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C-H Activation

Meta-Dimethylation of Arenes via Catellani Reaction from Aryl Thianthrenium Salts

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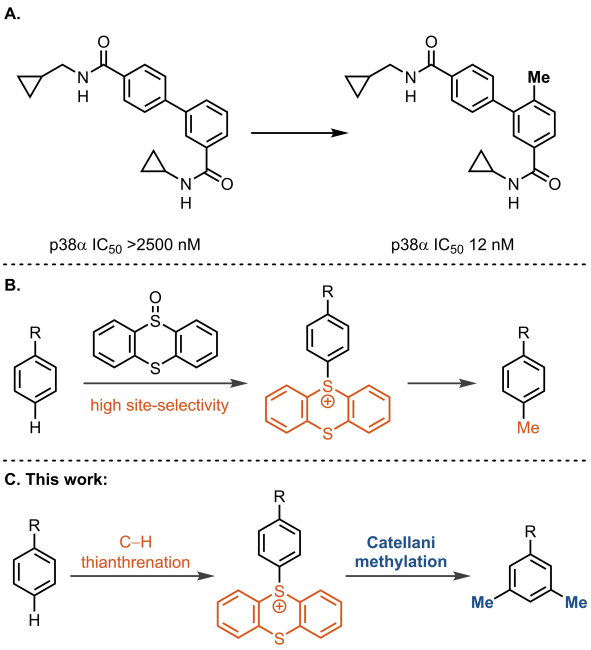
Abstract: Here we report the reaction of aryl thianthrenium salts that allows selective functionalization of the *meta* position of arenes. The combination of a site-selective thianthrenation with a Catellani reaction provides access to 3,5-dimethylated arenes. The developed reaction is complementary to the previously discovered reductive *ipso*-alkylation of aryl thianthrenium salts and extends the possibilities for late-stage methylation of arenes with a single aryl thianthrenium salt.

Late-stage methylation is a transformation of interest for drug development[1,2] because installation of methyl groups in drug candidates can lead to an increase of potency.[1,3] One of the strategies for late-stage methylation relies on aryl thianthrenium salts as intermediates, which can be synthesized directly from arenes with high site-selectivity.[4] In addition to late-stage methylation, aryl thianthrenium salts have been useful as intermediates in other transformations for small molecule modifications[5–7] as well as fragment couplings.[4,8] However, transformations of aryl thianthrenium salts only allow to functionalize the *para* position of monosubstituted arenes without the demonstrated possibility of selective functionalization at *ortho* or *meta* positions in monosubstituted arenes. Here we report a Catellani reaction with aryl thianthrenium salts that allows for selective functionalization in the *meta* position. For monosubstituted arenes, the reaction affords 3,5-dimethylated arenes in a two-step sequence. The process is complementary to the previously reported reductive *ipso*-alkylation reaction of aryl thianthrenium salts and extends the possibilities for functionalization of arenes via a single aryl thianthrenium salt.

The "magic methyl effect" refers to the enhancement of biological activity of molecules that can result from adding a methyl group ($-CH_3$), often increasing potency, selectivity, or metabolic stability (Scheme 1A).[1,3] This subtle structural change can shift molecular conformation, affect binding interactions, or improve lipophilicity, making it a powerful approach in drug design and structure optimization. The recognition of the "magic methyl effect" in drug development has prompted scientific research focused on late-stage C–H methylation. For example, Baran has reported a radical $C(sp^2)$–H methylation of various heteroarenes.[9]

Regioselectivity in direct arene C–H methylation can be controlled when directing groups are present. For example, cobalt-catalyzed *ortho*-methylation has been accomplished with a variety of suitable directing groups,[10] and rhodium-catalyzed *ortho*-methylation has been accomplished with the aid of mechanochemistry,[11] to name just a few modern examples for methylation reactions. Previously, our group



Scheme 1. (A) The "magic" methyl effect in the drug development. (B) Site-selective thianthrenation for late-stage functionalization of arenes including *para*-methylation. (C) **This work**: Catellani reaction on aryl thianthrenium salts for *meta*-dimethylation of arenes.

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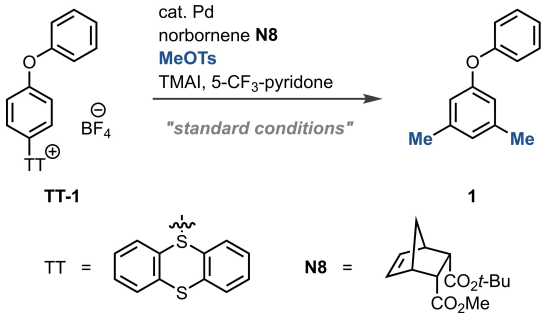
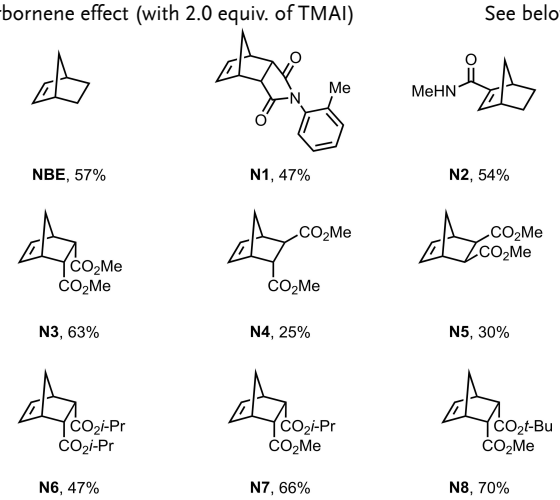
Table 1: Optimization of the reaction conditions.

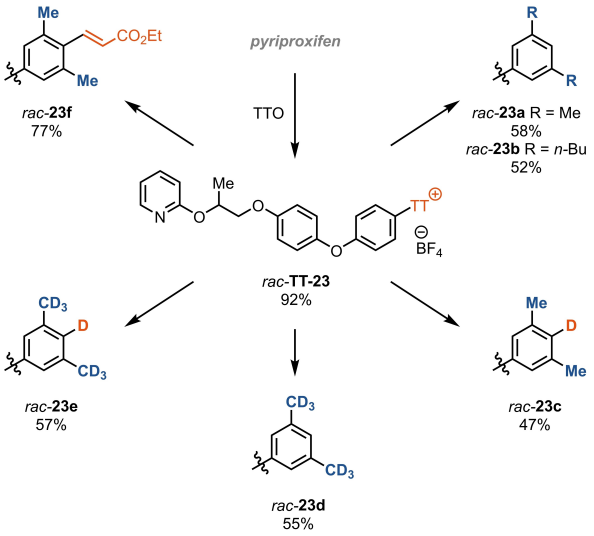


Changes in reaction conditions	Yield
None	74%
No TMAI	32%
No 5-CF_3-pyridone	43%
1.0 equiv. of **N8**	70%
Norbornene effect (with 2.0 equiv. of TMAI)	See below



Reaction conditions: TT-1 (0.1 mmol), MeOTs (3.0 equiv.), $Pd(OAc)_2$ (10 mol%), P(2-fur)$_3$ (22 mol%), **N8** (2.0 equiv.), sodium formate (2.0 equiv.), Cs_2CO_3 (2.5 equiv.), TMAI (0.5 equiv.), 5-CF_3-pyridone (20 mol%), THF (0.1 M), 70 °C, 18 h. Yields were determined by ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard.

has reported a two-step C–H methylation of arenes via the intermediacy of arylthianthrenium salts.[4,12] Although the positional selectivity of thianthrenation is high,[13] only *ipso* substitution reactions of complex arylthianthrenium salts have been accomplished (Scheme 1B). To address the challenge we sought to combine C–H thianthrenation with the Catellani reaction. Catellani reactions are useful for rapid multifunctionalization of arenes using the ability of norbornene (NBE) to reversibly engage in migratory insertion into arylpalladium species and serve as a traceless directing group for *ortho* C–H functionalization.[14] Since a catalytic version of the reaction was achieved,[15] many variations of the process have been developed allowing to insert different functional groups in *ortho*[16–20] and *ipso*[16,21,22] positions of the corresponding aryl halides. Catellani reactions of arylthianthrenium salts for olefination-alkylation sequences have been published in 2024;[23,24] the pharmacologically meaningful introduction of methyl groups, with a hydride capping has not yet been accomplished.



Scheme 2. Late-stage functionalization of pyriproxifen including deuterium labelling. Reaction conditions: Standard conditions, *n*-BuOTs was used as *n*-Bu source, CD_3OTs was used as CD_3- source, DCOONa was used as D- source, ethyl acrylate was used instead HCOONa for **23 e**.

Combination of aryl thianthrenium salts with the Catellani reaction would bring complementary site-selectivity to all *ipso*- substitutions of thianthrenyl moiety that have been already developed. The desired reaction would require a convenient source of a methyl group for *ortho*-C–H-functionalization and a readily available hydride source as an *ipso*-termination reagent. So far, there have been a few methods developed for *ortho*-C–H alkylation in Catellani-type reactions using various sources of hydride in order to close the catalytic cycle with *ipso*-hydrogenation.[25–27] We studied the reaction of thianthrenium salt **TT-1** with methyl tosylate and sodium formate as source of hydride, and identified that the reaction proceeds most efficiently, when tetramethylammonium iodide (TMAI) and 5- CF_3-pyridone were added in addition to norbornene derivative **N8** (Table 1, for further details, see SI, Table S1 and S8). We hypothesized that addition of an external ligand such as iodide would allow to trap and stabilize cationic palladium-(II) complexes because thianthrene only binds weakly to Pd(II), if at all, as well as reduce side reactions.[28–30] 2-Pyridone and its derivatives are known for promoting C–H activation proceeding via concerted metalation-deprotonation (CMD) and their electronic properties can be readily tuned.[27,31–35] There was a significant influence of the norbornene derivative on the yield of the reaction, for example, 5,6-disubstituted norbornene diesters were the best choice for the most efficient methylation, while both stereochemistry and the size of the alkyl group were important (Table 1, the bottom Figure). Previously used by Zhou,[25] norbornene derivative **N1** did not improve reaction yield, when compared to norbornene, leading to 47% yield. The norbornene derivative **N2**, developed by Dong[27] to facilitate *ortho*-C–H activation did not improve the reaction yield either. The use of 5,6-*endo*-*cis*-dimethyl ester **N3** improved the reaction yield from 57%, obtained with

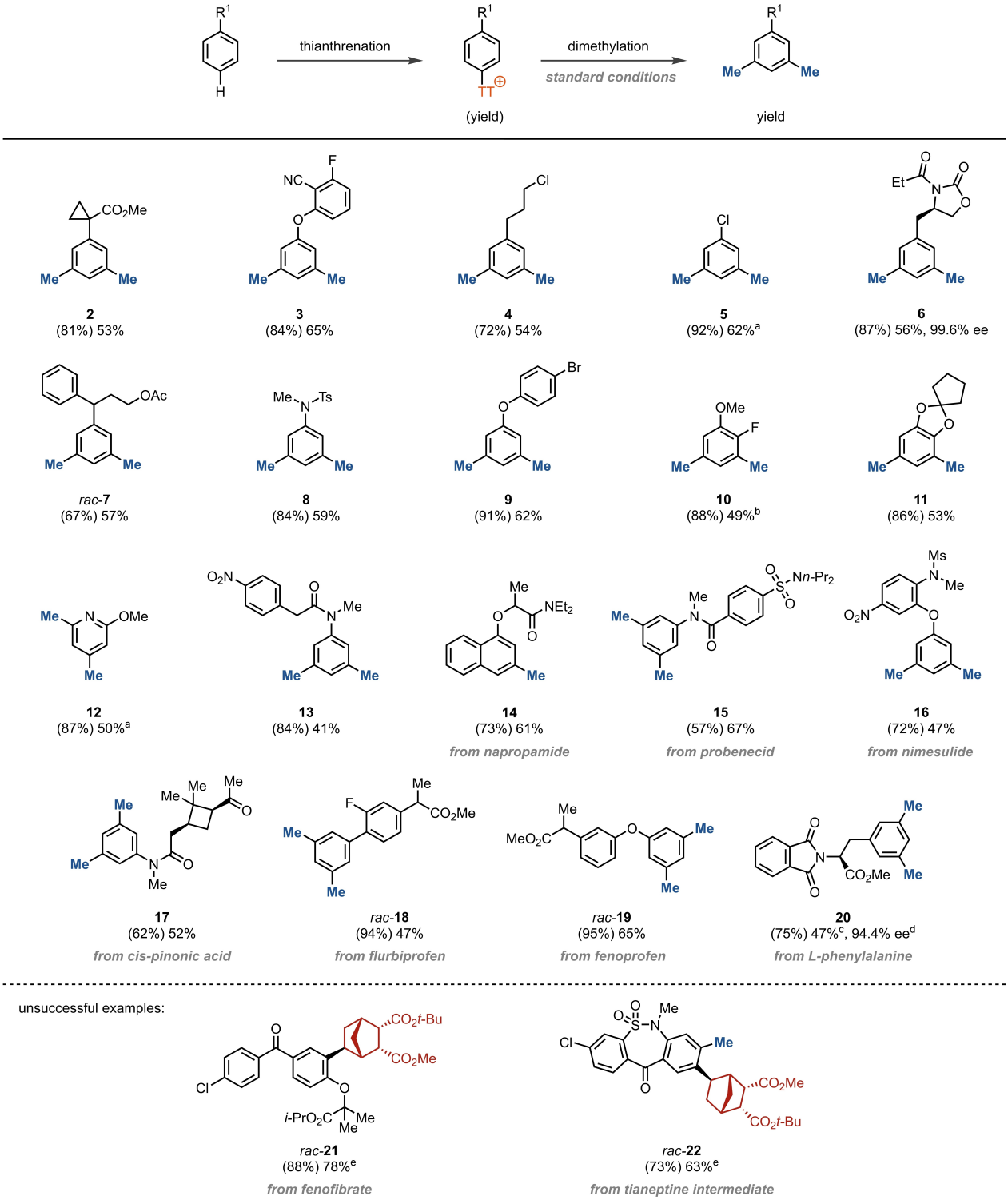


Figure 1. Substrate scope of Catellani methylation on aryl thianthrenium salts. Thianthrenation conditions: arene (1.0 equiv.), TTO (1.0 equiv.), TFAA (3.0 equiv.), TfOH or $HBF_4 \cdot Et_2O$ (1.2 equiv), MeCN (0.25 M), 0 °C to 25 °C, 16 h. Standard conditions: aryl thianthrenium salt (0.5 mmol), MeOTs (3.0 equiv.), $Pd(OAc)_2$ (10 mol%), $P(2\text{-fur})_3$ (22 mol%), **N8** (2.0 equiv.), sodium formate (2.0 equiv.), Cs_2CO_3 (2.5 equiv.), TMAI (0.5 equiv.), 5-CF_3-pyridone (20 mol%), THF (0.1 M), 70 °C, 18 h. [a] NMR yield. [b] 66% NMR yield. [c] 0.4 mmol scale [d] starting from 97.5% ee N-Phth-Phe-OMe [e] mixture of regioisomers.

unsubstituted norbornene, to 63%. Larger size of both alkyl groups of the esters resulted in a lower yield, for example 47% for *endo-cis*-diisopropyl ester **N6**, employed previously by Ding[36] for alkylation of phenylalanine derivatives. Change of only one ester alkyl group for a bulkier *tert*-butyl group resulted in a slightly higher yield of methylation,

reaching 70 %. The unsymmetrical norbornene **N8** was identified as optimal catalyst, leading to a 74 % yield of the dimethylated product **1** when 0.5 eq. of TMAI was used. The excess of norbornene **N8** can be recovered from the reaction mixture. Furthermore, the amount of **N8** used can be reduced to 1.0 equiv., resulting in only a slight decrease in yield (70 % instead of 74 %).

The dimethylation of aryl thianthrenium salts with methyl tosylate occurred efficiently on thianthrenium salts obtained from *mono* substituted arenes. Various functional groups are tolerated, such as esters (**2**, **7**, **18**, **19**, **20**), amides (**13**, **14**, **15**, **17**), sulfonamides (**8**, **15**, **16**), imide (**20**), halides (**3**, **4**, **5**, **9**, **10**, **18**), nitriles (**3**), carbamates (**6**), nitro groups (**13**, **16**) as well as a cyclopropane (**2**) and a pyridine ring (**12**, **21**). Although base is used, the stereocenters that were probed remained intact. For example compound **6** and the protected L-phenylalanine **20** retained high enantiopurity after methylation (for **6**: 99.6 % ee, for **20**: 94.4 % ee). Chemoselective engagement of the thianthrene substituent in the presence of an aryl bromide allows for further functionalizations (compound **9**). Functionalization of arenes with more complex substitution patterns than monosubstituted arenes was accomplished as well, for example as shown for compounds **10**, **11**, and napropamide **14**. Late-stage methylation of complex molecules was further substantiated with examples such as derivatives of probenecid **15**, nimesulide **16**, *cis*-pinonic acid **17**, flurbiprofen **18**, fenoprofen **19** and L-phenylalanine **20**. The reaction does not tolerate functional groups that are readily alkylated, such as sulfonamides with N–H bonds. Additionally, a "*meta*-constraint" was observed, when methylation of thianthrenium salts derived from fenofibrate and tianeptine were attempted, leading to side products with incorporated norbornene **N8** (compounds **21** and **22**, Figure 1). The developed method is applicable to transformations beyond dimethylation, allowing the introduction of other alkyl groups such as *n*-butyl (**23b**, (Scheme 2)). Moreover, other coupling partners such as ethyl acrylate (**23f**) could be used (Scheme 2). Deuterium labelling can also readily accomplished as shown for pyriproxifen, allowing the *ortho*-di(trideutero)methylation or *ipso*-deuteration of the corresponding aryl thianthrenium salt (compounds **23c**–**e**).

A DFT computational study on the crucial initial steps post oxidative addition to the aryl thianthrenium salt of the catalytic cycle using Orca 5[37] with the r^{2}SCAN-3c[38] level of theory (full computational details are provided in the SI, see the Computational Data part) is consistent with conventional Catellani reactivity. The first C–H functionalization step was simulated in order to investigate the electronic and steric effects of the intermediates shown in Figure 3. The first ligand exchange step is thermodynamically favorable ($\Delta G = -3.9$ kcal/mol). The resulting Int 2 with the coordinated pyridone, undergoes a concerted metalation-deprotonation (CMD) step (TS) with a barrier of $\Delta G^{\ddagger} = 17.9$ kcal/mol. This step is consistent with previous computational studies on a similar system with a different ligand framework.[27] The next stable intermediate that is formed is the Int 3 with the pyridone protonated and 5-membered metallacycle fully formed. Notably, the C–H activation proceeds without the de-coordination of pyridone.

To understand why pyridone is beneficial during the CMD process, another substituted intermediate was computationally investigated. When a protonated carbonate is acting as the proton acceptor directly coordinated to the Pd^{II} metal center, the energy barrier for the CMD step ($\Delta G^{\ddagger}$) increases by 1.5 kcal/mol. The increase suggests that pyridone is a more effective proton acceptor, facilitating the progression of the reaction.

It is conceivable that it may contribute to the prevention of the generation of byproducts resulting from the early reduction of species formed subsequent to the migratory insertion step (presented in the Figure 2). The early

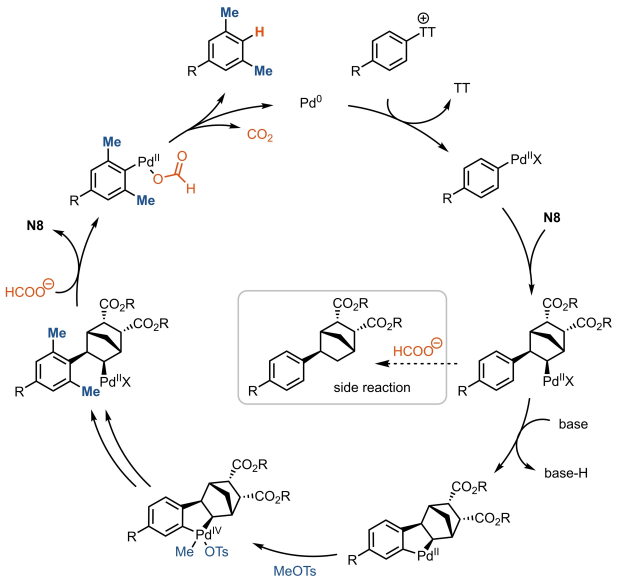


Figure 2. Simplified mechanism of Catellani-type dimethylation on aryl thianthrenium salts.

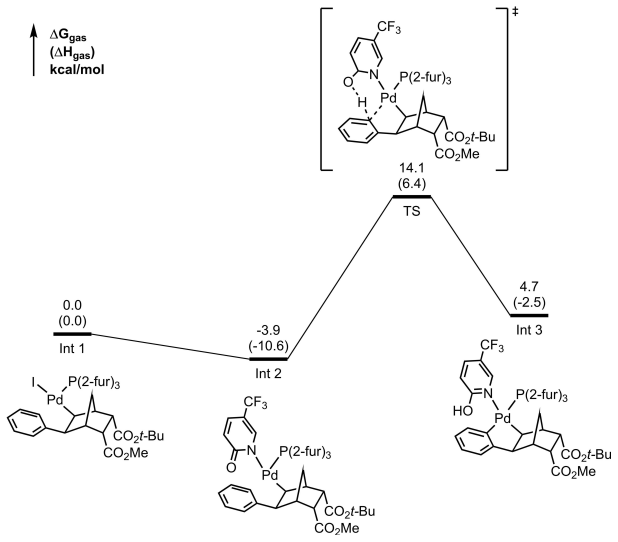


Figure 3. The computed reaction profile for the CMD step.

termination of the reaction is more likely to occur when the C–H activation exhibits a higher energy barrier, which may be attributed to the electronic properties of the system or steric hindrance, as evidenced by compounds **21** and **22**.

In conclusion, we report the Catellani reaction of aryl thianthrenium salts as substrates, leading to a selective *meta*-functionalization of arenes. Our two-step strategy enables the 3,5-dimethylation of arenes, including from complex molecules, starting from arenes. The developed reaction is complementary to previously reported *ipso*-methylation of aryl thianthrenium salts and expands the possibilities of late-stage functionalization of complex molecules using aryl thianthrenium salts as intermediates.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: methylation · late-stage functionalization · aryl thianthrenium salt · Catellani reaction · C–H activation

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