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A Modular Dual-Tasked C-H Methylation via the Catellani Strategy

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ABSTRACT: We report a dual-tasked methylation based on cooperative palladium/norbornene catalysis. Readily available (hetero)aryl halides (39 iodides and 4 bromides) and inexpensive MeOTs or trimethylphosphate are utilized as the substrates and methylating reagent, respectively. Six types of *ipso* terminations can modularly couple with this *ortho* C-H methylation to constitute a versatile methylation toolbox for preparing diversified methylated arenes. This toolbox features inexpensive methyl sources, excellent functional-group tolerance, simple reaction procedures, and scalability. Importantly, it can be uneventfully extended to isotope-labeled methylation by switching to the corresponding reagents CD_3OTs or $^{13}CH_3OTs$. Moreover, this tool-box can be applied to late-stage modification of bio-relevant substrates with complete stereo-retention. We believe these salient and practical features of our dual-tasked methylation toolbox will be welcomed by academic and industrial researchers.

Introduction

Extensive studies have revealed that the introduction of a methyl group can modulate the solubility, hydrophilicity, and conformation of a drug candidate, thus leading to a profound impact on its biological activity, pharmacokinetic profile, as well as physical properties, which is called the "magic methyl effect" in medicinal chemistry.[1] For example, in a recent report, the remarkable advantage that the methylation can have on potency (over 2000-fold boost) has been demonstrated (Figure 1A).[2] A survey of Njarðarson's Top 200 Pharmaceutical Products by Retail Sales in 2018[3] shows that more than 47% of small-molecule drugs contain at least one methyl group, with typical examples presented in Figure 1B. In addition, the introduction of trideuteriomethyl (CD_3) group has also been widely attempted during the optimization of drug candidates,[4] and several clinically important deuterated compounds have been developed. For instance, Austedo[4c] is a marketed antichorea drug approved by FDA in 2017, CTP-786[4d] and SD-560[4e] are now in clinical trials (Figure 1C). Therefore, (deuterated)methylation has become one of the most widely used strategies to modify bioactive compounds in medicinal chemistry.[1,5] Efficient methods for selective methylation, particularly C-H bond methylation, are highly desirable.[1b,6]

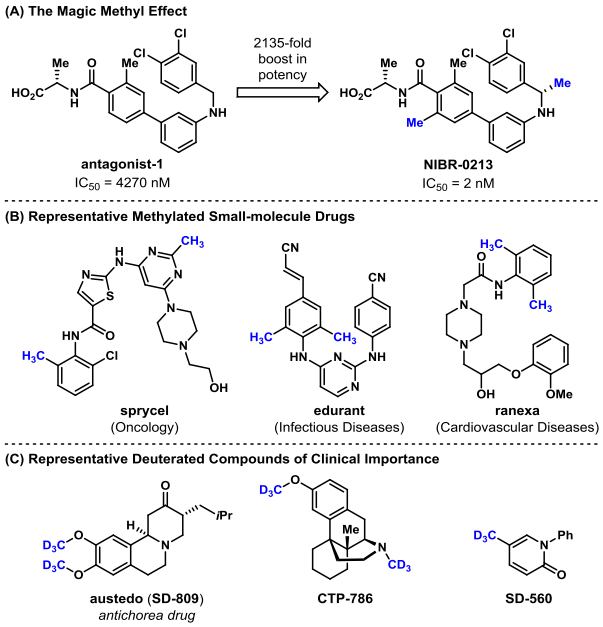


Figure 1. The Importance of Methylation in Pharmaceutical

Until now, substantial progress has been made for installing methyl groups on (hetero)arenes.[6,7-21] Since the early work by Minisci,[7] the radical-type innate C-H methylation of heteroarenes has been developed successfully due to the efforts of Baran,[8] DiRocco,[9] Macmillan,[10] Li[11] and others.[12] Meanwhile, transition-metal-catalyzed methylation of a C-H or C-X bond involving the use of methyl organometallic reagents (lithium[13], magnesium,[14] tin,[15] boron,[16] zinc,[17] aluminum,[18] silicon[19] *etc*), methyl electrophiles[20] or others[21] has also boomed in the past two decades. Despite powerful, these methods possess some limitations, including: a) the requirement of a directing group;[18b,20c,20d] b) narrow substrate scope;[13] c) harsh reaction conditions (high temperature, strong base and oxidants).[20h-j] In addition, due to the very limited availability and high cost of CD_3-containing organometallic reagents,[13,20f] these methods have a pronounced limitation when the installation of a CD_3 group is desired. Moreover, these methods are commonly *single-tasked*: the operations only lead to sheer methylations (Figure 2A).

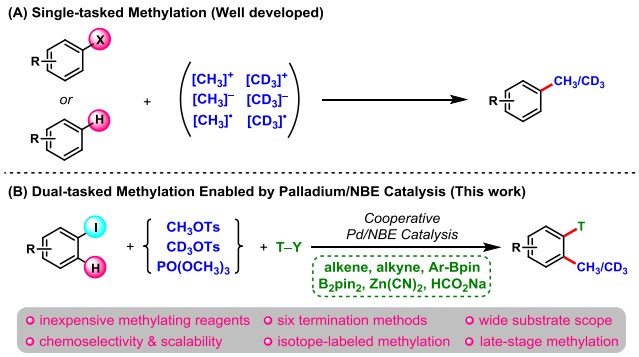


Figure 2. Strategies for Arene Methylation

The cooperative palladium/norbornene (NBE) catalysis (namely the Catellani reaction)[22] is a powerful strategy that allows the expeditious synthesis of highly substituted arenes, through sequential *ortho* C-H functionalization and *ipso* termination of aryl iodides.[23,24] Hence, based on this chemistry, we surmise whether a *dual-tasked methylation* can be developed by coupling the *ortho*-C-H methylation with the diversified *ipso*-cross coupling reactions of aryl iodides (Figure 2B). We believe such a method will possess huge synthetic potential to access more diversified methylated arenes, thereby meet the increasing needs from medicinal chemists.[1b,25a] However, Catellani-type *ortho* C-H methylations with methyl halides (*or* pseudohalide) have been rarely reported.[25] Only the group of Lautens[25b], Wilson[25a] and Dong[25c] successively reported the *ortho*-C-H-methylation of (hetero)aromatic iodide with iodomethane as the methylating reagent, albeit just one example each was showed respectively. This deficit probably owes to the high volatility and reactivity of methyl halides under the Catellani-type reaction conditions.[25b,c] Thus, we thought the incorporation of other methylating reagents with a lower reactivity might enable this *dual-tasked methylation*. After careful evaluation, we treated CH_3OTs as the promising candidate, based on the following reasons. First, CH_3OTs indeed exhibits a lower reactivity since the dissociation energy of the C-O bond in CH_3OTs is significantly higher than the C-I bond in iodomethane.[26] Second, iodide ion[27] can readily react with CH_3OTs to slowly release iodomethane and maintain a low concentration, thereby the potential side reactions could be significantly reduced.[28] Third, CH_3OTs is an inexpensive reagent, and the isotope labeled version CD_3OTs is also commercially available.[29] Actually, CH_3OTs and CD_3OTs have already been utilized as the methylation reagent in transition-metal catalyzed cross-coupling[30] and C-H functionalization reactions.[28]

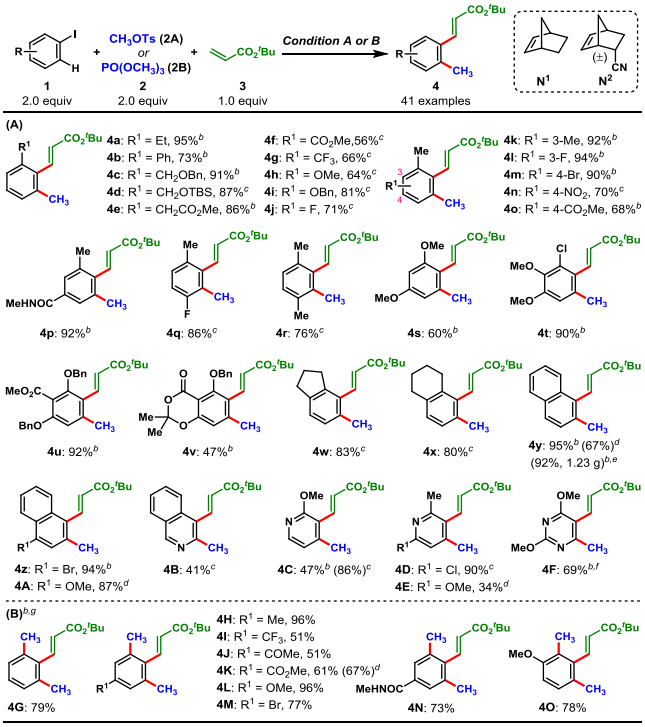
Herein, we report a dual-tasked *ortho* C-H methylation of aryl iodides enabled by cooperative palladium/NBE catalysis. It features an inexpensive methyl source, excellent functional-group tolerance, simple reaction procedure, and scalability. Importantly, six types of *ipso* terminations can modularly couple with this *ortho* C-H methylation to provide a versatile methylation toolbox for preparing diversified methylated arenes. Moreover, this strategy can be uneventfully extended to isotope-labeled methylation by switching to the corresponding reagents CD_3OTs and $^{13}CH_3OTs$[31] (Figure 2B).

Results and Discussion

To develop the promising dual-tasked *ortho* C-H methylation of aryl iodides through palladium/NBE cooperative catalysis, we first studied the reaction of 2-ethyliodobenzene (**1a**) with CH_3OTs (**2A**) (other methyl sulfonates were also screened, see **Table S1**), while employing *tert*-butyl acrylate (**3**) as the Heck-type terminating reagent.[25a] Through extensive reaction conditions optimization (see **Table S2** of Supporting Information for details), it was identified that the desired methylated product **4a** was obtained with the highest yield (95%) while running the reaction with $Pd_2(dba)_3$ (5 mol%) as the catalyst, TFP (11 mol%) as the ligand, the cyano derivative of NBE (**N**^{2}, 2.0 equiv)[32] as the mediator, and Cs_2CO_3 (2.5 equiv) as the base in MeCN (0.2 M) at 80 °C (Table 1, **Standard Condition A**). It is noteworthy that significant ligand effect was observed for this transformation. When the bulky ligand XPhos was employed, the poor yields of **4a** were obtained. In contrast, the use of small TFP as the ligand dramatically increased the yield to 99% (95% isolated yield) (**Table S2**).

With the standard reaction condition in hand, we began to explore the reaction scope with respect to the aryl iodides. Gratifyingly, a large variety of aryl iodides were able to undergo methylation with CH_3OTs (**2A**) and **3** to furnish the desired products **4** in moderate to excellent yields (47–96%) (Table 1). In principle, aryl iodides containing electron-withdrawing, electron-donating and electron-neutral substituents all proved to be competent substrates. The reaction also exhibited high chemoselectivity: various functional groups, including fluoro

Table 1. Scope of Aryl Iodides that Undergo Methylation with CH_3OTs or $PO(OMe)_3$.[a]

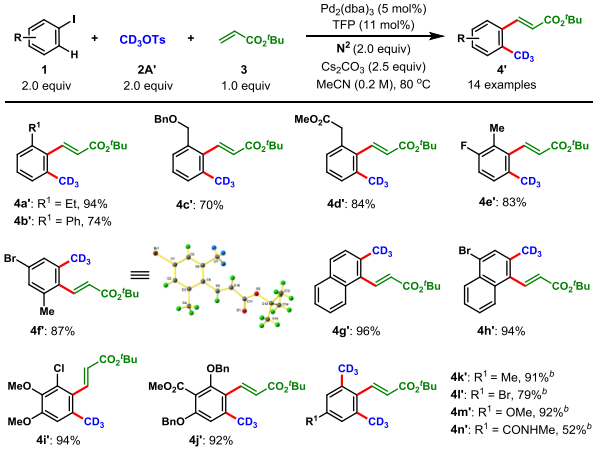


[a]All reactions were performed on a 0.2 mmol scale. Isolated yields were reported. **Condition A**: $Pd_2(dba)_3$ (5 mol%), TFP (11 mol%), **N**^{2} (2.0 equiv), **2A** (2.0 equiv), Cs_2CO_3 (2.5 equiv), MeCN (0.2 M), 80 °C; **Condition B**: $Pd(OAc)_2$ (10 mol%), TFP (22 mol%), **N**^{1} (2.0 equiv), **2B** (2.0 equiv), Cs_2CO_3 (2.5 equiv), DMA (0.1 M), 80 °C. [b]Condition A was applied. [c]Condition B was applied. [d]Aryl bromide was used instead of aryl iodide with $Pd(OAc)_2$ (10 mol%) as the catalyst, 1,4-dioxane as the solvent, while other reaction parameters were the same as **Condition A**. [e]The reaction was performed on a 5.0 mmol scale. [f]Reaction temperature was increased to 100 °C. [g]4.0 equiv of **2A** was applied.

(**4j**, **4l** and **4q**), chloro (**4t** and **4C**), bromo (**4m**, **4z** and **4K**), methoxy (**4h**, **4s**, **4t**, **4B**, **4D**, **4J** and **4M**), benzyloxy (**4c**, **4i**, **4u** and **4v**), TBS-protected hydroxy (**4d**), nitro (**4n**), trifluoromethyl (**4g** and **4G**), carbonyl (**4H**), ester (**4e**, **4f**, **4o**, **4u**, **4v** and **4I**), and amide (**4p** and **4L**) groups, were compatible with the reaction conditions. Notably, the acidic α-CH of the carbonyl group in **1e** and **1H** as well as NH in aryl amides **1p** and **1L** (which were nucleophilic under basic conditions to react with MeI)[28] were well tolerated in the reaction. In addition, the use of densely functionalized aryl iodides **1t** and **1u** as starting materials led to penta-substituted aromatics **4t**–**u** in excellent yields. As to **1v**, since the acetonalide-embeded lactone motif was unstable under basic conditions, the corresponding penta-substituted arene **4v** was only isolated in 47% yield. Importantly, various heteroaryl iodides (**1A**–**D**) were also suitable substrates to this methylation process. Notably, this procedure was scalable as demonstrated by the methylation of 1-iodonaphthalene (**1y**), which was successfully performed on a 5.0 mmol scale to afford the product **4y** in 92% yield (1.23 gram) (Table 1A). It is worth mentioning that the reactions of aryl iodides without *ortho* substituents (**1E**–**M**) led to the dimethylation products (**4E**–**M**), while 4.0 equiv of **2A** should be used correspondingly (Table 1B). For example, iodobenzene (**1E**) and 3-methoxy iodobenzene (**1M**) reacted with **2A** and **3** smoothly to provide the *bis*-methylated products **4E** and **4M** in 79% and 78% yields, respectively. More importantly, besides the success of *ortho* C-H methylation of aryl iodides, aryl bromides were also identified as the suitable substrates for this transformation, eg. **4y**, **4A**, **4E** and **4K**. This is an intriguing and practical feature since such kind of Catellani reactions were rarely reported.[25c]

Besides **2A**, we found that another inexpensive methylation reagent trimethylphosphate ($PO(OCH_3)_3$, **2B**)[20k] was also competent for this transformation, as exemplified by the formation of methylated products **4d**, **4f**–**j**, **4n**, **4q**, **4r**, **4w**, **4x**, and **4A**–**C** in 41–90% yields (Table 1A). Especially for heteroaryl iodides **1B** and **1C**, the methylated products (**4B** and **4C**) were obtained in excellent yields while applying **2B** as the methylating reagent. Nevertheless, a modification of the reaction condition was required when **2B** was used instead of **2A**, which included applying $Pd(OAc)_2$ (10 mol%) as the catalyst, TFP (22 mol%) as the ligand, NBE (**N^1**, 2.0 equiv) as the mediator, and DMA as the solvent (0.1 M) (Table 1A, **Standard Condition B**).

Table 2. Scope of Aryl Iodides that Undergo Methylation with CD_3OTs.[a]

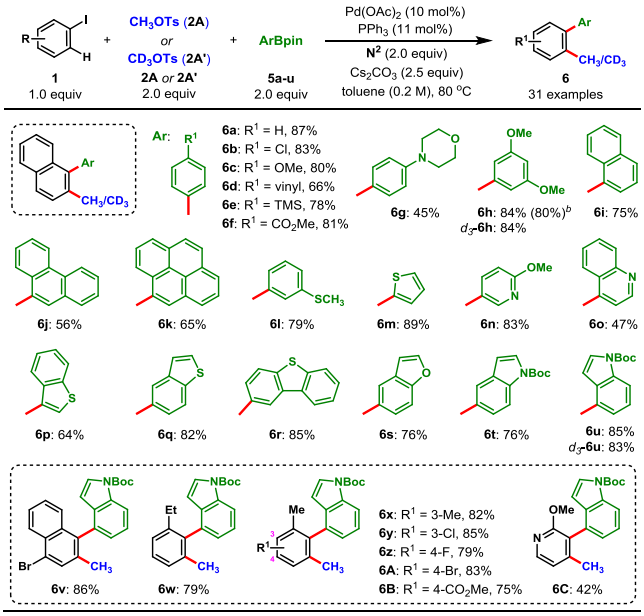


[a]All reactions were performed on a 0.2 mmol scale. Isolated yields were reported. [b]4.0 equiv of **2A′** was applied.

Due to the value of labeled methyl groups in medicinal chemistry,[4] we examined whether this approach could be applied to introduce CD_3 to arenes, utilizing commercially available CD_3OTs (**2A′**)[29] as the methylation reagent. To our delight, **2A′** showed very similar reactivity as **2A** under **Standard Condition A** (Table 2). The cross-coupling of **2A′** with *ortho* substituted aryl iodides (**1**) and olefin (**3**) afforded the corresponding deuterated methylation products (**4a′**–**4j′**) in good to excellent yields (70-96%). The structure of **4f′** was unambiguously assigned by X-ray crystallographic analysis (CCDC 1935063). For aryl iodides without *ortho* substituents, the corresponding deuterated dimethylation product **4k′**–**4n′** were obtained in 52–92% yields. Given the availability and low cost of **2A′**, our method provides a practical and affordable access to CD_3-functionalized arenes.[4]

Following the success of terminating the methylation-involved Catellani procedure through a Heck reaction, we proceeded to examine other types of termination methods, therefore expanding the utility of this methylation strategy. Considering the wide accessibility of arylboronic acids and their derivatives, we investigated the Suzuki–Miyaura termination.[33] Just through minor modifications of the previous Heck termination **Standard Condition A** of Table 1 (see **Table S3** of Supporting Information for details), we found a large group of pinacol arylborates (**5a**–**u**) could be utilized to react with 1-iodonaphthalene (**1y**) and **2A**, providing the *ortho*-methylated unsymmetrical biaryls (**6a**–**u**) in moderate to good yields (45–89%) (Table 3). It is noteworthy that this procedure possessed excellent functional group tolerance as to pinacol arylborates. For example, chloro (**6b**), methoxy (**6c**, **6h** and **6n**), vinyl (**6d**), trimethylsilyl (**6e**), ester (**6f**), morpholino (**6g**) and methylthio (**6l**) groups were compatible with the reaction conditions. More importantly, various pinacol heteroarylborates (**5m**–**u**) were also proved to be suitable terminating reagents, which include thiophene, pyridine, quinoline, benzothiophene, dibenzothiophene, benzofu-

Table 3. Catellani-type Methylation Terminated by Suzuki Coupling.[a]

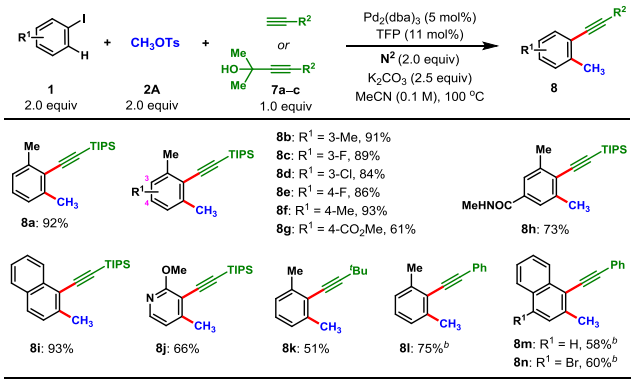


[a]All reactions were performed on a 0.2 mmol scale. Isolated yields were reported. [b]The reaction was performed on a 4.0 mmol scale.

ran, and indole motifs that are ubiquitous and essentially important in small molecule drug discovery.[34] Meanwhile, the scope of aryl iodide (**1**) was further probed, with **2A** and arylborate **5u** as the methylating and terminating reagent, respectively. Just as expected, eight different aryl iodides including one hetero-aryl iodide reacted with **2A** and **5u** smoothly to provide the corresponding *ortho*-methylated unsymmetrical biaryls (**6v**–**6C**) in moderate to good yields (42–86%). It is worthwhile mentioning that the deuterated version of methylation was tested on arylborates **5h** and **5u**, with **1y** and **2A′** as the reaction partners. Again, the reactions took place uneventfully to afford the products d_3-**6h** and d_3-**6u** in 84% and 83% yield, respectively (Table 3). Notably, a scale-up operation (4.0 mmol) of this methylation procedure was successfully performed to obtain 0.89 gram of product **6h** (80% yield), with no notable decrease in yield.

Next, we investigated this Catellani-type methylation process using Sonogashira coupling as the *ipso*-termination process.[35] As shown in Table 4, various aryl iodides **1** could react soomthly with **2A** and the terminating reagent (triisopropylsilyl)acetylene (**7a**) under slightly modified reaction conditions compared to **Standard Condition A** of Table 1 (see **Table S4** of Supporting Information for details), that included the switch to a medium strong base K_2CO_3, an increase of the reaction temperature to 100 °C and lowering the reaction concentration. A series of *ortho*-methylated phenylacetylenes (**8a**–**j**) were obtained in good to excellent yields (61–93%). Besides **7a**, *t*-butyl acetylene (**7b**)[35c] and 2-methyl-4-phenylbut-3-yn-2-ol (**7c**)[35b] were also suitable termination reagents, providing the corresponding products (**8k**–**n**) in 51–75% yields. Notably, while **7c** was used, the stronger base Cs_2CO_3 should be employed to promote the reaction efficiency.

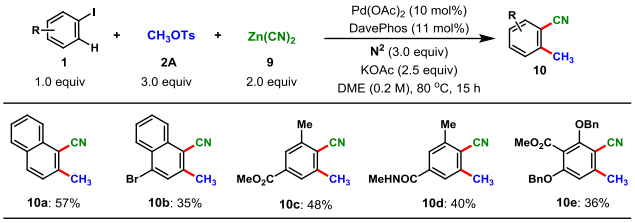
Table 4. Catellani-type Methylation Terminated by Sonogashira Coupling.[a]



[a]All reactions were performed on a 0.2 mmol scale. Isolated yields were reported. [b]2-methyl-4-phenylbut-3-yn-2-ol was applied as the terminating reagent, and Cs_2CO_3 was used as the base correspondingly.

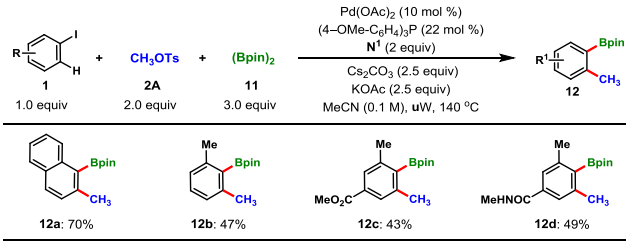
Additionally, the more challenging *ipso*-cyanation,[25b,36] *ipso*-borylation[37] and *ipso*-hydrogenation[38] terminations were also demonstrated applicable to this *ortho*-methylation approach (Table 5–7). As to *ipso*-cyanation termination, $Zn(CN)_2$ (**9**)[36] was identified as the ideal reagent. After a careful modification of the reaction conditions (see **Table S5** of Supporting Information for details), aryl iodides (**1**) were able to react with **2A** and **9** to deliver the desired *ortho*-methylated benzonitrile products (**10a**–**e**) in 35–57% yields (Table 5). For *ipso*-borylation

Table 5. Methylation Terminated by Cyanation.[a]



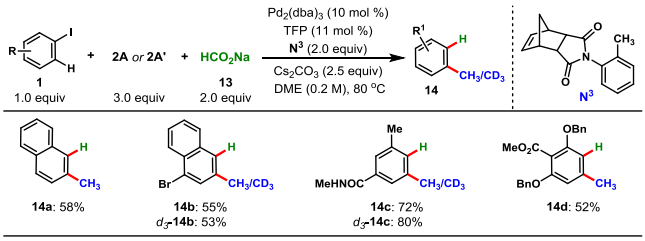
[a]All reactions were performed on a 0.2 mmol scale. Isolated yields were reported.

Table 6. Methylation Terminated by Borylation.[a]



[a]All reactions were performed on a 0.2 mmol scale. Isolated yields were reported.

Table 7. Methylation Terminated by Hydrogenation.[a]

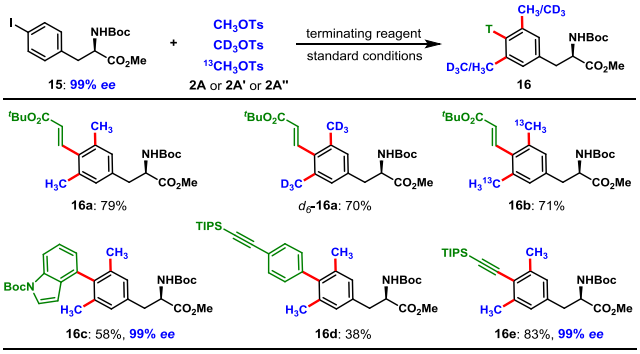


[a]All reactions were performed on a 0.2 mmol scale. Isolated yields were reported.

termination, $(Bpin)_2$ (**11**)[37] was chosen as the reagent. Similarly, modification of the reaction conditions was required to promote this transformation (see **Table S6** of Supporting Information for details). Under the microwave-driven conditions, aryl iodides (**1**) reacted with **2A** and **11** to deliver the *ortho*-methylated pinacol arylborates (**12a**–**d**) in 43–70% yields (Table 6). Remarkably, the incorporated Bpin function in **12a**–**d** would enable them to access a diverse range of important aromatics.[37a] As to *ipso*-hydrogenation termination, sodium formate (HCO_2Na, **13**)[38c] was identified as the optimal hydride donor. After minor modifications of **standard condition A** of Table 1, including the employment of the novel mediator **N**^{339} and a solvent change to DME (see **Table S7** of Supporting Information for details), aryl iodides (**1**) reacted smoothly with **2A** and **13** to deliver the desired *meta*-methylated arenes (**14a**–**d**) in moderate to good yields (52–72%). Correspondingly, when **2A′** was used as the methylating reagent, the *meta*-trideuteriomethylated arenes d_3-**14b** and d_3-**14c** were obtained in 53% and 80% yield, respectively (Table 7).

The inherent value of our dual-tasked C-H methylation strategy was showcased by its applicability to bio-relevant substrates (Table 8 and Scheme 1). As depicted in Table 8, when the derivative of enantiopure 4-iodophenylalanine **15** (99% *ee*) was subjected to these aforementioned protocols, six bismethylated derivatives of phenylalanine (**16a**–**e** and d_6-**16a**) were readily prepared in 38–83% yields. For example, **15** reacted

Table 8. Methylation of Biologically Important Substrate.[a]

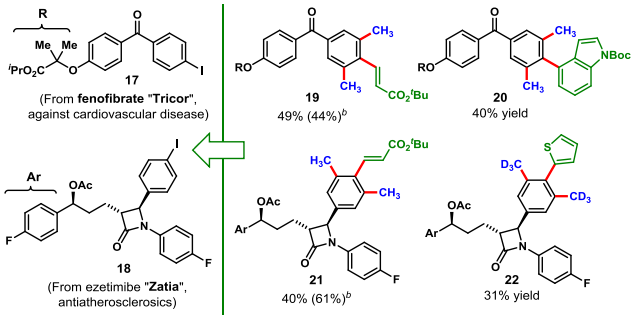


[a]All reactions were performed on a 0.2 mmol scale, and 4.0 equiv of methylating reagent was applied. Isolated yields were reported.

well with **2A** or deuterated **2A′** or ^{13}C labeled $^{13}CH_3OTs$ (**2A″**) [31] to afford **16a** as well as its isotope labeled siblings d_6-**16a** and **16b** in good yields, while using olefin **3** as the terminating reagent. In addition, Suzuki and Sonogashira coupling could also be applied as the termination strategies to further diversify the bismethylated phenylalanine, as exemplified by the formation of **16c**–**e** in moderate to good yields. It is noteworthy that these reactions proceeded with complete stereo-retention to afford the corresponding products (**16c** and **16e**) with 99% *ee*, which is very important for future applications of these novel unnatural *α*-amino acid derivatives in biological and medicinal studies.

Furthermore, we applied this dual-tasked C-H methylation toolbox for late-stage functionalization[40] of medicinal agents. Aryl iodides **17** (from antihyperlipidemic drug **fenofibrate** "**Tricor**")[41] and **18** (from antiatherosclerosics drug **ezetimibe** "**Zatia**")[41] were selected as the representatives for modification (Scheme 1). Three *bis*-methylated derivatives (**19**–**21**) and one deuterated *bis*-methylated derivative (**22**) were readily generated in 31%–61% yields, using Heck (with **3**) or Suzuki (with **5m** or **5u**) termination. These examples revealed the potential and modularity of our method in bioactive molecules late-stage functionalization and diversity-oriented synthesis[42] to quickly generate a wide variety of *ortho*-methylated bioactive arenes, which will surely facilitate the related structure–activity relationship (SAR) study in drug discovery.

Scheme 1. Late-stage Modification of Medicinal Agents.[a]



[a]All reactions were performed on a 0.2 mmol scale, and 4.0 equiv of methylating reagent was applied. Isolated yields were reported. [b]Trimethylphosphate (**2B**) was used instead of **2A**, and the reaction conditions changed accordingly.

Conclusion

We have developed a dual-tasked methylation based on palladium/NBE cooperative catalysis. Readily available (hetero)aryl iodides and inexpensive MeOTs or trimethylphosphate are utilized as the substrates and the methylating reagent, respectively. Six types of *ipso* terminations including Heck, Suzuki, Sonogashira, cyanoation, borylation and hydrogenation, can modularly couple with this *ortho* C-H methylation, thereby constituting a versatile methylation toolbox for preparing diversified methylated arenes. This strategy features inexpensive methyl sources, excellent functional-group tolerance, simple reaction procedures, and scalability. Importantly, it can be uneventfully extended to isotope-labeled methylation by switching to the corresponding reagents CD_3OTs or $^{13}CH_3OTs$. Moreover, this toolbox can be applied to late-stage modification of bio-relevant substrates with complete stereo-retention. These salient and practical features of our dual-tasked methylation toolbox will undoubtedly be welcomed by academic and industrial researchers.

ASSOCIATED CONTENT

Supporting Information. Experimental details, spectra, and X-ray crystallography. This material is available free of charge via the Internet at http://pubs.acs.org.

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