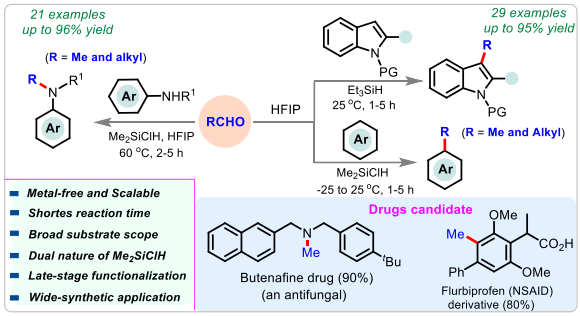
Silane-mediated, Facile and Selective C(sp²)−H and *N*−Methylation using Formaldehyde

Jabir Khan, Neha Taneja†, Naveen Yadav†, Chinmoy K. Hazra*

ABSTRACT: The use of (*para*)-formaldehyde for the selective reductive methylation of C(sp²)−H and N−H bonds, utilizing a combination of silane and hexafluoroisopropanol (HFIP) as activators, is reported. Overcoming the complexity of C(sp²)−H methylation on aryl and heteroaryl substrates, the process utilizes Friedel–Crafts alkylation, followed by silane as a hydride donor under mild acidic medium. The developed protocol offers a promising avenue for converting amines into their monomethylated counterparts with excellent yields. Mechanistic insights into the reductive methylation process are provided, highlighting the role of silane and HFIP in achieving good selectivity. This scalable transformation is well-suited for general alkylation using various non-activated aliphatic aldehydes under mild conditions in a shorter reaction time and is also adaptable for the late-stage methylation of pharmaceuticals and natural products. Notably, the method has been successfully employed for the efficient synthesis of the antifungal drug Butenafine and non-steroidal anti-inflammatory drug (NSAID) Flurbiprofen derivative.



KEYWORDS: *Methylation, Reductive Friedel–Crafts alkylation, (para)-Formaldehyde, Silane, hexafluoroisopropanol.*

The primary underpinning of organic synthesis revolves around the C−H functionalization.[1] In this context, C(sp²)–H and N–H alkylation have been cornerstones in executing intricate chemical synthesis. Consequently, Friedel–Crafts alkylation manifests itself as a quintessential method for C(sp²)–H alkylation, which is important in industry and academia.[2] In particular, C–H and N–H methylation hold significant importance as the "magic methyl" effect becomes coveted in medicinal chemistry. This is evident in the development of the FDA-approved anticancer drug Tazemetostat, where the addition of methyl groups to precursors **A**–**D** resulted in a significant potency increase (IC_{50}) of 10-fold or more (Figure 1). Tazemetostat functions by inhibiting enhancer of zeste homolog 2 (EZH2).[3]

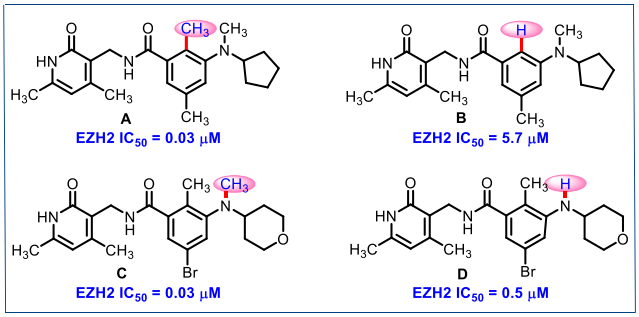


Figure 1. The "magic methyl" effect during the discovery of Tazemetostat.

While Friedel−Crafts C(sp²)–H alkylation demonstrates remarkable utility, it does exhibit limitations, including the requirement for harsh and strict anhydrous conditions and the generation of a mixture of products during alkylation. However, new advances in this research area are also being made, including the use of methylating agents such as methanol[4] CO_2,[5] metal-catalyzed cross-coupling[6] Friedel−Crafts benzylation and allylation,[7] and metal-catalyzed C−H activation.[8] Recently Oestrich group achieved the C(sp²)–H methylation with methanol (Scheme 1A).[4] In 2015 Parnes reported the thiol-promoted alkylation using aldehydes (Scheme 1B).[7a] C−H methylation of heteroarene using CO_2/H_2 under boron-assisted cobalt catalyzed reaction has been recently published by the Shi group (Scheme 1C).[5b] Lately, employing methanol faces challenges due to its higher dehydrogenative activation barrier,[9] and utilizing benign CO_2 remains a significant challenge due to the thermodynamic stability of the parent molecule.[10]

Conventional methods for amine methylation typically involve activated methyl groups like toxic methyl iodide,[11] dimethyl sulfoxide,[12] or dimethyl carbonate.[13] While transition-metal-catalyzed methylation is efficient and cost-effective, its applicability is limited.[14] A move towards sustainable chemistry involves using more environmentally friendly reagents such as MeOH,[15] CO_2,[16] HCOOH,[17] (*para*)-formaldehyde[18] as the carbon source for methylation achieving selectivity in alkylation under sustainable conditions remains an ongoing challenge. The Ru-catalyzed methylation using methanol as a C1 source for the selective mono-methylation of amines has been shown by Hong *et al.* (Scheme 1D).[15a] A straightforward efficient, mild chemical system that facilitates both C–H and N–H methylation has not yet been reported. Addressing economic and environmental concerns, we present our investigation into using (*para*)-formaldehyde with silane as a reductant combined with HFIP for

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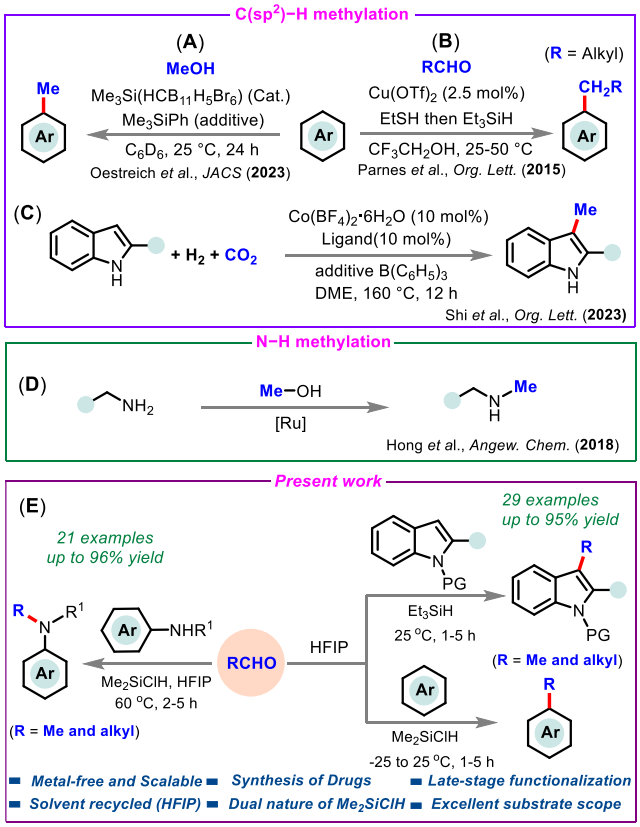
efficient C(sp^2)–H and N–H methylation of arenes and heteroarenes (Scheme 1E).

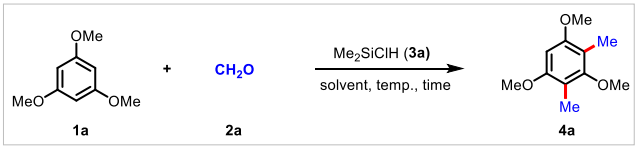
This novel transformation relies on HFIP-assisted *in situ* generated activated complex of the (*para*)-formaldehyde with silane under mildly acidic conditions and further utilizes Me_2SiClH as a hydride source resulting in methylation. HFIP is crucial in ensuring reaction selectivity and preventing over-methylation, owing to its hydrogen-bond donation ability (HBD).[19] Apart from methylation, this reaction is also suitable for C– and N–alkylation using various aliphatic aldehydes and is compatible with various functional groups. This transformative process eliminates the need for toxic methylating reagents and can be applied directly for the methylation of essential biologically active compounds and simultaneously gave easy access to the antifungal drug Butenafine and NSAID Flurbiprofen derivative.



Scheme 1. Reported method for the selective methylation/alkylation (**A**→**D**) and **E** (*this work*).

RESULTS AND DISCUSSION: C(sp^2)–H methylation is rather challenging over N–H methylation. To establish the optimal reaction conditions for C–methylation, we commenced our investigation using 1,3,5-trimethoxybenzene (**1a**) as a model substrate in the presence of (*para*)-formaldehyde (CH_2O, **2a**) and dimethylchlorosilane (Me_2SiClH, **3a**) as a reducing agent with HFIP as solvent (Table 1). First, we screened the reaction at room temperature and under heating conditions (60 °C) and found some traces of methylated product with nonspecific decomposition in the reaction (Table 1, entries 1 and 2). However, lowering the temperature from 0 °C to -25 °C could give promising results with a yield up to 40% (Table 1, entries 3 and 4). Screening of other solvents, such as $PhCF_3$, DCE, and TFE, revealed HFIP to be the most effective solvent for this transformation (Table 1, entries 5–7). To further improve the yield, we modulated the mole ratio of (*para*)-formaldehyde and witnessed a significant rise in the yield of **4a** with 5.0 equiv. (Table 1, entry 8). However, any subsequent elevation to 10.0 equiv. was found to have a detrimental effect on the reaction (Table 1, entry 9). Silanes such as Et_3SiH and Ph_3SiH were found to be inappropriate for the titled methylation (Table 1, entries 10 and 11). In the absence of Me_2SiClH, no product was observed under otherwise standard conditions (Table 1, entry 12). Reaction time is also an important parameter, and up to 84% yield of **4a** was achieved after 2 h (Table 1, entry 13).

Table 1. Variation of the Reaction Conditions[a]



Entry	2a	Solvent	Temp. (°C)	% Yield of 4a
1	3.0 equiv.	HFIP	rt	Trace
2	3.0 equiv.	HFIP	60	Trace
3	3.0 equiv.	HFIP	0	20
4	3.0 equiv.	HFIP	-25	40
5	3.0 equiv.	$PhCF_3$	60	Trace
6	3.0 equiv.	DCE	60	Trace
7	3.0 equiv.	TFE	60	Trace
8	5.0 equiv.	HFIP	-25	86
9	10.0 equiv.	HFIP	-25	50
10[b]	5.0 equiv.	HFIP	-25	Trace
11[c]	5.0 equiv.	HFIP	-25	Trace
12[d]	5.0 equiv.	HFIP	-25	Trace
13[e]	**5.0 equiv.**	**HFIP**	**-25**	**84**

[a]Reaction conditions: **1a** (1.0 equiv., 0.2 mmol), **2a** (5.0 equiv., 1.0 mmol, M.W.: 30.02 as monomer), and **3a** (4.0 equiv., 0.8 mmol) in HFIP (0.5 mL) for 5 h. [b]Et_3SiH (4.0 equiv., 0.8 mmol). [c]Ph_3SiH (4.0 equiv., 0.8 mmol). [d]Without **3a**. [e]2 h. All are isolated yields. DCE = 1,2-dichloroethane, TFE = 2,2,2-trifluoroethanol, $PhCF_3$ = trifluorotoluene and HFIP = 1,1,1,3,3,3-Hexafluoro-2-propanol.

Having identified the optimized reaction conditions, we first assessed the scope of C–H methylation reactions of a range of arenes and heteroarenes (**1b**–**1t**). When treated with 1,2,4-trimethoxybenzene with (*para*)-formaldehyde (**2a**) in the presence of Me_2SiClH in HFIP at -25 °C, this compound was observed to be completely selective for the mono-methylation and gave **4b** in 95% yield as compared to the methylation of **1a**. This underlines the effect of the substitution pattern in this transformation. Replacement of 3-OMe with the less bulky and electron-donating methyl group shows good reactivity at room temperature and selectively afforded the tri-methylated product

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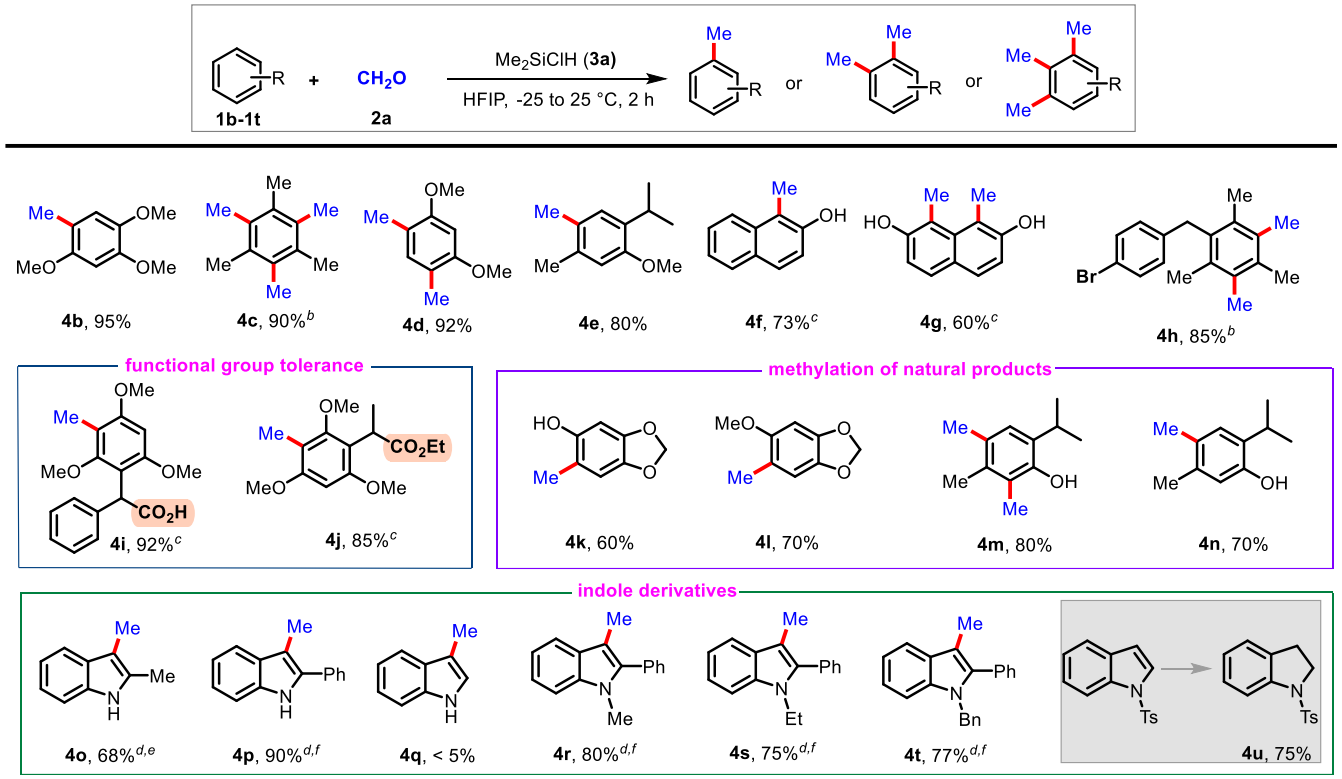
4c in 90% yield. 1,3-Dimethoxy benzene (**1d**) was preferentially alkylated twice to give the product **4d**. The reaction of 1-isopropyl-2-methoxy-4-methylbenzene with CH_2O regioselectively gave the mono-methylated product **4e** in good yield. Despite increased stearic hindrance, naphthalen-2-ol and naphthalen-2,7-diol selectivity furnished the corresponding α-methylated products **4f** and **4g** respectively. Structurally complex mesitylene analogue serve as excellent substrate for the methylation and selectively provided the multi-functionalized benzene core motif **4h** in 85% yield. Similarly, 2,4,6-trimethoxy benzene with an additional acid or ester functional groups performed well and delivered the selective mono-methylated products **4i** and **4j** respectively in excellent yields. Delightfully, our designed protocol worked well for the late-stage methylation of naturally occurring antidepressant Sesamol and its methoxy derivative led to selective mono-methylated products **4k** and **4l** respectively. Similarly, natural anti-oxidant Thymol underwent smooth methylation to afford the di-methylated product **4m** in 80% yield. Interestingly, reducing the amount of (*para*)-formaldehyde to 3.0 equiv. improved selectivity for mono-methylation yielding **4n** with 70% yield.

Searching for heteroarenes suitable for methylation, we became interested in the medicinally privileged core motif of indoles.[20] Moreover, achieving the direct and selective C–3 alkylation of indoles proves to be a surprisingly challenging transformation, as reactions with simple alkyl halides are synthetically unproductive.[21,22] Indoles substituted with the electron-donating and bulky group such as–Me and–Ph on the C–2 position smoothly methylated to deliver the corresponding mono-methylated products **4o** and **4p** respectively. The reaction of **1o** (2-phenyl-1*H*-indole) could be performed on a useful scale of 3.0 mmol only with a slight decrease in the yield of **4p** (82%, *see SI page S23*). Note that the parent indole failed to undergo methylation and produced a trace amount of products. The *N*–methyl, *N*–ethyl and *N*-benzyl indoles were efficiently mono-methylated to the respective products **4r**–**4t**. However, *N*-Ts indole did not participate in the methylation rather it performed partial reduction of the five-member ring by the silane to give **4u** (75%).

Table 2. Substrate Scope for C−H Methylation of Arenes[a]



[a]Reaction conditions: Ar-H (1.0 equiv., 0.2 mmol), **3a** (4.0 equiv., 0.8 mmol), and CH_2O (5.0 equiv., 1.0 mmol, M.W.: 30.02 as monomer) in HFIP solvent (0.5 mL) at -25 °C. [b]25 °C, 5 h. [c]-10 °C. [d]Et_3SiH (4.0 equiv., 0.8 mmol). [e]5 h. [f](formalin, 37% solution in H_2O, 15 µL).

To expand the applicability of our devised methodology, we implemented the standard optimized conditions for N–H methylation as well. Subsequently, we further optimized the reaction conditions for the selective C–N bond formation (*see Table S1 in the SI page 6*). We explored the reactivity of electron-rich and electron-deficient amines with (*para*) formaldehyde as methyl source with Me_2SiClH as a reductant in HFIP at 60 °C. Anilines bearing electron-withdrawing functional groups at the *para* position, *viz.* –CN/–NO_2/–Br and –COOMe, exhibited a preference for mono-*N*–methylation under optimized reaction conditions, yielding major products **5a**–**5d** with up to 75% yield, showcasing remarkable functional group tolerance. Additionally, minor products, *N*, *N*-dimethylated compounds **6a**–**6d**, were also obtained in lower yields. Nevertheless, 4-phenoxy aniline, being electronically rich, demonstrates superior selectivity for mono-*N*–methylation, yielding product **5e** with 85% yield. The reaction of di-(-Cl, -Me) or tri-(-OMe) substituted

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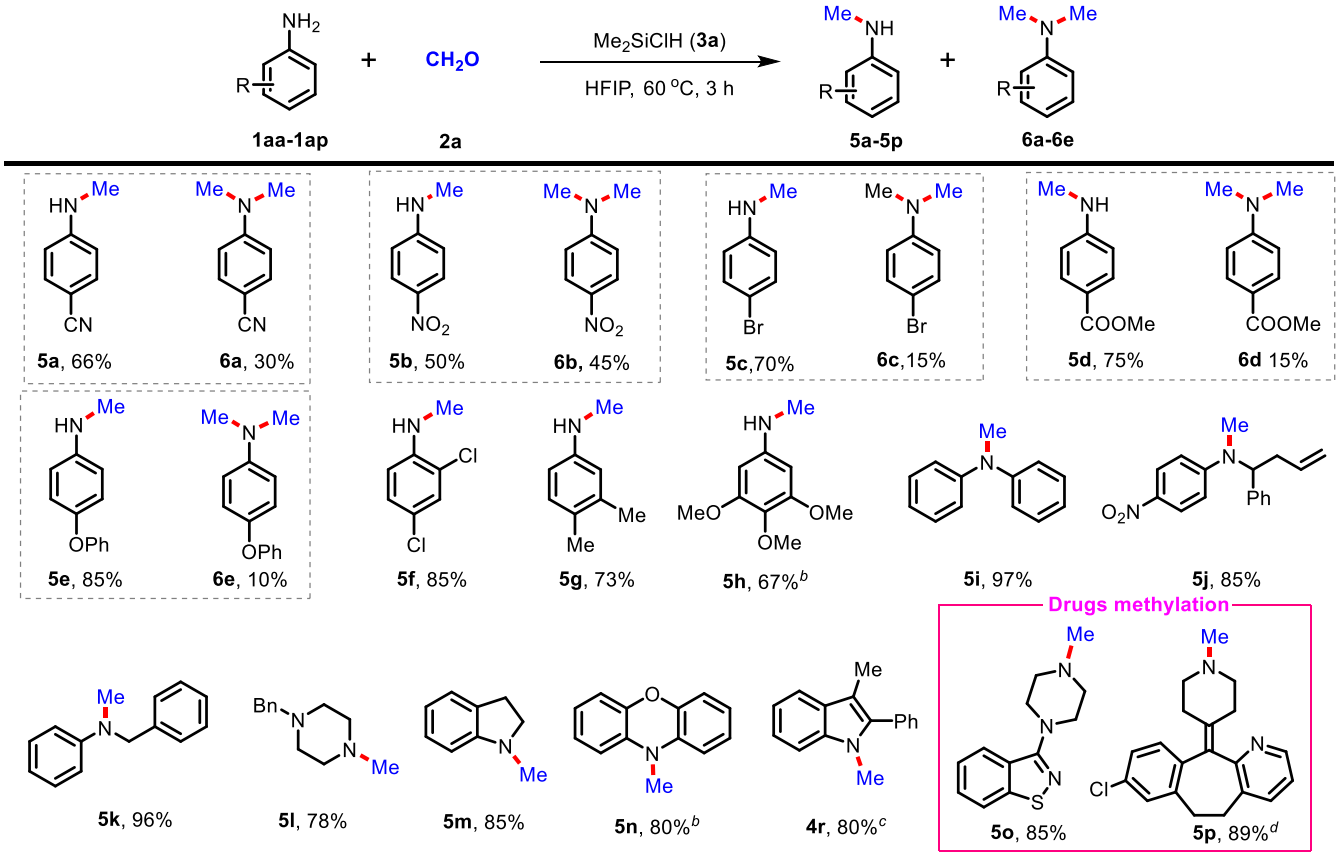
anilines with (*para*)-formaldehyde, regioselectively afforded the mono-methylated products **5f**, **5g,** and **5h** respectively in 67–85% yields displaying tolerance to both steric and electronic variations. It is worthy of note that the presented N–H methylation was found to be compatible with secondary anilines. We selectively obtained mono-methylated products from diphenylamine, 4-nitro-*N*-(1-phenylbut-3-en-1-yl) aniline, and *N*-benzyl aniline derivatives (**5i**–**5k**) with yields ranging from 85-97%. The magnificent performance of CH_2O with silane in HFIP was further highlighted by the *N*–methylation of medicinally privileged heterocyclic compound *viz.* 1-benzylpiperazine, indoline, and 10*H*-phenoxazine, which afforded corresponding products **5l**–**5n** in high yields and selectivity. The direct *N*-methylation of indole is challenging without using any base. However, to our delight, 3-methyl-1*H*-indole smoothly reacted with CH_2O (37% solution in H_2O) to afford the corresponding *N*-methylated indole **4r** in 80% yield. Finally, we examined the viability of this N–H methylation strategy for the late-stage functionalization of hetrocylic 3-(piperazine-1-yl) benzo[d]isothiazole (Lurasidone fragment) and 8-chloro-11-(piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo [5,6] cyclohepta[1,2-b] pyridine (Desloratadine), which regioselectively participated in the reaction and furnished the mono-*N*-methylated amines **5o** and **5p** respectively in excellent yields.

Table 3. Substrate Scope for N−H Methylation of Arenes[a]



[a]Reaction conditions: Amines (1.0 equiv., 0.2 mmol), Me_2SiClH (2.0 equiv., 0.4 mmol), and CH_2O (3.0 equiv., 0.6 mmol, M.W.: 30.02 as monomer) in HFIP solvent (0.5 mL) at 60 °C. [b]-10 °C. [c]Et_3SiH ((2.0 equiv., 0.4 mmol)) with formalin (37% solution in H_2O, 18 µL) at 25 °C. [d]Et_3SiH (2.0 equiv., 0.4 mmol) at 60 °C.

The serendipitous advancement of this methylation using paraformaldehyde and displaying remarkable versatility, prompted us to contemplate the potential for conducting broad C– and N–alkylation reactions (Table 4). Initially, we examined the particularly demanding C(sp^2)–H alkylation of 1,3,5-trimethoxybenzene, exploring various aldehydes beyond (*para*)-formaldehyde. Gratifyingly, reactions conducted under the established conditions with extended acetaldehyde (**2b**), propionaldehyde (**2c**), *n*-butyraldehyde (**2e)**, and enlarged aldehyde (isobutyraldehyde (**2d**) proficiently delivered the corresponding alkylated products with high selectivity (**7a**–**7d,** 73-81%). Considering the biological importance of *N*-containing heteroarene, we next studied the C-alkylation of Sesamol (a natural organic compound that is a component of sesame seeds and sesame oil) and indoles. The parent Sesamol and indole successfully underwent C-butylation resulting in **7e** and **7f**, respectively. Furthermore, indoles bearing an *N*-methyl group were found to be compatible with *n*-butyraldehyde (**2e**), acetaldehyde (**2b**), and isobutyraldehyde (**2d**), yielding exclusively the C-monoalkylated products (**7g**–**7i**, 60-75%). Finally, we witnessed the *N*-alkylation of arenes and heteroarenes under standardized conditions. 4-Bromoaniline seamlessly reacted with isobutyraldehyde and

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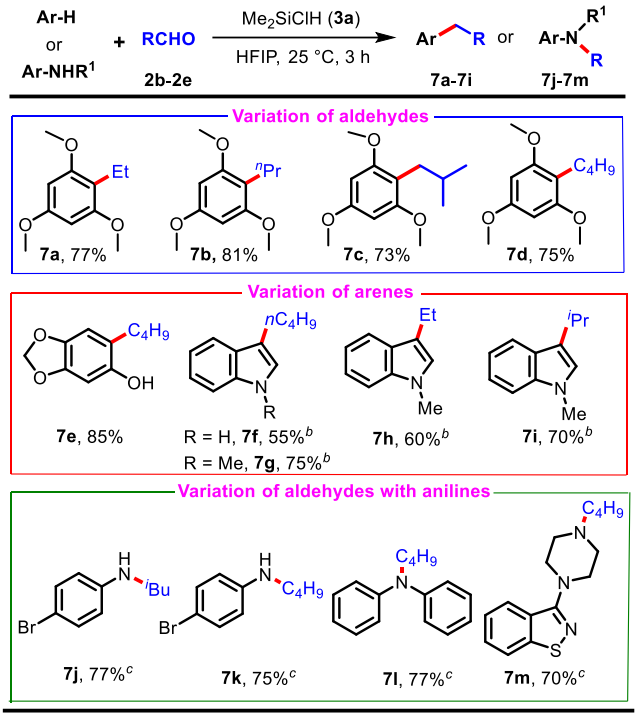
butyraldehyde to furnish **7j** and **7k** respectively, products that serve as excellent substrates for cross-coupling reactions. Particularly noteworthy was the effective butylation of sterically hindered and structurally complex amines, resulting in the exclusive production of mono-*N*–alkylation compounds **7l** and **7m.**

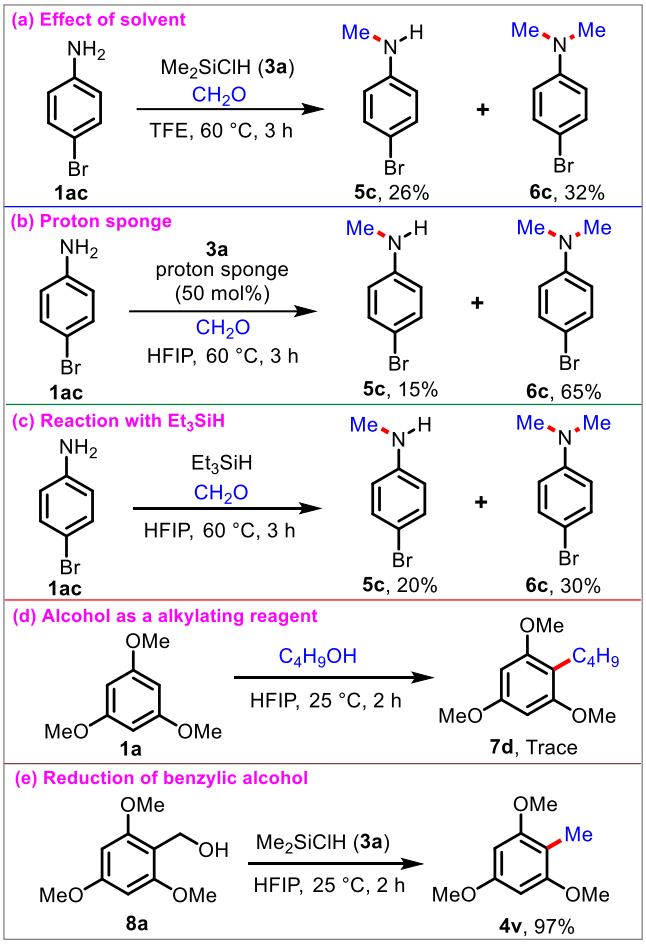
Table 4. Substrate Scope for C−H/N−H Alkylation[a]



[a]Reaction condition: Ar-H (1.0 equiv., 0.2 mmol) or Ar-NHR[1] (1.0 equiv., 0.2 mmol), **3a** (2.0 equiv., 0.4 mmol), and RCHO (5.0 equiv., 1.0 mmol) in HFIP solvent (0.5 mL) at 25 °C. [b]Et_3SiH (2.0 equiv., 0.4 mmol). [c]60 °C.

Control experiments were conducted, as shown in Scheme 2, to probe the possible reaction pathway for the methylation approach. From our prior studies[23] and based on previous reports[19] we anticipated the role of the H-bond donation ability (HBD) of HFIP for the selective mono *N*–methylation of primary amines. We have performed the reactions of *p*-bromo aniline (**1ac**) and (*para*)-formaldehyde with Me_2SiClH at 60 °C in TFE (2,2,2-trifluoroethanol) as a solvent (Scheme 2a). We have observed that in comparison to HFIP, the reaction conducted in TFE exhibited significantly lower selectivity and yield. Further, the methylation of *p*-bromo aniline was carried out in the presence of a proton scavenger (*N*, *N*, *N'*, *N'*-tetramethyl-1,8-naphthalene diamine), and the formation of *N*, *N*-di-methylated product **6c** over the **5c** suggested the presence of acidic environment are crucial for the selective mono-methylation (Scheme 2b). Substituting Et_3SiH for the more acidic Me_2SiClH in the methylation of *p*-bromoaniline under optimized conditions produced the *N*, *N*-di-methylated product as the major one. This further clarified the essential role of a suitable acidic environment for achieving selective mono-methylation (Scheme 2c). To unravel the mechanistic details of C–methylation, we utilized alcohol as a C1 source instead of butanal under the same conditions. This led to the traces of C–alkylated **7d**, helping to eliminate the possibility of a conventional Friedel–Crafts mechanism (Scheme 2d). We subsequently confirmed the viability of the alkylation followed by a reduction in the context of C–methylation. Hence, we examined compound **8a** (an intermediate in FC alkylation) as a reactant under the optimized reaction conditions, yielding the desired methylated product in high yields. (Scheme 2e).

Scheme 2. Control Experiments[a]



[a]Reaction conditions: (a) **1ac** (0.2 mmol), **3a** (0.4 mmol), and CH_2O (0.6 mmol) in TFE. (b) **1ac** (0.2 mmol), **3a** (0.4 mmol), CH_2O (0.6 mmol), and proton sponge (1,8-Bis (dimethyl amino) naphthalene, 0.1 mmol) in HFIP. (c) **1ac** (0.2 mmol), Et_3SiH (0.4 mmol), and CH_2O (0.6 mmol) in HFIP. (d) **1a** (0.2 mmol) and C_4H_9OH (0.6 mmol) in HFIP. (e) **8a** (0.2 mmol), **3a** (0.4 mmol) in HFIP.

From these control experiments, we postulated the reaction mechanism for C–methylation and *N*–methylation. The first step for both reactions is the HFIP-assisted activation of (*para*)-formaldehyde (Figure 2a) either through the formation of imine[24] (*N*-methylation) or by the activated complex formation between (*para*)-formaldehyde and the silane (C-methylation). The resultant imine is rapidly reduced by the Me_2SiClH to form *N*-monomethylated aniline. Further, condensation of secondary aniline is not much supportive thus reducing the chances of over-methylation (Figure 2b). In the case of C–methylation, the

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activated formaldehyde, as evidenced by the downfield shift of the HFIP hydroxy group in Figure 2a, undergoes attack by the electron-rich arene to form species **A**. This process contrasts with the traditional Friedel–Crafts alkylation, which necessitates anhydrous conditions. After re-aromatization of species **A** to **B**, the removal of the leaving group occurs through the stabilization of the benzylic carbocation by the electronic cloud of the aromatic ring, facilitated by a resource.[25] This process leads to the generation of species **C**. Subsequently, species **C** undergoes reduction by hydride ions delivered by the silane to form the desired product (Figure 2c).

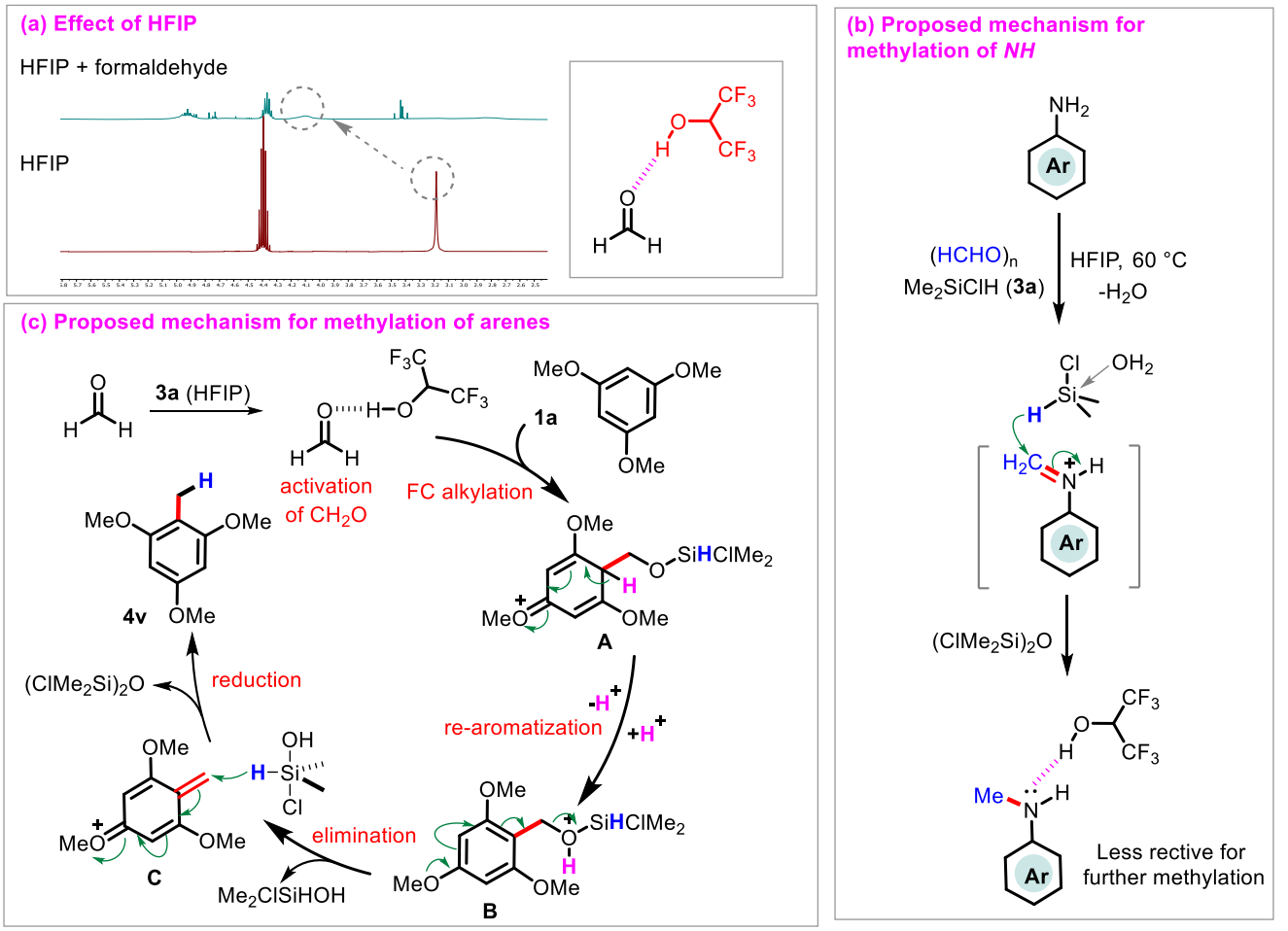
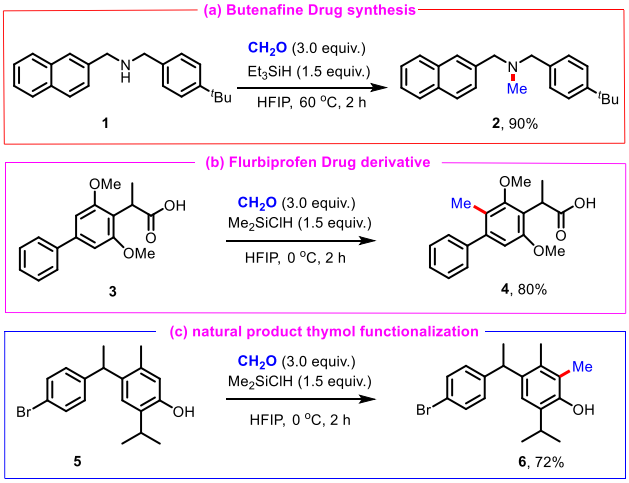


Figure 2. Proposed Reaction Mechanism.

We further demonstrated the strategic significance of our developed methodology by efficiently synthesizing established pharmaceutical compounds: Butenafine (**2**) (an antifungal) and Flurbiprofen (**4**, NSAID). The synthesis of Butenafine commenced with amide bond formation between 2-naphthoic acid and (4-(*tert*-butyl) phenyl) methanamine, followed by reduction to produce **1** (*see SI page 21*). Subsequently, *N*–methylation of **1** yielded **2** with 90% yield. For the synthesis of the non-steroidal anti-inflammatory drug Flurbiprofen derivative, we initiated the process with reductive arylation of pyruvic acid to form **3** (*see SI page 22*), which then underwent C–methylation to furnish **4** with an 80% yield. Methylating the heavily hindered alkyl-functionalized thymol **5** to produce its structurally more intricate analog **6**, with an overall yield of 72% exemplified the distinct behavior of the titled transformation.

Scheme 3. Synthesis of Drugs



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Conclusion: In summary, we devised an efficient, facile method for C–H methylation utilizing (*para*)formaldehyde as a C1 source and a combination of hydrosilane with HFIP. While formally enabling C(sp^2)–H methylation in arenes and heteroarenes (indoles), the present transformation effectively achieves the selective *N*–H methylation of anilines without employing any transition-metal catalysis and base. Mechanistic analysis highlights the pivotal role of HFIP coordination properties in achieving selectivity. Thus, owing to the common and environment-benign reagent for C–H and N–H alkylation at mild conditions, the titled transformation offers an easy-to-handle and scalable method for synthesizing densely functionalized aromatic molecules. This metal-free methylation provides a potentially appealing complement for the successful derivatization of complex natural products and the synthesis of targeted drugs in good yields.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http:// pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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