Catalytic *Ortho* C-H Methylation and Trideuteromethylation of Arylthianthrenium Salts via the Catellani Strategy

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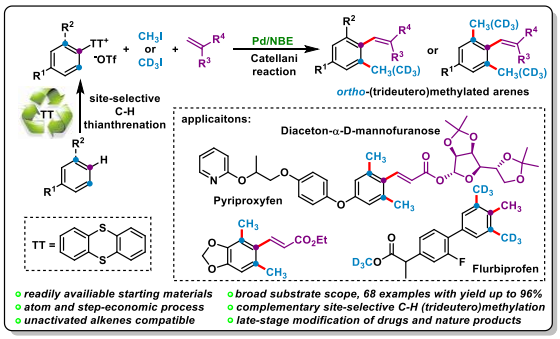
Supporting Information Placeholder



ABSTRACT: We reported a Pd/NBE cooperative catalyzed *ortho* C−H methylation and trideuteromethylation of arylthianthrenium salts, enabling the efficient synthesis of a wide variety of (trideutero)methylated arenes in moderate to good yields. The method demonstrates excellent tolerance towards functional groups, scalability, and potential extension to the late-stage functionalization of biorelevant molecules. In combined with C−H thianthrenation of arenes, this approach provides an effective method for the site-selective C−H (trideutero)methylation of arenes. Additionally, this reaction represents the first example of a Catellani reaction involving aryl sulfonium salts.

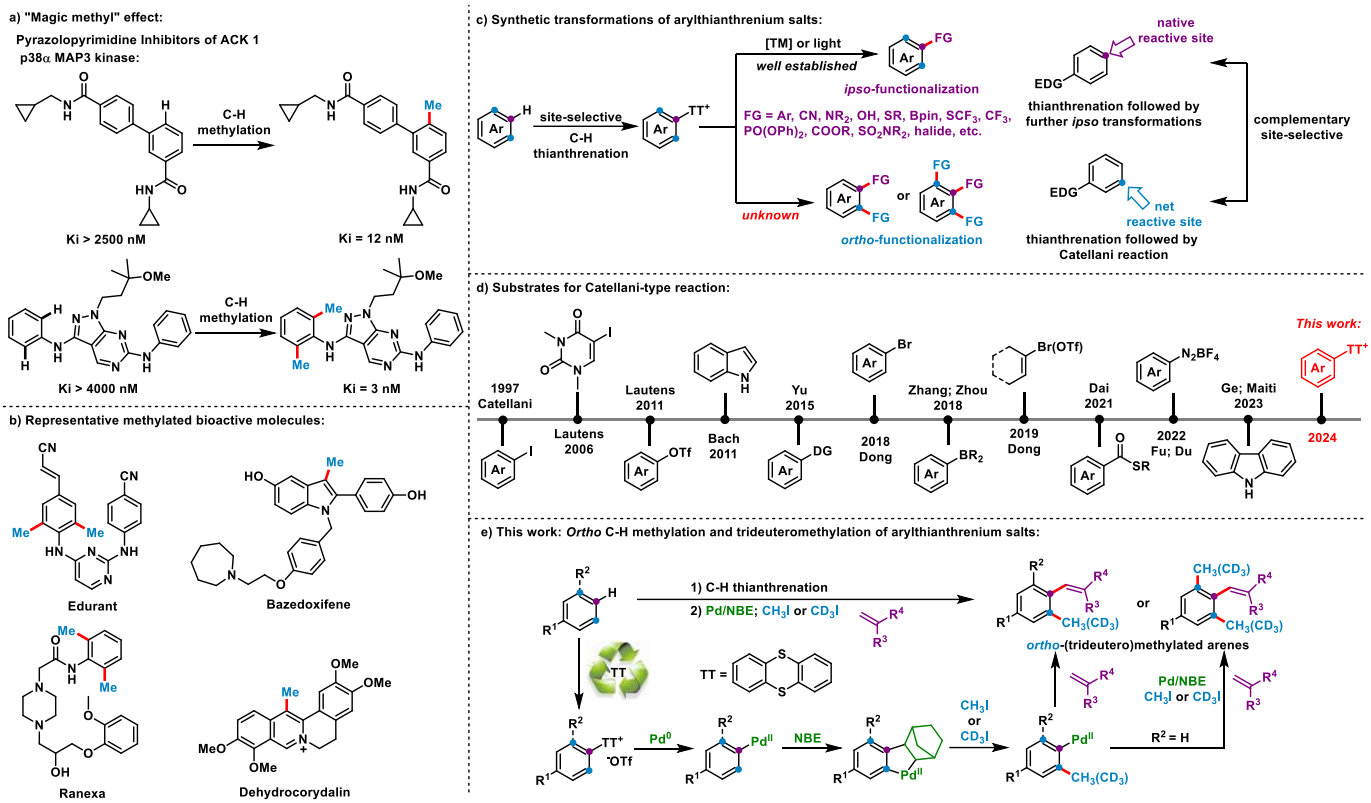
The "magic methyl" effect has attracted significant attention in medicinal chemistry due to the notable pharmacological effects that are observed when a C−H bond is converted to a C−Me bond.[1] The methyl group can influence the molecular conformation, metabolism and lipophilicity of medicinal candidates, thereby impacting pharmacokinetic parameters, biological activities and pharmacodynamic effects (Scheme 1a).[2] For example, the incorporation of a methyl group to p38α MAP3 kinase resulted in a 200-fold increase in the binding affinity (Ki). In addition, methylated arenes, as a commonly occurring structural motif, are prevalent in drugs and natural products (Scheme 1b). Therefore, the development of an efficient strategy for the rapid construction of methylated arenes would significantly encourage pharmaceutical chemists to investigate the "magic methyl" effect in medications and expedite the discovery of new drugs.[3]

Sulfonium salts have captivated chemists for over a century due to their significant chemical reactivity.[4] Among these, thianthrenium salts have recently garnered significant attention from chemists due to their similarity to organic halides, their ability to undergo oxidative addition to transition metals, and their easy single-electron reduction.[5] In recent years, Ritter,[6] Wang,[7] Zhao[8] and others[9] have demonstrated the significant synthetic potential of arylthianthrenium salts, which are generated through the thianthrenation of C−H bonds, in various reactions. However, the reactivity observed in all reactions is the *ipso*-functionalization of arylthianthrenium salts. To date, there are no reports on achieving functionalization at the *ortho*-position (Scheme 1c). The Pd/NBE cooperative catalysis, known as the Catellani reaction,[10] allows for the *ipso*-*ortho* difunctionalization of arenes, offering a unique opportunity to address the aforementioned challenge. We expect that the regioselective C(sp^2)−H thianthrenation of the arene, followed by *ortho*-functionalization, will enable the introduction of functional groups at positions that complement the results of C(sp^2)−H thianthrenation (Scheme 1c).

Since its discovery by Catellani in 1997,[11] the Catellani reaction is now recognized as a potent method for the modular synthesis of highly substituted arenes. In recent decades, Lautens,[12] Dong,[13] Zhou,[14] Liang,[15] and other researchers[16] have made significant advancements in this field, establishing this methodology as a reliable route for synthesizing complex arenes. In contrast to the diverse variations of nucleophilic and electrophilic reagents, the substrates used in Catellani-type reactions have been mainly confined to aryl halides (triflates),[11,17,18] aryl thioesters,[19] aryl diazonium salts,[20] aryl boronic acids,[21] vinyl halides (triflates),[22,23] indoles,[24] carbazoles,[25] arenes with directing groups,[26] and the exploitation of arylthianthrenium salts has remained elusive (Scheme 1d). In this paper, we reported the first

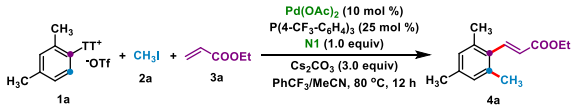
ortho C−H methylation and trideuteromethylation of arylthianthrenium salts enabled by Catellani reaction (Scheme 1e). Moreover, *ipso* C−H methylation has also been demonstrated. These methods have enabled the rapid synthesis of a wide variety of methylated or trideuteromethylated arenes, ensuring complete control of site-selectivity. Importantly, the byproduct thianthrene (TT) can be recovered and further oxidized to thianthrene 5-oxide (TTSO) for the next thianthrenation cycle, thus contributing to environmental sustainability in chemistry.

Scheme 1. Background and design.

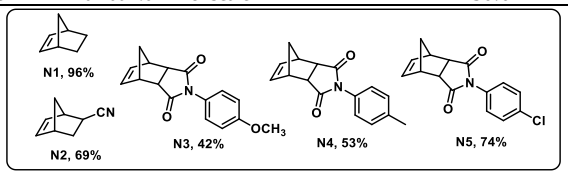


A model study was initially conducted using aryl thianthrenium salt **1a**, which could be readily prepared through regioselective C(sp^2)-H thianthrenation of *m*-xylene (Table 1). To our delight, the reaction of **1a** with CH_3I **2a** and ethyl acrylate **3a** was performed in the presence of $Pd(OAc)_2$ (10 mol %), P(4-CF_3-C_6H_4)$_3$ (25 mol %), **N1** (1.0 equiv), and Cs_2CO_3 (3.0 equiv) in $PhCF_3$/MeCN (1:1) at 80 °C for 12 h to afford the desired *ortho*-methylation/*ipso*-alkenylation product **4a** in 96% isolated yield (entry 1). The utilization of alternative NBE (**N2-N5**) led to diminished reaction performance (entry 2). Moreover, other ligands such as TFP and PPh_3 showed comparatively reduced effectiveness compared to P(4-CF_3-C_6H_4)$_3$ (entry 3). Substitution of Cs_2CO_3 with K_2CO_3 or CsOAc resulted in unsatisfactory yields in both cases (entry 4). Additionally, the utilization of other solvents, such as toluene, CH_3CN, and $PhCF_3$ led to diminished yields (entry 5). Notably, the reaction can proceed smoothly at room temperature, but the reaction time needs to be extended to 48 h (entry 6). Control experiments unequivocally demonstrated the essentiality of both $Pd(OAc)_2$ and **N1** for the desired transformation (entry 7). The scalability of this process has been demonstrated, with the desired product **4a** obtained in a 90% yield when the reaction was conducted on a 2.0 mmol scale (entry 8).

Table 1. Effects of reaction parameters.[a]



Entry	Deviation from "*standard conditions*"	**4a**[b]
1	none	96%
2	**N2-N5** instead of **N1**	Listed below
3	TFP, PPh_3 instead of P(4-CF_3-C_6H_4)$_3$	72%, 80%
4	K_2CO_3, CsOAc instead of Cs_2CO_3	36%, 29%
5	Toluene or MeCN or $PhCF_3$ as solvent	41%, 84%, 88%
6	Run at 30 °C for 48 h	89%
7	No $Pd(OAc)_2$ or **N1**	0%, 0%
8	Run at 2.0 mmol scale	90%



[a] Reaction conditions: the reactions were conducted using **1a** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.4 mmol), $Pd(OAc)_2$ (10 mol %), P(4-CF_3-C_6H_4)$_3$ (25 mol %), **N1** (0.2 mmol), Cs_2CO_3 (0.6 mmol) in 2.0 mL $PhCF_3$/MeCN (1:1) under a nitrogen atmosphere for 12 h. [b] Isolated yields.

Upon identifying the optimized reaction conditions, we proceeded to investigate the scope of the reaction (Scheme 2). A series of commercially available (hetero)arenes were converted

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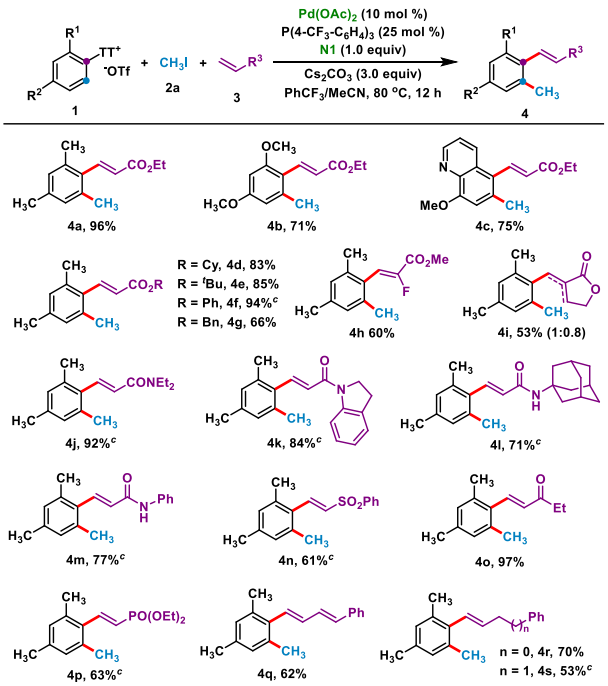
into the corresponding aryl thianthrenium salts, and then further transformed into the *ortho*-methylation products **4a-4c** (71-96%) under the optimal conditions. Furthermore, a range of acrylates were effectively integrated into the target products (**4d-4g**) with reasonable to satisfactory yields. Notably, α-fluoro-substituted acrylates and cyclic acrylates could also be utilized to give the corresponding products **4h** and **4i** in 60% and 53% yield, respectively. Additionally, various acrylamides could be successfully incorporated into the desired products (**4j-4m**) in 71-92% yields, demonstrating that the acidic proton was not problematic. Apart from acrylates and acrylamides, other electron-deficient olefins, including vinyl sulfone (**4n**), vinyl ketone (**4o**), and vinyl phosphonate (**4p**), could be readily introduced at the *ipso* position. Furthermore, phenyl diene could successfully afford the corresponding target product **4q** in 62% yield. It is important to highlight that unactivated alkenes are also compatible with this reaction system, producing the corresponding products **4r** and **4s** with yields of 70% and 53%, respectively.

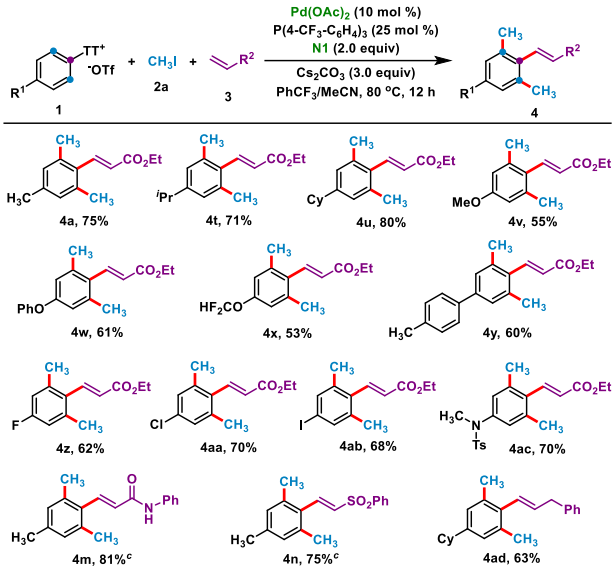
Scheme 2. Substrate scope of *ortho*-monomethylation.[a,b]



[a] Reaction conditions: the reactions were conducted using **1** (0.2 mmol), **2a** (0.4 mmol), **3** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), P(4-CF_3-C_6H_4)$_3$ (0.05 mmol), **N1** (0.2 mmol), Cs_2CO_3 (0.6 mmol) in 2.0 mL $PhCF_3$/MeCN (1:1) under a nitrogen atmosphere for 12 h. [b] Isolated yields. [c] **3** (0.2 mmol).

Additionally, the practicality of this methodology was further demonstrated through the modular assembly of various *ortho*-bimethylated arenes using 4.0 equivalents of CH_3I (Scheme 3). When *ortho*-unsubstituted aryl thianthrenium salts were used as substrates, the corresponding *ortho*-dimethylation products **4a**, **4t-4z**, **4m**, **4n**, **4aa-4ad** could obtained in 53-81% yields. Broad functional groups such as isopropyl (**4t**), cyclohexyl (**4u**), methoxyl (**4v**), phenoxyl (**4w**), difluoromethoxyl (**4x**), aryl (**4y**), fluoro (**4z**), chloro (**4aa**), iodo (**4ab**), and amino (**4ac**) groups were all well-tolerated. Significantly, this conversion exhibited good tolerance towards halogen atoms (Cl or I), offering numerous possibilities for subsequent derivatization via cross-coupling reactions. Moreover, acrylamide, vinyl sulfone and 4-phenyl-1-butene were identified as suitable substrates, furnishing the corresponding *ortho*-dimethylation products **4m**, **4n** and **4ad** in 63%-81% yields.

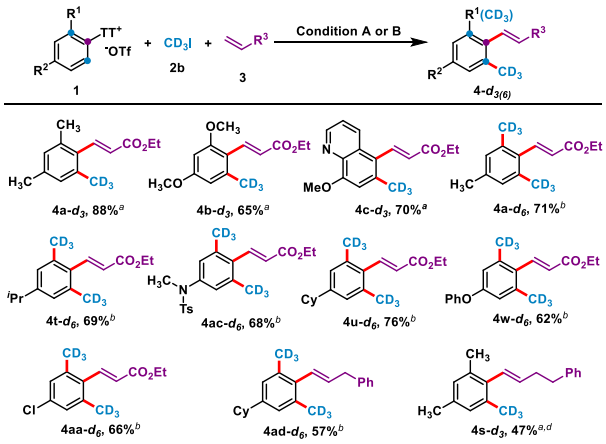
Scheme 3. Substrate scope of *ortho*-dimethylation[a,b]



[a] Reaction conditions: the reactions were conducted using **1** (0.2 mmol), **2a** (0.8 mmol), **3** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), P(4-CF_3-C_6H_4)$_3$ (0.05 mmol), **N1** (0.4 mmol), Cs_2CO_3 (0.6 mmol) in 2.0 mL $PhCF_3$/MeCN (1:1) under a nitrogen atmosphere for 12 h. [b] Isolated yields. [c] **3** (0.2 mmol).

Incorporating a trideuteromethyl group into a drug candidate can significantly enhance its key pharmacokinetic, physicochemical, and metabolic properties. Hence, it is crucial to devise an alternative method for the direct and site-selective C–H trideuteromethylation. Next, we further investigated the potential of employing this methodology for the selective introduction of the trideuteromethyl group at the *ortho*-position of arylthianthrenium salts (Scheme 4). We were delighted to find that employing CD_3I as a trideuteromethyl source under standard conditions resulted in the formation of the corresponding *ortho*-trideuteromethylated products in moderate to good yields. Moreover, both activated and unactivated alkenes were suitable as terminating reagents in this transformation. Significantly, no deuterium-hydrogen exchange was observed under the reaction conditions, ensuring that the products were fully deuterated at the methyl groups.

Scheme 4. Substrate scope of *ortho*-trideuteromethylation.[c]



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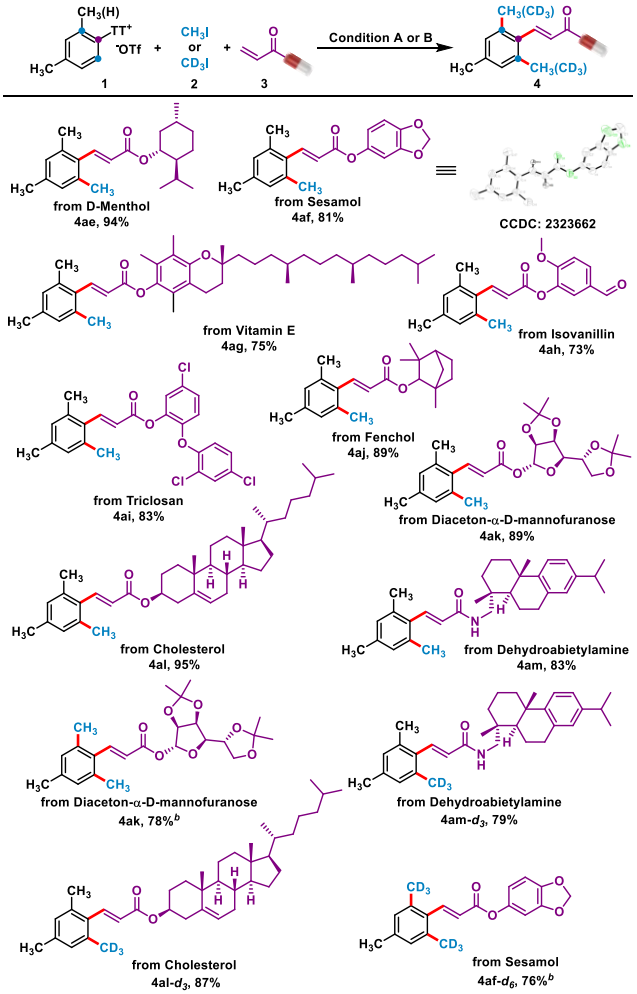
[a] Condition A: **1** (0.2 mmol), **2b** (0.4 mmol), **3** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), P(4-CF_3-C_6H_4)$_3$ (0.05 mmol), **N1** (0.2 mmol), Cs_2CO_3 (0.6 mmol) in 2.0 mL $PhCF_3$/MeCN (1:1) under a nitrogen atmosphere for 12 h. [b] Condition B: **1** (0.2 mmol), **2b** (0.8 mmol), **3** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), P(4-CF_3-C_6H_4)$_3$ (0.05 mmol), **N1** (0.4 mmol), Cs_2CO_3 (0.6 mmol) in 2.0 mL $PhCF_3$/MeCN (1:1) under a nitrogen atmosphere for 12 h. [c] Isolated yields. [d] **3** (0.2 mmol).

Encouraged by the aforementioned experimental results, we proceeded to explore the compatibility of drugs and natural products (Scheme 5). Alkenes derived from biorelevant molecules, such as D-Menthol, Sesamol, Fenchol, Vitamin E, Isovanillin, Triclosan, Diaceton-α-D-mannofuranose, Cholesterol, and Dehydroabietylamine, could efficiently produce the corresponding *ortho*-methylation, *ipso*-alkenylation products **4ae**-**4am** in 73-95% yields. The structure of **4af** was definitively confirmed via single-crystal X-ray diffraction analysis.[27] In addition, we were pleased to observe the favorable compatibility of biorelevant molecules in the *ortho*-methylation and *ortho*-trideuteromethylation reaction systems, affording the respective products **4ak**, **4am-*d*$_3$**, **4al-*d*$_3$**, and **4af-*d*$_6$** in satisfactory yields.

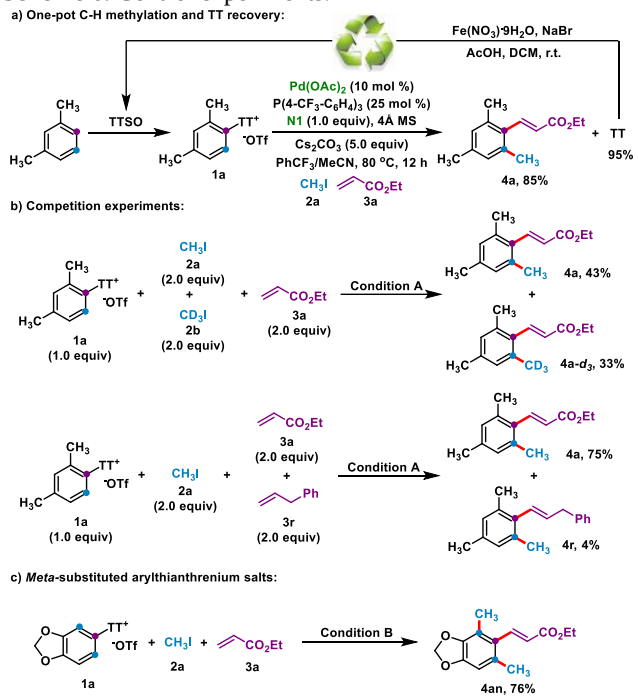
Scheme 5. Synthetic Applicability.[a,c]



[a] Condition A: **1** (0.2 mmol), **2** (0.4 mmol), **3** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), P(4-CF_3-C_6H_4)$_3$ (0.05 mmol), **N1** (0.2 mmol), Cs_2CO_3 (0.6 mmol) in 2.0 mL $PhCF_3$/MeCN (1:1) under a nitrogen atmosphere for 12 h. [b] Condition B: **1** (0.2 mmol), **2** (0.8 mmol), **3** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), P(4-CF_3-C_6H_4)$_3$ (0.05 mmol), **N1** (0.4 mmol), Cs_2CO_3 (0.6 mmol) in 2.0 mL $PhCF_3$/MeCN (1:1) under a nitrogen atmosphere for 12 h. [c] Isolated yields.

In response to the pressing challenges of efficiency and environmental sustainability in chemistry, we investigated the one-pot C-H thianthrenation/*ortho*-methylation process and the recoverability and recyclability of thianthrene (TT). It was satisfying to achieve the desired product **4a** in 85% yield, while recovering TT in 95% yield, which can be further oxidized to TTSO for the subsequent thianthrenation cycle (Scheme 6a). Subsequently, various competitive experiments were conducted separately (Scheme 6b). An assessment of the reactivities of CH_3I and CD_3I resulted in the corresponding products **4a** and **4a-*d*$_3$** in 43% and 33% yield, respectively. Furthermore, we investigated the competitive reactions of activated and unactivated alkenes, revealing that activated alkenes exhibited a higher reaction rate. The "*meta* constraint" typically presents the primary challenge in Catellani reaction.[28] It is noteworthy that *meta*-substituted arylthianthrenium salts could yield the *ortho*-methylated product **4an** in 76% yield (Scheme 6c).

Scheme 6. Control experiments.

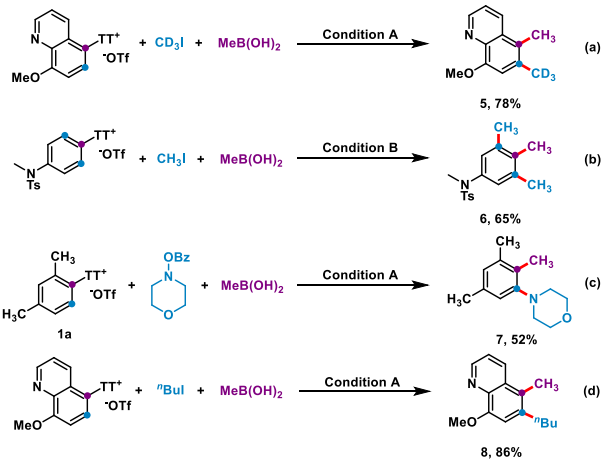


Besides *ortho*-C−H methylation of arylthianthrenium salts with CH_3I, the *ipso*-C−H methylation also proceeded smoothly using $MeB(OH)_2$ as a nucleophile (Scheme 7). Under the optimal conditions, the *ortho*-trideuteromethylation and *ipso*-methylation product **5** was obtained in 78% yield (Scheme 7a), while the *ortho*- and *ipso*-trimethylation product **6** was obtained in 65% yield (Scheme 7b). To further demonstrate the feasibility of this protocol, we conducted an *ortho*-amination/*ipso*-methylation cascade of arylthianthrenium salts, resulting in the formation of **7** in 52% yield (Scheme 7c). Remarkably, apart from CH_3I, other alkylating reagents, such as ^{n}BuI, were suitable electrophiles for producing the *ortho*-butylation and *ipso*-methylation product **8** in 86% yield (Scheme 7d).

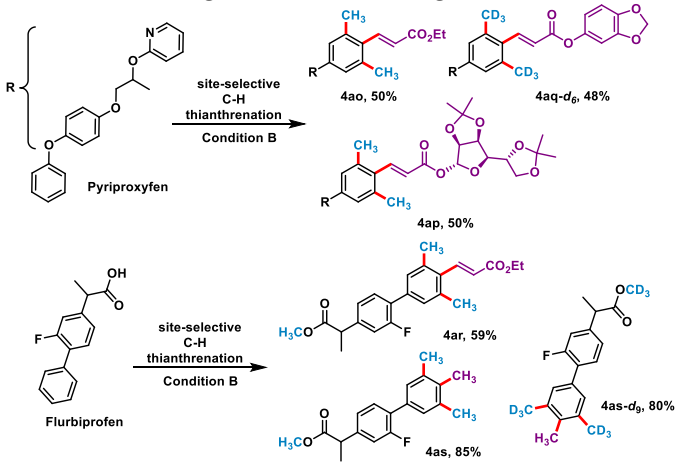
Finally, to showcase the practical application of this protocol, we performed late-stage functionalization of drugs (Scheme 8). Pyriproxyfen and Flurbiprofen were chosen as representative models for modification. The corresponding (trideutero)methylated derivatives **4ao, 4ap, 4aq-*d*$_6$, 4ar, 4as, 4as-*d*$_9$** were readily obtained in 48-85% using alkenes or $MeB(OH)_2$ termination.

These examples demonstrated the potential of our strategy for the rapid synthesis of methylated bioactive molecules, which is expected to facilitate the exploration of structure-activity relationships in drug discovery.

Scheme 7. Further developments.



Scheme 8. Late-Stage Modification of drugs.



In conclusion, we have developed the first Pd/NBE cooperative-catalyzed *ortho* C−H methylation and trideuteromethylation of arylthianthrenium salts. Numerous readily available arenes were smoothly transformed into the desired (trideutero)methylated arenes through sequential C−H thianthrenation and Catellani reaction. This approach is more atom-economic and less wasteful due to the recovery of thianthrene. Furthermore, the practical application in medicinal chemistry was demonstrated through late-stage functionalization of relevant biorelevant molecules and synthetic applications.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We are grateful to the National Natural Science Foundation of China (21901184; 21572160; 22101245) and the Natural Science Foundation of Tianjin City (20JCQNJC00400) for their generous financial support.

REFERENCES

(1) (a) Aynetdinova, D.; Callens, M. C.; Hicks, H. B.; Poh, C. Y. X.; Shennan, B. D. A.; Boyd, A. M.; Lim, Z. H.; Leitch, J. A.; Dixon, D. J. Installing the "Magic Methyl" - C-H Methylation in Synthesis. *Chem. Soc. Rev.* **2021**, *50*, 5517-5563. (b) Sun, Q.; Soulé, J.-F. Broadening of Horizons in the Synthesis of CD_3-Labeled Molecules. *Chem. Soc. Rev.* **2021**, *50*, 10806-10835. (c) Steverlynck, J.; Sitdikov, R.; Rueping, M. The Deuterated "Magic Methyl" Group: A Guide to Site-Selective Trideuteromethyl Incorporation and Labeling by Using CD_3 Reagents. *Chem. Eur. J.* **2021**, *27*, 11751-11772.

(2) (a) Wencel-Delord, J. Decorating and Diversifying Drugs. *Nat. Chem.* **2020**, *12*, 505-506. (b) Corcoran, E. B.; Schultz, D. M. Manganese Catalyst Enables Exploration of the Magic Methyl Effect. *Nature* **2020**, *580*, 592-593. (c) Schönherr, H.; Cernak T. Profound Methyl Effects in Drug Discovery and a Call for New C-H Methylation Reactions. *Angew. Chem., Int. Ed.* **2013**, *52*, 12256-12267.

(3) For recent examples, see: (a) Wu, Z.; Wei, F.; Wan, B.; Zhang, Y. Pd-Catalyzed *ipso*,*meta*-Dimethylation of *ortho*-Substituted Iodoarenes *via* a Base-Controlled C-H Activation Cascade with Dimethyl Carbonate as the Methyl Source. *J. Am. Chem. Soc.* **2021**, *143*, 4524-4530. (b) Gao, Q.; Shang, Y.; Song, F.; Ye, J.; Liu, Z.-S.; Li, L.; Cheng, H.-G.; Zhou, Q. Modular Dual-Tasked C-H Methylation *via* the Catellani Strategy. *J. Am. Chem. Soc.* **2019**, *141*, 15986-15993. (c) Zhang, Z.; Chen, X.; Li, X.-S.; Wang, C.-T.; Niu, Z.-J.; Zhang, B.-S.; Liu, X.-Y.; Liang, Y.-M. *Ortho* C-H Hydroxyalkylation or Methylation of Aryl Iodides by Ethers and TMSI *via* a Catellani Strategy. *Org. Lett.* **2022**, *24*, 6897-6902. (d) Friis, S. D.; Johansson, M. J.; Ackermann, L. Cobalt-Catalysed C-H Methylation for Late-Stage Drug Diversification. *Nat. Chem.* **2020**, *12*, 511-519.

(4) For selected reviews, see: (a) Kaiser, D.; Klose, I.; Oost, R.; Neuhaus, J.; Maulide, N. Bond-Forming and -Breaking Reactions at Sulfur(IV): Sulfoxides, Sulfonium Salts, Sulfur Ylides, and Sulfinate Salts. *Chem. Rev.* **2019**, *119*, 8701-8780. (b) Péter, Á.; Perry, G. J. P.; Procter, D. J. Radical C-C Bond Formation Using Sulfonium Salts and Light. *Adv. Synth. Catal.* **2020**, *362*, 2135-2142. (d) Fan, R.; Tan, C.; Liu, Y.; Wei, Y.; Zhao, X.; Liu, X.; Tan, J.; Yoshida, H. A Leap Forward in Sulfonium Salt and Sulfur Ylide Chemistry. *Chin. Chem. Lett.* **2021**, *32*, 299-312.

(5) For selected reviews, see: (a) Chen, X.-Y.; Wu, Y.; Wang, P. Recent Advances in Thianthrenation/Phenoxathiination Enabled Site-Selective Functionalization of Arenes. *Synthesis* **2022**, *54*, 3928-3940. (b) Meng, H.; Liu, M.-S.; Shu, W. Organothianthrenium Salts: Synthesis and Utilization. *Chem. Sci.* **2022**, *13*, 13690-13707. (c) Kelly, C. B.; Padilla-Salinas, R. Late Stage C-H Functionalization *via* Chalcogen and Pnictogen Salts. *Chem. Sci.* **2020**, *11*, 10047-10060.

(6) Hartmann, P.; Bohdan, K.; Hommrich, M.; Juliá, F.; Vogelsang, L.; Eirich, J.; Zangl, R.; Farès, C.; Jacobs, J. B.; Mukhopadhyay, D.; Mengeler, J. M.; Vetere, A.; Sterling, M. S.; Hinrichs, H.; Becker, S.; Morgner, N.; Schrader, W.; Finkemeier, I.; Dietz, K.-J.; Griesinger C.; Ritter, T. Chemoselective Umpolung of Thiols to Episulfoniums for Cysteine Bioconjugation. *Nat. Chem.* **2023**, DOI: 10.1038/s41557-023-01388-7. (b) Berger, F.; Plutschack, M. B.; Riegger, J.; Yu, W.; Speicher, S.; Ho, M.; Frank, N.; Ritter, T. Site-Selective and Versatile Aromatic C-H Functionalization by Thianthrenation. *Nature* **2019**, *567*, 223-228. (c) Engl, P. S.; Häring, A. P.; Berger, F.; Berger, G.; Pérez-Bitrián, A.; Ritter, T.

C-N Cross-Couplings for Site-Selective Late-Stage Diversification *via* Aryl Sulfonium Salts. *J. Am. Chem. Soc.* **2019**, *141*, 13346-13351. (d) Ye, F.; Berger, F.; Jia, H.; Ford, J.; Wortman, A.; Börgel, J.; Genicot, C.; Ritter, T. Aryl Sulfonium Salts for Site-Selective Late-Stage Trifluoromethylation. *Angew. Chem., Int. Ed.* **2019**, *58*, 14615-14619.

(7) (a) Chen, X.-Y.; Li, Y.-N.; Wu, Y.; Bai, J.; Guo, Y.; Wang, P. Cu-Mediated Thianthrenation and Phenoxathiination of Arylborons. *J. Am. Chem. Soc.* **2023**, *145*, 10431-10440. (b) Chen, X.-Y.; Huang, Y.-H.; Zhou, J.; Wang, P. Pd-Catalyzed Site-Selective Borylation of Simple Arenes *via* Thianthrenation. *Chin. J. Chem.* **2020**, *38*, 1269-1272. (c) Zhang, Y.-L.; Wang, G.-H.; Wu, Y.; Zhu, C.-Y.; Wang, P. Construction of α-Amino Azines *via* Thianthrenation-Enabled Photocatalyzed Hydroarylation of Azine-Substituted Enamides with Arenes. *Org. Lett.* **2021**, *23*, 8522-8526. (d) Chen, X.-Y.; Nie, X.-X.; Wu, Y.; Wang, P. *para*-Selective Arylation and Alkenylation of Monosubstituted Arenes Using Thianthrene S-oxide as a Transient Mediator. *Chem. Commun.* **2020**, *56*, 5058-5061.

(8) (a) Chen, C.; Wang, M.; Lu, H.; Zhao, B.; Shi, Z. Enabling the Use of Alkyl Thianthrenium Salts in Cross-Coupling Reactions by Copper Catalysis. *Angew. Chem., Int. Ed.* **2021**, *60*, 21756-21760. (b) Wang, M.; Zhang, X.; Ma, M.; Zhao, B. Palladium-Catalyzed Synthesis of Esters from Arenes through C-H Thianthrenation. *Org. Lett.* **2022**, *24*, 6031-6036.

(9) (a) Liu, M.-S.; Du, H.-W.; Cui, J.-F.; Shu, W. Intermolecular Metal-Free Cyclopropanation and Aziridination of Alkenes with XH_2 (X=N, C) by Thianthrenation. *Angew. Chem., Int. Ed.* **2022**, *61*, e202209929. (b) Zhang, J.; Wu, X.-F. Palladium-Catalyzed Carbonylative Synthesis of Diaryl Ketones from Arenes and Arylboronic Acids through C(sp^2)-H Thianthrenation. *Org. Lett.* **2023**, *25*, 2162-2166. (c) Tang, S.; Zhao, X.; Yang, L.; Li, B.; Wang, B. Copper-Catalyzed Carboxylation of Aryl Thianthrenium Salts with CO_2. *Angew. Chem., Int. Ed.* **2022**, *61*, e202212975. (d) Chen, C.; Wang, Z.-J.; Lu, H.; Zhao, Y.; Shi, Z. Generation of non-Stabilized Alkyl Radicals from Thianthrenium Salts for C-B and C-C Bond Formation. *Nat. Commun.* **2021**, *12*, 4526. (e) Cabrera-Afonso, M. J.; Granados, A.; Molander, G. A. Sustainable Thioetherification *via* Electron Donor-Acceptor Photoactivation Using Thianthrenium Salts. *Angew. Chem., Int. Ed.* **2022**, *61*, e202202706. (f) Ye, Y.; Zhu, J.; Xie, H.; Huang, Y. Rhodium-Catalyzed Divergent Arylation of Alkenylsulfonium Salts with Arylboroxines. *Angew. Chem., Int. Ed.* **2022**, *61*, e202212522. (g) Aukland, M. H.; Šiaučiulis, M.; West, A.; Perry, G. J. P.; Procter, D. J. Metal-Free Photoredox-Catalysed Formal C-H/C-H Coupling of Arenes Enabled by Interrupted Pummerer Activation. *Nat. Catal.* **2020**, *3*, 163-169. (h) Tian, Z.-Y.; Lin, Z.-H.; Zhang, C.-P. Pd/Cu-Catalyzed C-H/C-H Cross Coupling of (Hetero)Arenes with Azoles through Arylsulfonium Intermediates. *Org. Lett.* **2021**, *23*, 4400-4405.

(10) For reviews, see: (a) Wang, J.; Dong, G. Palladium/Norbornene Cooperative Catalysis. *Chem. Rev.* **2019**, *119*, 7478-7528. (b) Ye, J.; Lautens, M. Palladium-Catalysed Norbornene-Mediated C-H Functionalization of Arenes. *Nat. Chem.* **2015**, *7*, 863-870. (c) Patel, M.; Desai, B.; Ramani, A.; Dholakiya, B. Z.; Naveen, T. Recent Developments in the Palladium-Catalyzed/Norbornene-Mediated Synthesis of Carbo- and Heterocycles. *ChemistrySelect* **2021**, *6*, 8085-8106. (d) Chen, Z.; Zhang, F. Recent Progress on Catellani Reaction. *Tetrahedron* **2023**, *134*,133307. (e) Cheng, H.-G.; Chen, S.; Chen, R.; Zhou, Q. Palladium(II)-Initiated Catellani-Type Reactions. *Angew. Chem., Int. Ed.* **2019**, *58*, 5832-5844. (f) Cheng, H.-G.; Jia, S.; Zhou, Q. Benzo-Fused-Ring Toolbox Based on Palladium/Norbornene Cooperative Catalysis: Methodology Development and Applications in Natural Product Synthesis. *Acc. Chem. Res.* **2023**, *56*, 573-591.

(11) Catellani, M.; Frignani, F.; Rangoni, A. A Complex Catalytic Cycle Leading to a Regioselective Synthesis of *o*,*o*'-Disubstituted Vinylarenes. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119-122.

(12) (a) Lautens, M.; Piguel, S. A New Route to Fused Aromatic Compounds by Using a Palladium-Catalyzed Alkylation-Alkenylation Sequence. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045-1046. (b) Candito, D. A.; Lautens, M. Palladium-Catalyzed Domino Direct Arylation/N-Arylation: Convenient Synthesis of Phenanthridines. *Angew. Chem., Int. Ed.* **2009**, *48*, 6713-6716. (c) Bressy, C.; Alberico, D.; Lautens, M. A Route to Annulated Indoles *via* a Palladium-Catalyzed Tandem Alkylation/Direct Arylation Reaction. *J. Am. Chem. Soc.* **2005**, *127*, 13148-13149.

(13) (a) Liu, X.; Zhou, Y.; Qi, X.; Li, R.; Liu, P.; Dong, G. Palladium/Norbornene-Catalyzed Direct Vicinal Di-Carbo-Functionalization of Indoles: Reaction Development and Mechanistic Study. *Angew. Chem., Int. Ed.* **2023**, *62*, e202310697. (b) Liu, X.; Fu, Y.; Chen, Z.; Liu, P.; Dong, G. *Ortho*-C-H Methoxylation of Aryl Halides Enabled by a Polarity-Reversed N-O Reagent. *Nat. Chem.* **2023**, *15*, 1391-1399. (c) Huo, J.; Fu, Y.; Tang, M. J.; Liu, P.; Dong, G. Escape from Palladium: Nickel-Catalyzed Catellani Annulation. *J. Am. Chem. Soc.* **2023**, *145*, 11005-11011. (d) Rago, A. J.; Ye, R.; Liu, X.; Dong, G. A Four-Component Reaction to Access 3,3-Disubstituted Indolines *via* the Palladium-Norbornene-Catalyzed *ortho* Amination/*ipso* Conjunctive Coupling. *Chem. Sci.* **2024**, DOI: 10.1039/D3SC06409C.

(14) (a) Zhou, L.; Cheng, H.-G.; Li, L.; Wu, K.; Hou, J.; Jiao, C.; Deng, S.; Liu, Z.; Yu, J.-Q.; Zhou, Q. Synthesis of Planar Chiral Ferrocenes *via* Enantioselective Remote C-H Activation. *Nat. Chem.* **2023**, *15*, 815-823. (b) Liu, Z.-S.; Deng, S.; Gao, Q.; Hua, Y.; Cheng, H.-G.; Zhou, Q. Construction of Axially Chiral Biaryls *via* Atroposelective *ortho*-C-H Arylation of Aryl Iodides. *ACS Catal.* **2023**, *13*, 2968-2980. (c) Liu, Z.-S.; Xie, P.-P.; Hua, Y.; Wu, C.; Ma, Y.; Chen, J.; Cheng, H.-G.; Hong, X.; Zhou, Q. An Axial-to-Axial Chirality Transfer Strategy for Atroposelective Construction of C-N Axial Chirality. *Chem* **2021**, *7*, 1917-1932. (d) Liu, Z.-S.; Hua, Y.; Gao, Q.; Ma, Y.; Tang, H.; Shang, Y.; Cheng, H.-G.; Zhou, Q. Construction of Axial Chirality *via* Palladium/Chiral Norbornene Cooperative Catalysis. *Nat. Catal.* **2020**, *3*, 727-733.

(15) (a) Du, X.; Yang, X.; Wang, H.; Li, X.; Wang, M.; Li, X.; Tao, Y.; Yang, Y.; Tan, X.; Ren, F.; Zhou, P.-X.; Liang, Y.-M. Homoallyl Alcohol as an Allylation Reagent for Termination of the Catellani-Lautens Reaction *via* Retro-Allylation. *Org. Chem. Front.* **2023**, *10*, 898-904. (b) An, Y.; Zhang, X.-Y.; Ding, Y.-N.; Li, Y.; Liu, X.-Y.; Liang, Y.-M. Enantioselective Synthesis of Both Axially and Planar Chiral Ferrocenes *via* Axial-to-Planar Diastereoinduction. *Org. Lett.* **2022**, *24*, 7294-7299. (c) An, Y.; Zhang, B.-S.; Ding, Y.-N.; Zhang, Z.; Gou, X.-Y.; Li, X.-S.; Wang, X.; Li, Y.; Liang, Y.-M. Palladium-Catalyzed C-H Glycosylation and Retro Diels-Alder Tandem Reaction *via* Structurally Modified Norbornadienes (smNBDs). *Chem. Sci.* **2021**, *12*, 13144-13150.

(16) (a) Zhang, B.-S.; Yang, Y.-X.; Olivera, J. C. A.; Zhang, Z.-Q.; Warratz, S.; Wang, Y.-M.; Li, S.-X.; Wang, X.-C.; Gou, X.-Y.; Liang, Y.-M.; Quan, Z.-J.; Ackermann, L. Combined C-H Amination and Intermolecular Alkyne Insertion for a Three-Component Cyclization. *Cell Rep. Phys. Sci.* **2023**, DOI: 10.1016/j.xcrp.2023.101647. (b) Zheng, Y.-X.; Jiao, L. Hybrid Cycloolefin Ligands for Palladium-Olefin Cooperative Catalysis. *Nat. Synth.* **2022**, *1*, 180-187. (c) Wang, F.-Y.; Li, Y.-X.; Jiao, L. Functionalized Cycloolefin Ligand as a Solution to *ortho*-Constraint in the Catellani-Type Reaction. *J. Am. Chem. Soc.* **2023**, *145*, 4871-4881. (d) Ding, M.; Ou, P.; Li, X.; Yu, Y.; Niu, M.; Yang, Y.; Huang, Y.; Wang, Z.-X.; Huang, X. Alkyne Insertion Enabled Vinyl to Acyl 1,5-Palladium Migration: Rapid Access to Substituted 5-Membered-Dihydrobenzofurans and Indolines. *Angew. Chem., Int. Ed.* **2023**, *62*, e202300703. (e) Wang, J.; Qin, C.; Lumb, J.-P.; Luan, X. Regioselective Synthesis of Polyfunctional Arenes by a 4-Component Catellani Reaction. *Chem* **2020**, *6*, 1855-1858. (f) Lv, W.; Chen, Y.; Wen, S.; Ba, D.; Cheng, G. Modular and Stereoselective Synthesis of C-Aryl Glycosides *via* Catellani Reaction. *J. Am. Chem. Soc.* **2020**, *142*, 14864-14870. (g) Sukowski, V.; Borselen, M. V.; Mathew, S.; Bruin, B. D.; Fernández-Ibáñez, M. Á. *meta*-C-H Arylation of Aniline Derivatives *via* Palladium/S,O-Ligand/Norbornene Cooperative Catalysis. *Angew. Chem., Int. Ed.* **2023**, e202317741. (h) Wang, Z.; Li,

T.; Zhao, J.; Shi, X.; Jiao, D.; Zheng, H.; Chen, C.; Zhu, B. Expeditious Synthesis of 6-Fluoroalkyl-Phenanthridines via Palladium-Catalyzed Norbornene-Mediated Dehydrogenative Annulation. *Org. Lett*. **2018**, *20*, 6640-6645. (i) Chen, C.; Liu, L.; Sun, W.; Ding, J.; Zhu, Y.-P.; Zhu, B. Pd/NBE-Catalyzed Sequential Carbamoylation/Olefination of Aryl Iodides. *Org. Chem. Front.* **2020**, *7*, 3179-3185.

(17) Dong, Z.; Lu, G.; Wang, J.; Liu, P.; Dong, G. Modular *ipso*/*ortho* Difunctionalization of Aryl Bromides *via* Palladium/Norbornene Cooperative Catalysis. *J. Am. Chem. Soc*. **2018**, *140*, 8551-8562.

(18) Blanchot, M.; Candito, D. A.; Larnaud, F.; Lautens, M. Formal Synthesis of Nitidine and NK109 *via* Palladium-Catalyzed Domino Direct Arylation/***N***-Arylation of Aryl Triflates. *Org. Lett.* **2011**, *13*, 1486-1489.

(19) Han, M.-L.; Chen, J.-J.; Xu, H.; Huang, Z.-C.; Huang, W.; Liu, Y.-W.; Wang, X.; Liu, M.; Guo, Z.-Q.; Dai, H.-X. Palladium/Norbornene-Catalyzed Decarbonylative Difunctionalization of Thioesters. *J. Am. Chem. Soc. Au* **2021**, *1*, 1877-1884.

(20) Fu, Y.; Guo, L.-L.; Zhang, Y.-X.; Du, Z. Palladium/Norbornene Cocatalyzed Catellani-Type Domino Reaction with Aryl Diazonium Salts. *Eur. J. Org. Chem.* **2022**, e202201175.

(21) (a) Chen, S.; Liu, Z.-S.; Yang, T.; Hua, Y.; Zhou, Z.; Cheng, H.-G.; Zhou, Q. The Discovery of a Palladium (II)-Initiated Borono-Catellani Reaction. *Angew. Chem., Int. Ed.* **2018**, *57*, 7161-7165. (b) Shi, G.; Shao, C.; Ma, X.; Gu, Y.; Zhang, Y. Pd(II)-Catalyzed Catellani-Type Domino Reaction Utilizing Arylboronic Acids as Substrates. *ACS Catal.* **2018**, *8*, 3775-3779.

(22) Wang, J.; Dong, Z.; Yang, C.; Dong, G. Modular and Regioselective Synthesis of All-Carbon Tetrasubstituted Olefins Enabled by an Alkenyl Catellani Reaction. *Nat. Chem.* **2019**, *11*, 1106-1112.

(23) Blaszykowski, C.; Aktoudianakis, E.; Bressy, C.; Alberico, D.; Lautens, M. Preparation of Annulated Nitrogen-Containing Heterocycles *via* a One-Pot Palladium-Catalyzed Alkylation/Direct Arylation Sequence. *Org. Lett*. **2006**, *8*, 2043-2045.

(24) Jiao, L.; Bach, T. Palladium-Catalyzed Direct 2-Alkylation of Indoles by Norbornene-Mediated Regioselective Cascade C-H Activation. *J. Am. Chem. Soc.* **2011**, *133*, 12990-12993.

(25) Elsaid, M.; Ge, R.; Liu, C.; Maiti, D.; Ge, H. Site-Selective C-H Functionalization of Carbazoles. *Angew. Chem., Int. Ed.* **2023**, *135*, e202303110.

(26) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. Ligand-enabled *meta*-C-H activation using a transient mediator. *Nature* **2015**, *519*, 334-338.

(27) CCDC 2323662 (**4af**) contains the supplementary crystallographic data for this paper.

(28) Wang, J.; Zhou, Y.; Xu, X.; Liu, P.; Dong, G. Entry to 1,2,3,4-Tetrasubstituted Arenes through Addressing the "*Meta* Constraint" in the Palladium/Norbornene Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 3050-3059.