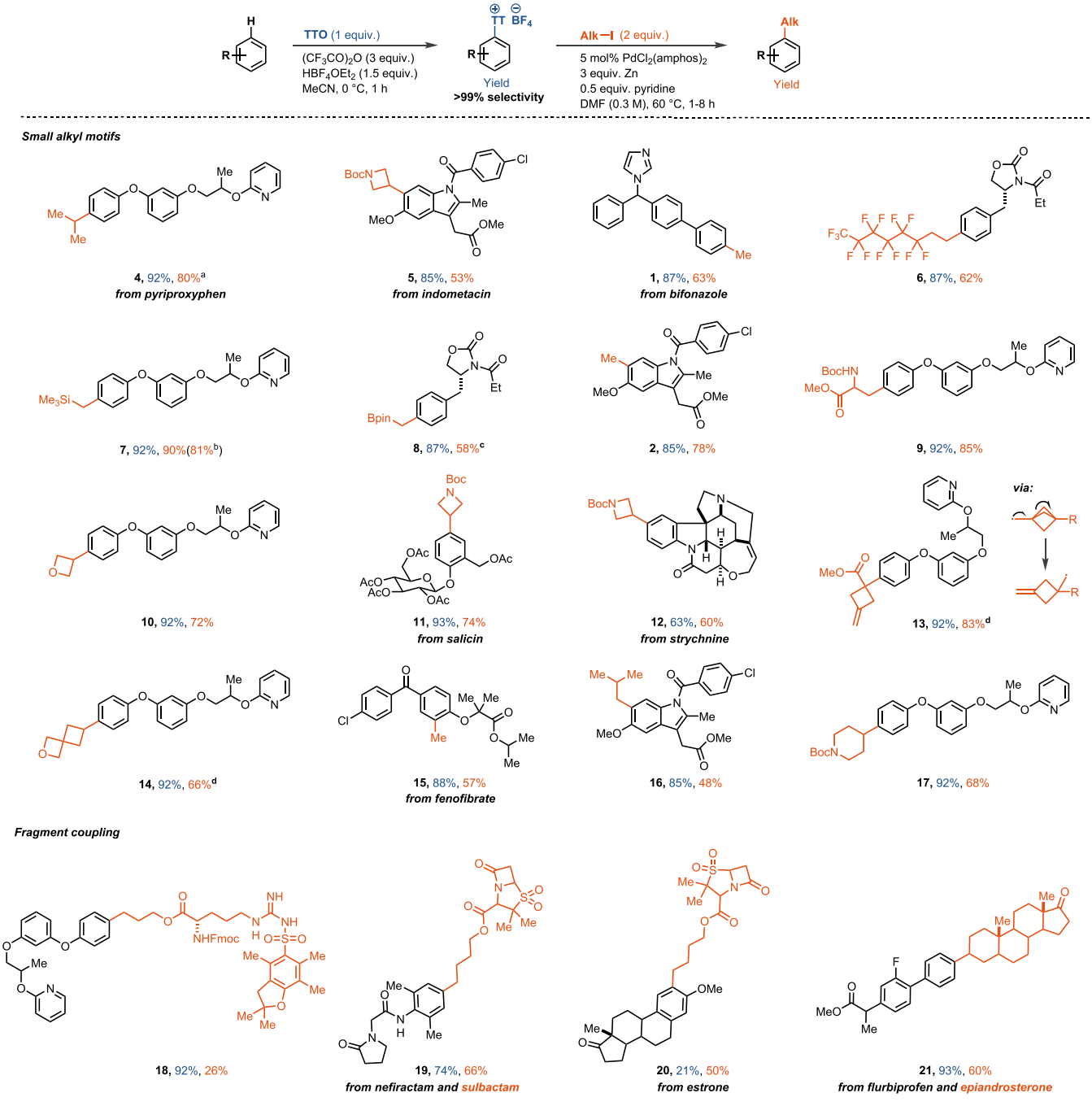
Scheme 3. Substrate Scope for the Alkylation of Aryl Thianthrenium Salt[a]



[a]General conditions unless otherwise noted: aryl thianthrenium salt (0.3 mmol), alkyl iodide (0.6 mmol), $PdCl_2(amphos)_2$ (15.0 μmol), pyridine (0.15 mmol), DMF (0.3 M). [a]>20:1 ratio of *i*-PrAr:*n*-PrAr product. [b]3.0 mmol scale. [c]Pyridine was omitted. [d]Reactions carried with aryl thianthrenium salt (0.2 mmol) and $MgCl_2$ (3 equiv) as additive. Yields in blue correspond to yield of C−H thianthrenation. Yields in orange correspond to yield of alkylation of aryl thianthrenium salts. Yields of thianthrenation were obtained from refs 5, 6a, 6b, 6c, 6d, and 6e.

nation sequence, we cannot exclude a single electron transfer mechanism.

In conclusion, we present a method for the site-selective alkylation of aryl thianthrenium salts via a two-step C−H functionalization/reductive alkylation sequence that grants access to alkylated arenes that cannot be obtained with comparable selectivities by other, undirected aryl C−H alkylation methods. By forming the zinc reagent *in situ*, we bypass the need to preform an organometallic reagent prior to the cross-coupling event, which from a synthetic point of view and in terms of practicality provides an advantage to other, related Negishi-type aryl alkylations, including our previously reported selective aryl alkylations that only work with selected alkylzinc reagents.[6a,7g] The excellent site-selectivity and robust reactivity enable us to engage complex fragments, which could be of value in medicinal chemistry. We believe this work represents a valuable conceptual extension to existing reductive Csp^2-Csp^3 cross-coupling reactions with improved efficiency, reactivity, and synthetic utility.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c03459.

Experimental procedures and NMR spectra (PDF)

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Author Contributions

B.L. conceived the project and optimized the aryl alkylation. B.L. and P.G. expanded the substrate scope. B.L. analyzed the data and wrote the Supporting Information. B.L. and T.R. wrote the manuscript. T.R. directed the project.

Notes

The authors declare the following competing financial interest(s): A patent application (number EP18204755.5, Germany) dealing with the use of thianthrene and its derivatives for C-H functionalization has been filed and F.B. and T.R. may benefit from royalty payments.

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