Theoretical Study for Evaluating and Discovering Organic Hydride Compounds as Potential Novel Methylation Reagents

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ABSTRACT: Methylation reaction is a fundamental chemical reaction that plays an important role in the modification of drug molecules, DNA, as well as proteins. This work focuses on seeking potential novel methylation reagents through a systematic investigation of the thermodynamics and reactivity of methyl-substituted organic hydride radical cations (XH⁺’s). In this work, 45 classical and important XH⁺’s were designed to investigate the relationship between their structure and reactivity, to find excellent or potential methylation reagents. The Gibbs free energy and activation free energy of XH⁺ to release the methyl radical in MeCN at 298.15 and 355 K are calculated with the density functional theory (DFT) method to quantitatively measure the reactivity of XH⁺ as a methylation reagent in this work. The relationships between structures and reactivities on XH⁺’s as methylation reagents are well examined. Since we have calculated the Gibbs free energy and activation free energy of trifluoromethyl-substituted organic hydride compound radical cations (X’H⁺’s) releasing trifluoromethyl radicals in MeCN with the DFT method in our previous work, accordingly, the relationship of thermodynamics and reactivity between X’H⁺ releasing trifluoromethyl radical and XH⁺ releasing methyl radical is discussed in detail. Excitingly, 4 XH⁺’s (1H⁺, 3H⁺~4H⁺, and 44H⁺) are found to be excellent methyl radical reagents, while 9 XH⁺’s (5H⁺, 6H⁺, 9H⁺, 10H⁺, 12H⁺, 13H⁺, 15H⁺, 43H⁺, and 45H⁺) are found to be potential methyl radical reagents in chemical synthesis. The molecular library and reactivity database of novel methylation reagents could be established for synthetic chemists to query and use. Our work may offer a theoretical basis and reference experience for screening different substituted organic hydride compounds (YRHs) as alkylation reagents.

1. INTRODUCTION

The introduction of the methyl group to drug molecules is helpful to improve their binding affinity, biological availability, and metabolic stability (called “magic methyl effect”), which greatly changes the pharmacological properties of bioactive molecules. Methylation plays an important role in the modification of drug molecules, DNA, as well as proteins. According to different reaction mechanisms, the methylation agents are divided into three classes, i.e., electrophilic methylation reagents, nucleophilic methylation reagents, and free radical methylation reagents. At present, great progress has been made in the methylation reaction. Many chemists have made outstanding contributions in this field, and a large number of new methyl reagents and new methylation reactions have been developed, especially electrocatalytic, visible-light-induced, or transition-metal-catalyzed methylation, in recent years. In 2021, Dixon and co-workers published an important review about C–H methylation in chemical synthesis, which covered the various methylation reagents and diverse strategies employed to realize the selective installation of the C–Me bond in extensive chemical structures. However, there still are challenges in the methylation process, including (1) developing milder, economic, and green methylation methods, and (2) achieving higher chemical selectivity as well as stereoselectivity. It is urgent and inspiring to develop novel and excellent methylation reagents to be used in various drug synthetic reactions or other chemical reactions.

Recently, various substituted organic hydride compounds, especially 4-substituted-Hantzsch esters, have been widely investigated as alkylation reagents in chemical reactions. Therefore, we initiated a project to evaluate and reveal the reactivities of substituted organic hydride compounds as alkylation reagents in chemical reactions two years back. It is well known that, for a chemical reaction, Gibbs free energy (∆G°) is the thermodynamic driving force, which reflects whether the reaction can happen or not, while activation free energy (∆G°a) is an important kinetic parameter that reflects the reaction rate. For substituted organic hydride compounds (XRH), XRH could be activated as XRH⁺ by single-electron oxidants, photocatalysts, or electrochemical conditions and the key step is the elementary step of XRH⁺ releasing R⁺ so the Gibbs free energy [∆G°RD(XRH⁺)] and the activation free energy [∆G°aRD(XRH⁺)] of the XRH⁺...
releasing the R-radical could be used to quantitatively measure the reactivity of XRH as the alkylation reagent (RD is an abbreviation for radical-donating in this work).

In 2020, we investigated the essential factors that determine whether a 4-substituted organic hydride radical cation (XRH$^{•+}$) is a great alkylation reagent and evaluated the reactivity of various XRH$^{•+}$s as alkylation agents (Scheme 1a). In 2021, we further evaluated the antioxidant reactivities of XRH$^{•+}$s with different substituents (Scheme 1b), and in 2022, we have calculated the Gibbs free energy [denoted as Δ$^{\circ}$G$_{RD}$ (XRH$^{•+}$)] (for 298 K) and Δ$^{\circ}$G′$_{RD}$ (XRH$^{•+}$) (for 355 K)] and the activation free energy [denoted as ΔG′′$_{RD}$ (XRH$^{•+}$)] (for 298 K) and ΔG′′′$_{RD}$ (XRH$^{•+}$) (for 355 K)] of 47 trifluoromethyl-substituted organic hydride compound radical cations (XH$^{•+}$) releasing the trifluoromethyl radical in MeCN at 298.15 and 355 K with the density functional theory (DFT) method (Scheme 1c). Fifteen XH$^{•+}$s with a 1,4-dihydropyridine structure and three XH$^{•+}$s with a 3,4-dihydropyrimidin-2-one structure are identified to be novel excellent and potential trifluoromethylation reagents, respectively, according to their reactivity data.

Inspired by Prof. Dixon’s review and our previous work, we continued to focus on seeking potential novel methylation reagents through systematic investigation of the thermodynamics and reactivities of methyl-substituted organic hydride radical cations (XH$^{•+}$) (Scheme 1d). Unlike trifluoromethyl-substituted 46H$^{•+}$ and 47H$^{•+}$ in our previous work, the transition states (TS) of methyl-substituted 46H$^{•+}$ and 47H$^{•+}$
could not be located. Therefore, in this work, 45 classical and important XH**'s (Scheme 2) were selected to investigate the relationship between their structures and reactivities, including effects of heteroatoms, substituents, conjugation in structure, etc., to find potential novel methylation reagents. The Gibbs free energy and the activation free energy of XH**'s to release the methyl radical in MeCN at 298.15–355 K are calculated with the DFT method in this work. The molecular library and the reactivity database of novel methylation reagents could be established for synthetic chemists for query and use.

### Table 1. ΔG°_{RD}(XH**), ΔH°_{RD}(XH**), ΔS°_{RD}(XH**), ΔG°_{RD}(XH**), ΔH°_{RD}(XH**), and ΔS°_{RD}(XH**) of XH** to Release the Methyl Radical in MeCN at 298.15 K as well as T°

| XH** | ΔG°_{RD}(XH**) | ΔH°_{RD}(XH**) | ΔS°_{RD}(XH**) | T (°C) |
|------|----------------|----------------|----------------|-------|
| 1H** | 15.63          | 1.33           | 16.94          | 42.18 |
| 2H** | 19.67          | 6.43           | 20.10          | 4.45  |
| 3H** | 14.88          | 1.36           | 16.26          | 4.60  |
| 4H** | 15.58          | 0.66           | 16.35          | 2.57  |
| 5H** | 15.84          | 4.20           | 17.97          | 7.13  |
| 6H** | 18.23          | 4.00           | 19.49          | 4.23  |
| 7H** | 18.39          | 5.25           | 19.38          | 3.32  |
| 8H** | 19.88          | 7.64           | 21.09          | 4.07  |
| 9H** | 18.34          | 4.51           | 19.24          | 3.01  |
| 10H**| 18.20          | 3.77           | 18.82          | 2.07  |
| 11H**| 18.95          | 5.28           | 20.22          | 4.27  |
| 12H**| 18.93          | 3.91           | 18.96          | 3.10  |
| 13H**| 18.91          | 3.69           | 19.30          | 1.31  |
| 14H**| 20.38          | 5.23           | 20.72          | 1.16  |
| 15H**| 18.83          | 2.67           | 19.56          | 2.45  |
| 16H**| 22.58          | 8.37           | 23.70          | 3.75  |
| 17H**| 22.15          | 7.96           | 23.32          | 3.90  |
| 18H**| 22.67          | 9.17           | 23.84          | 3.90  |
| 19H**| 22.92          | 10.45          | 24.18          | 4.21  |
| 20H**| 21.19          | 8.57           | 22.61          | 4.79  |
| 21H**| 28.25          | 16.02          | 29.69          | 4.86  |
| 22H**| 28.42          | 16.52          | 30.57          | 7.19  |
| 23H**| 20.21          | 8.06           | 21.88          | 5.62  |
| 24H**| 21.42          | 9.16           | 22.72          | 4.35  |
| 25H**| 27.49          | 14.61          | 28.03          | 4.82  |
| 26H**| 26.67          | 13.75          | 27.73          | 4.37  |
| 27H**| 26.33          | 13.31          | 27.68          | 4.53  |
| 28H**| 27.14          | 14.98          | 28.33          | 4.00  |
| 29H**| 24.94          | 11.40          | 25.68          | 2.47  |
| 30H**| 24.02          | 10.62          | 25.17          | 3.86  |
| 31H**| 26.84          | 13.80          | 27.72          | 2.98  |
| 32H**| 37.09          | 27.48          | 39.41          | 7.77  |
| 33H**| 24.63          | 10.49          | 25.30          | 2.25  |
| 34H**| 27.85          | 10.99          | 28.44          | 1.95  |
| 35H**| 27.46          | 11.08          | 27.86          | 1.32  |
| 36H**| 26.96          | 10.61          | 27.53          | 2.23  |
| 37H**| 32.01          | 19.47          | 32.49          | 3.17  |
| 38H**| 31.46          | 18.61          | 32.20          | 2.51  |
| 39H**| 34.22          | 22.49          | 35.35          | 3.77  |
| 40H**| 34.16          | 22.52          | 35.29          | 3.81  |
| 41H**| 30.90          | 12.96          | 31.39          | 1.64  |
| 42H**| 29.22          | 12.30          | 28.90          | 1.07  |
| 43H**| 16.59          | 4.25           | 16.91          | 1.07  |
| 44H**| 14.87          | 1.49           | 15.83          | 3.22  |
| 45H**| 16.72          | 4.81           | 18.03          | 4.39  |

"Refrsenotes the temperature when the Gibbs free energy is zero. ^Note: The units of ΔG°_{RD}(XH**), ΔH°_{RD}(XH**), ΔG°_{RD}(XH**), ΔH°_{RD}(XH**), and ΔH°_{RD}(XH**) are kcal/mol. ΔG°_{RD}(XH**) = [ΔH°_{RD}(XH**) − ΔG°_{RD}(XH**)]/T, with the unit being cal mol⁻¹ K⁻¹; ΔS°_{RD}(XH**) = [ΔH°_{RD}(XH**) − ΔH°_{RD}(XH**)]/T, with the unit being cal mol⁻¹ K⁻¹; T° refers to the temperature when ΔG° is zero, T° = ΔH°/ΔS°, with the unit being °C.

### 2. RESULTS AND DISCUSSION

Quantum chemical calculations and wave-function analyses in this work were performed using Gaussian 16, ORCA 4.1.1, 35,36 and MultiWFN 3.7. The detailed computation methods (including functionals, basis sets, solvent models, etc.) are given in the Supporting Information. Gibb
energies [denoted as $\Delta G_{RD}(XH^*)$] at 298.15 K and $\Delta G_{RD}(XH^*)$ at 355 K (b.p. of MeCN)], enthalpy changes [denoted as $\Delta H_{RD}(XH^*)$] at 298.15 K and $\Delta H_{RD}(XH^*)$ at 355 K], entropy changes [denoted as $\Delta S_{RD}(XH^*)$] at 298.15 K and $\Delta S_{RD}(XH^*)$ at 355 K], activation free energies [denoted as $\Delta G_{RD}'(XH^*)$] at 298.15 K and $\Delta G_{RD}'(XH^*)$ at 355 K], activation enthalpy changes [denoted as $\Delta H_{RD}'(XH^*)$] at 298.15 K and $\Delta H_{RD}'(XH^*)$ at 355 K], and activation entropy changes [denoted as $\Delta S_{RD}'(XH^*)$] at 298.15 K and $\Delta S_{RD}'(XH^*)$ at 355 K] of XH*’s to release the methyl radical in MeCN were calculated, and the results are shown in Tables 1 and 2.

After carefully examining the data in Tables 1 and 2, the main discussions and conclusions are listed as follows.

2.1. Relationship among $\Delta G_{RD}(XH^*)$, $\Delta G_{RD}(XH^*)$, and Reactivity on XH as Methylation Reagents.

2.1.1. Linear Correlation between $\Delta G_{RD}(XH^*)$ and $\Delta G_{RD}(XH^*)$.

It is clear that the $\Delta G_{RD}(XH^*)$ values range from 1.33 kcal/mol (1H*) to 27.48 kcal/mol (32H*), while $\Delta G_{RD}(XH^*)$ ranges from 14.87 kcal/mol (44H*) to 37.09 kcal/mol (32H*). The $\Delta G_{RD}(XH^*)$ values and $\Delta G_{RD}(XH^*)$ values span as much as 26.15 and 22.22 kcal/mol, respectively, meaning that the chemical structures have a significant effect on the reactivities of XH* to release a methyl radical. For a clear visual exhibition, the intrinsic relationship between $\Delta G_{RD}(XH^*)$ and $\Delta G_{RD}(XH^*)$ is shown in Figure 1a. It can be seen from Figure 1a that the $\Delta G_{RD}(XH^*)$ values increase along with the increase in the $\Delta G_{RD}(XH^*)$ values, and a certain linear correlation between $\Delta G_{RD}(XH^*)$ and $\Delta G_{RD}(XH^*)$ is found with the equation $\Delta G_{RD}(XH^*) = 0.899\Delta G_{RD}(XH^*) + 14.554$ ($R^2 = 0.929$, defined as eq 1), which means if the $\Delta G_{RD}(XH^*)$ was obtained, the $\Delta G_{RD}(XH^*)$ can be estimated with the linear equation (eq 1).

At the same time, the relationship between $\Delta G_{RD}'(XH^*)$ and $\Delta G_{RD}'(XH^*)$ is shown in Figure 1b. A certain linear correlation between $\Delta G_{RD}'(XH^*)$ and $\Delta G_{RD}'(XH^*)$ is also found with the equation $\Delta G_{RD}'(XH^*) = 0.895\Delta G_{RD}'(XH^*) + 16.434$ ($R^2 = 0.925$, defined as eq 2), which can be used to predict the $\Delta G_{RD}'(XH^*)$ value at 355 K when the $\Delta G_{RD}'(XH^*)$ is available. If eq 1 is compared with eq 2, it can be found that the two activation free energy equations have almost exactly the same slope, while the intercept of eq 2 is larger than that of eq 1 by 1.85, which indicates that for two methyl radical transfer reactions with the same thermodynamic driving forces at 298.15 and 355 K, the $\Delta G_{RD}'(XH^*)$ value at 355 K is 1.5 kcal/mol larger than the $\Delta G_{RD}(XH^*)$ value at 298.15 K.

Deeper reflecting on the activation free energy equations (eq 1), 0.899$\Delta G_{RD}(XH^*)$, is considered as the reaction driving force, but the intercept (very larger than 0) undoubtedly belongs to reaction resistance, so the activation free energy is the sum of both reaction driving force [0.899$\Delta G_{RD}(XH^*)$] and reaction resistance (intercept), because the intercept is a very large positive value to greatly reduce the thermodynamic driving force according to its definition in eq 1). The more negative the thermodynamic driving force [0.899$\Delta G_{RD}(XH^*) < 0$] and the smaller the reaction resistance (intercept) is, the smaller the activation free energy [$\Delta G_{RD}(XH^*)$] is. However, when the Gibbs free energies are larger than 0 [$\Delta G_{RD}(XH^*) > 0$], the Gibb free energies [0.899$\Delta G_{RD}(XH^*)$] convert to reaction resistance

| $\Delta G_{RD}(XH^*)$ | $\Delta G_{RD}(XH^*)$ | $\Delta H_{RD}(XH^*)$ | $\Delta H_{RD}(XH^*)$ | $\Delta S_{RD}(XH^*)$ | $\Delta S_{RD}(XH^*)$ |
|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| 1H*                  | 2.14                 | 20.22                | 29.43                | 3.82                 | 39.05                |
| 2H*                  | 4.13                 | 24.91                | 30.52                | 5.83                 | 40.75                |
| 3H*                  | 6.44                 | 29.32                | 31.76                | 7.56                 | 42.92                |
| 4H*                  | 8.46                 | 33.81                | 33.27                | 9.13                 | 44.96                |
| 5H*                  | 10.61                | 38.27                | 34.74                | 10.55                | 47.01                |
| 6H*                  | 12.27                | 42.72                | 36.19                | 11.90                | 48.96                |

Table 2. $\Delta G_{RD}(XH^*)$, $\Delta H_{RD}(XH^*)$, and $\Delta S_{RD}(XH^*)$ to Release the Methyl Radical in MeCN at 355 K.

Note: The units of $\Delta G_{RD}(XH^*)$, $\Delta H_{RD}(XH^*)$, and $\Delta S_{RD}(XH^*)$ are kcal/mol, $\Delta S_{RD}(XH^*) = \Delta H_{RD}(XH^*) - T\Delta C_{PD}(XH^*)$, where $\Delta C_{PD}(XH^*)$ are unit being cal mol$^{-1}$ K$^{-1}$; $\Delta S_{RD}(XH^*) = \Delta H_{RD}(XH^*) - T\Delta C_{PD}(XH^*) = \Delta G_{RD}(XH^*) - T\Delta C_{PD}(XH^*)$. $\Delta C_{PD}(XH^*)$ is the unit being cal mol$^{-1}$ K$^{-1}$. 

[0.899$\Delta G_{RD}(XH^*) > 0$] from the reaction driving forces [0.899$\Delta G_{RD}(XH^*) < 0$].

2.1.2. Classification of 45 XH*s. Through further examining the calculation data in Table 1, all 45 XH*s can be divided into three classes (see Figures 1 and 2) using $\Delta G_{RD}(XH^*)$ and $\Delta G_{RD}(XH^*)$ values as the judgment criteria, which had been verified in our previous work.
2.1.2.1. Class 1: Excellent Methylation Reagents.

$\Delta G^o_{RD}(XH^+)$ and $\Delta G^o_{RD}(XH^+)$, with $\Delta G^o_{RD}(XH^+) \leq 2.5 \text{ kcal/mol}$ and $\Delta G^o_{RD}(XH^+) \leq 21 \text{ kcal/mol}$ at 298.15 K are considered to be excellent methyl radical reagents in organic synthesis although the $\Delta G^o_{RD}(XH^+)$ values are larger than 0 (Figure 1). Since $\Delta G^o = \Delta H^o - T\Delta S^o$, it can be concluded that if the $\Delta H^o$ and $\Delta S^o$ do not change much as the temperature increases, $\Delta G^o$ could be regulated to below 0 through increasing the reaction temperature. Then, $T_o$, which refers to the temperature when $\Delta G^o$ is zero, is calculated ($T_o = \Delta H^o / \Delta S^o$) according to the above hypothesis. From Table 1, it can be concluded that $T_o$ ranges from 38.76 to 80.02 °C when $\Delta G^o_{RD}(XH^+)$ increased.

![Figure 1](https://example.com/fig1)

Figure 1. (a) Relationship between $\Delta G^o_{RD}(XH^+)$ and $\Delta G^o_{RD}(XH^+)$ of 45 XH’s to release the methyl radical in MeCN at 298.15 K. (b) Relationship between $\Delta G^o_{RD}(XH^+)$ and $\Delta G^o_{RD}(XH^+)$ of 45 XH’s to release the methyl radical in MeCN at 355 K.

![Figure 2](https://example.com/fig2)

Figure 2. (a) Relationship between the $\Delta G^o_{RD}(XH^+)$ of 45 XH’s to release the methyl radical and $\Delta G^o_{RD}(XH^+)$ of 45 XH’s releasing the trifluoromethyl radical in MeCN at 298.15 K. (b) Relationship between $\Delta G^o_{RD}(XH^+)$ of 45 XH’s to release the methyl radical and $\Delta G^o_{RD}(XH^+)$ of 45 XH’s releasing the trifluoromethyl radical in MeCN at 298.15 K.

Scheme 3. (a) Excellent Methylation Reagents in Class 1; (b) Potential Methylation Reagents in Class 2
from 0.66 (9H**') to 1.49 kcal/mol (45H**') for four XH**'s (1H**, 3H**~4H**, and 44H**'), implying that the methylation reaction should be easily controlled using MeCN as the solvent at its boiling point (~355 K).

Therefore, four XH**'s (1H**, 3H**~4H**, and 44H**'), Scheme 3) in this work are identified as excellent methyl radical reagents in organic synthesis, with ΔG°_{RD}(XH**) ranging from 0.66 (4H**') to 1.49 kcal/mol (44H**') and ΔG°_{RD}(XH**) ranging from 14.87 (4H**') to 15.84 kcal/mol (1H**) in MeCN at 298.15 K. We further computed the ΔG°_{RD}(XH**) and ΔG°_{RD}(XH**) values of 45 H** to release the methyl radical in MeCN at 355 K (b.p. of MeCN), which are shown in Table 2. It can be seen that the ΔG°_{RD}(XH**) values of the four XH**'s including 1H**, 3H**~4H**, and 44H**' range from ~0.80 to ~1.65 kcal/mol (Table S1), which clearly show that they belong to excellent methyl radical reagents at 355 K in MeCN, which strongly supported the above deduction.

2.1.2.2. Class 2: Potential Methylation Reagents. XH**'s with 2.5 kcal/mol (<ΔG°_{RD}(XH**') ≤ 5 kcal/mol and ΔG°_{RD}(XH**) ≤ 19 kcal/mol at 298.15 K are considered to be potential methyl radical reagents in organic synthesis (Figure 1).35 Nine XH**'s (5H**, 6H**, 9H**, 10H**, 12H**, 13H**, 15H**, 43H**, and 45H**) in this work are found to be potential methyl radical reagents in organic synthesis, with ΔG°_{RD}(XH**) ranging from 2.67 (15H**) to 4.81 kcal/mol (45H**) and ΔG°_{RD}(XH**) ranging from 15.84 (5H**) to 18.91 kcal/mol (13H**). From the above discussions, it is clear that the Gibbs free energies decrease to below 0 with the increase in reaction temperature based on the equation ΔG° = ΔH° − TΔS°. According to the computed Gibbs free energies of ΔG°_{RD}(XH**) and ΔG°_{RD}(XH**) values of nine XH**'s to release the methyl radical in MeCN at 355 K (Tables 2 and S1), it is not difficult to find that the ΔG°_{RD}(XH**) values range from 0.42 to 2.49 kcal/mol, while the ΔG°_{RD}(XH**) values range from 15.43 to 18.83 kcal/mol (Figure 1b). Taking the calculation accuracy into consideration, XH**'s in class 2 can be used as potential methyl radical reagents by regulating various reaction solvents and raising the reaction temperature appropriately to achieve ΔG°_{RD}(XH**) values below 0.

2.1.2.3. Class 3: Not Methylation Reagents or Easily Synthesized Methyl-Substituted Organic Hydride Compounds. XH**'s with 5 kcal/mol (<ΔG°_{RD}(XH**) ≤ 18 kcal/mol (<ΔG°_{RD}(XH**') have the lowest reactivities, which cannot be used as methyl radical reagents in organic synthesis (Figure 1).35 If we want to make an attempt to increase the temperature making ΔG°_{RD}(XH**) < 0, the temperature should be extremely larger than 150 °C [150 °C (7H) ~ 700 °C (32H), Table 1], which is greatly beyond the boiling point of common solvents. Instead, since XH**'s in class 3 have high ΔG°_{RD}(XH**) and ΔG°_{RD}(XH**) values (indicating high thermodynamic and kinetic stabilities, respectively), XH**'s in class 3 can be easily synthesized using excellent or potential methylation reagent XH**'s in class 1, class 2, or other methylation reagents. Our work provides important basic calculation data and a guidance method to synthesize methyl-substituted organic hydride compounds as well.

The classification of methylation reagents including three classes, the corresponding judgment criteria, and the contained XH**'s investigated in this work are clearly displayed in Table 3 for chemists to quickly select and use in organic synthesis or drug modification.

Through further comparison on the computed results at 355 K (Table 2) with those at 298.15 K (Table 1), the differences in Gibbs free energies [ΔΔG° = ΔG°_{RD}(XH**) − ΔG°_{RD}(XH**')] (Table S2, 355 K) and activation free energies [ΔΔG° = ΔG°_{RD}(XH**) − ΔG°_{RD}(XH**')] (Table S2, 355 K) almost do not change when the temperature increases from 298.15 to 355 K, which also imply that the structure changes between the initial state (IS) and the transition state (TS) at 298.15 K are very similar to the structure changes at 355 K. Besides, it is clear that the ΔG°_{RD}(XH**) values decrease by ~2.3 kcal/mol (−2.44 kcal/mol ≤ ΔΔG° ≤ −2.10 kcal/mol), indicating the reactivity of XH** to release the methyl radical improves by ~2.3 kcal/mol when the temperature increases from 298.15 to 355 K. While the ΔH°_{RD}(XH**) (0.02 kcal/mol ≤ ΔΔΔH° ≤ 0.15 kcal/mol), and Δ(TΔS°) (−0.03 kcal/mol ≤ ΔΔΔTΔS° ≤ 0.60 kcal/mol) almost do not change from 298.15 to 355 K, since ΔΔG° is equal to the difference between ΔH° and Δ(TΔS°), so the ΔΔG° (−2.3 kcal/mol) must result from the contribution of entropy changes (ΔΔTΔS°) of the temperature influence between 298.15 and 355 K. The speculation is verified by the computed data in Table S2 (2.17 kcal/mol ≤ ΔΔΔTΔS° ≤ 2.57 kcal/mol). The great entropy changes [ΔΔTΔS° ≈ −2.3 kcal/mol] from 298.15 to 355 K strongly prove that the elementary step of XH** to release the methyl radical is an entropy-controlled process.

From the discussion in this section, we have obtained the linear equations: ΔG°_{RD}(XH**) = 0.895ΔG°_{RD}(XH**') + 14.554 (R² = 0.929, eq 1) at 298.15 K and ΔG°_{RD}(XH**) = 0.895ΔG°_{RD}(XH**') + 16.434 (R² = 0.925, eq 2) at 355 K.

### Table 3. Classification of Methylation Reagents Including 3 Classes, the Corresponding Judgment Criteria, and the Contained XH**'s Investigated in This Work

| class | classification | criteria (kcal/mol at 298.15 K) | XH**'s |
|-------|----------------|---------------------------------|--------|
| 1     | excellent methylation reagents | ΔG°_{RD}(XH**) ≤ 2.5 | 1H**, 3H**, 4H**, 44H** |
|       | | ΔG°_{RD}(XH**) ≤ 21 | (see Scheme 3) |
| 2     | potential methylation reagents | 2.5 < ΔG°_{RD}(XH**) ≤ 5 | 5H**, 6H**, 9H**, 10H**, 12H**, 13H**, 15H**, 43H**, 45H** |
|       | | ≤ 19 | (see Scheme 3) |
| 3     | not methylation reagents or easily synthesized methyl-substituted organic hydride compounds | 5 < ΔG°_{RD}(XH**) | 2H**, 7H**, 8H**, 11H**, 14H**, 16H**~42H** |
|       | | 18 < ΔG°_{RD}(XH**) | |
Scheme 4. Methyl Effect in Different Positions of Methyl-Substituted Organic Hydride Radical Cations (XH⁺’s) on Reactivities as Methylation Reagents

Since the \( \Delta G^0_{RD}(XH^+) \) values are \(-2.3 \) kcal/mol smaller than the \( \Delta G^0_{RD}(XH^+) \) values \([−2.44 \text{ kcal/mol} \leq \Delta \Delta G^0 \leq −2.10 \text{ kcal/mol}]\), the activation free energies of XH⁺ to release the methyl radical almost do not change even when the temperature increases from 298.15 to 355 K \((−0.42 \text{ kcal/mol} \leq \Delta \Delta G^0 \leq −0.06 \text{ kcal/mol})\). That is to say, \( \Delta \Delta G^0 = \Delta G^0_{RD}(XH^+) - \Delta G^0_{RD}(XH^+) = 0.895 \) \((\Delta G^0_{RD}(XH^+) - \Delta G^0_{RD}(XH^+)) + 1.88 \approx 0\), which explained the inherent relationship among temperature, Gibbs free energy, and activation free energy.

2.2. Relationships between Structures and Reactivities of XH⁺’s as Methylation Reagents. 2.2.1. Methyl Substitution in 2 and 6 Positions Makes XH⁺’s Better Methylation Reagents. For methyl substitution in 2 and 6 positions \((1H^+ vs 5H^+; 2H^+ vs 8H^+; 4H^+ vs 9H^+); see Scheme 4a\), the methyl substitution makes \( \Delta G^0_{RD}(XH^+) \) values decrease by 1.21−3.85 kcal/mol and \( \Delta G^0_{RD}(XH^+) \) values decrease by 0.21−2.76 kcal/mol, which means the methyl substitution increases the reactivities and makes the XH⁺ better methyl radical precursors.

2.2.1.2. Methyl Substitution in the N-Position Makes XH⁺ Worse Methylation Reagents. For the 1,4-dihydropyridine structure, the methyl substitution in the N-position \((1H^+ vs 6H^+; 5H^+ vs 7H^+; 13H^+ vs 14H^+); see Scheme 4b\) and for N-methylation in dihydroquinoline and dihydroacridine structures \((17H^+ vs 18H^+; 21H^+ vs 22H^+); see Scheme 4c\), the \( \Delta G^0_{RD}(XH^+) \) values increase by 0.50−2.67 kcal/mol and \( \Delta G^0_{RD}(XH^+) \) values increase by 0.17−2.60 kcal/mol, which means the methyl substitution decreases the reactivities of XH⁺ as methyl radical precursors.

2.2.1.3. Normally Methyl Substitution in the N-Position of 1,2-Dihydropyridines Makes XH⁺’s Better Methylation Reagents. For XH⁺’s with the 1,2-dihydro-structure \((29H^+ vs 30H^+; 34H^+ vs 35H^+; 37H^+ vs 38H^+; 39H^+ vs 40H^+; 41H^+ vs 42H^+); see Scheme 4d\), the methyl substitution in the N-position makes \( \Delta G^0_{RD}(XH^+) \) values more negative \((-0.06 to −0.92 \text{ kcal/mol})\) and the \( \Delta G^0_{RD}(XH^+) \) values varied from \(-0.86 to 0.09 \text{ kcal/mol}\), which means the methyl substitution in the N-position of 1,2-dihydro-structures could increase the reactivity of XH⁺ as methyl radical precursors.

For the effects of the methyl group in different positions on XH⁺ releasing methyl radicals, it is also found that the methyl groups at the 1-N-position of the 1,2-dihydro organic hydrides \((\text{Scheme 4d})\) do not have much effect as in the N-1-positions of 1,4-dihydropyridines \((\text{Scheme 4b})\). Maybe it is the position of the methyl substitution resulting in the interesting phenomenon. It is well known that the energy difference between the initial state \((\text{IS})\) and the final state \((\text{FS})\) determines the thermodynamic driving forces \(\Delta G^0\), while the energy difference between the initial state \((\text{IS})\) and the transition state \((\text{TS})\) determines the activation free energy \(\Delta G^0\). Similar to 1,4-dihydropyridines, the methyl substitution in the N-1-position of the 1,2-dihydro organic hydrides should have made XH⁺ worse methyl radical donors; however, the methyl substitution made XH have a higher energy in the initial state \((\text{IS})\) than that of the final state after releasing the methyl radical because of the large steric hindrance, so the thermodynamic driving force \((\Delta G^0 = G_{FS} - G_{IS})\) does not decrease too much compared with unmethylated 1,2-dihydro organic hydride. In addition, the large steric hindrance greatly promotes the release of the methyl radical in the transition state, so the activation free energy does not increase too much compared with unmethylated 1,2-dihydro organic hydride. Perhaps that is why the methyl groups at 1-N of the 1,2-dihydro organic...
Hydrids do not have much effect as in the 1,4-dihydropyridines. As one can see, the methyl substitution in different positions has different methyl effects, and the effect is quite complicated and coupled with the factor of the chemical structure, such as methyl substitution in position 2 and 6 makes XHs better methylation reagents, methyl substitution in the N-position makes XHs worse methylation reagents, and normally methyl substitution in the N-position of 1,2-dihydro-structures makes XHs better methylation reagents. These conclusions are derived from the $\Delta G_{RD}(XH^{+})$ and $\Delta G_{RD}(XH^*)$ data; however, unfortunately, we could not find a qualitative and quantitative analysis on the interesting results. Without doubt, the methyl group plays key roles in the configuration and energy of the initial state (IS), the transition state (TS), and the final state (FS), resulting in thermodynamic and kinetic differences compared with unmethylated organic hydrids.

2.2.2. Heteroatom Substitution Has Significant Impacts on Reactivities. 2.2.2.1. Heteroatom Substitution in Five-Member Ring Structures Makes XH$^+$s Worse Methylation Reagents. For XH$^+$s with a five-member ring structure (34H$^+$, 37H$^+$, and 39H$^+$; see Scheme 5), $\Delta G_{RD}(XH^*)$ values increase from 10.99 to 22.49 kcal/mol and $\Delta G_{RD}(XH^+)$ values increase from 27.85 to 34.22 kcal/mol as the heteroatom changes with the order N, S, and O, which means the S and O atoms have significant impacts on the reactivities and make XH$^+$s worse methyl radical reagents even if the electronegativity of S (2.58) is smaller than that of N (3.04).

It is true that heteroatom substitution has significant impacts on the reactivities. Compared with the N-atom in organic hydrides, despite the O-atom and the S-atom being electron-rich, their electron-donating abilities are far less than those of the N-atom, which lead to higher activation energies and lower thermodynamics driving forces. We consider that maybe it is the huge difference in the electron-donating abilities among N, O, and S atoms that cause the significant heteroatom effects on the reactivities.

2.2.3. There Is No Obvious and Certain Substituent Effect. For the 1,4-dihydropyridine structure with different substituents in the 3-position (15H$^+$, 13H$^+$, 10H$^+$, 12H$^+$, and 11H$^+$; see Scheme 6a), there is no good correlation between the electronegativity and reactivity. For example, compared with 15H$^+$, the $\Delta G_{RD}(XH^*+)$ values of 10H$^+$~13H$^+$ with the electron-withdrawing group in the 3-position decrease significantly from 3.74 kcal/mol (15H$^+$ without any substituent) to $-7.06$ kcal/mol (12H$^+$) on the order of $-\text{CN}$ (11H$^+$) $> -\text{CONH}_2$ (13H$^+$) $> -\text{CO}_2\text{Et}$ (10H$^+$) $> -\text{COCH}_3$ (12H$^+$), while the $\Delta G_{RD}(XH^+)$ values of 10H$^+$~13H$^+$ decrease significantly from 20.13 kcal/mol (15H$^+$) to 9.32 kcal/mol (12H$^+$) on the order of $-\text{CN}$ (11H$^+$) $> -\text{CONH}_2$ (13H$^+$) $> -\text{CO}_2\text{Et}$ (10H$^+$) $> -\text{COCH}_3$ (12H$^+$) (Scheme 6). The electron-withdrawing group in the 3-position could greatly improve reactivities of XH$^+$ to release the methyl radical from thermodynamics and kinetics, but the substituent constants or electron-withdrawing properties of substituents have no linear relationship with the changes in reactivities.

The effects of different substituents at different positions on reactivities of XH$^+$ to release the methyl radical are examined in Scheme 6b–e. It is clear that there are no obvious and simple substituent effects. This phenomenon shows that substituents do have important and complicated influences on the reactivity of XH$^+$ to release the methyl radical, but it will be difficult to predict the reactivity of XH$^+$'s as
methylene reagents by simply regulating and controlling the substituents with different electronegativities.

In all, the relationship between structures and reactivities on XH** releasing the methyl radical exhibits roughly the same regular pattern. Perhaps, the above conclusions are also applicable for other substituted organic hydride compound radical cations releasing radical in chemical reactions.

2.3. Relationship of Reactivity between X′H** and XH** as Trifluoromethylation and Methylation Reagents, Respectively. In our previous work, we have calculated the Gibbs free energy \[\Delta G_{RD}^o(XH^*)\] at 298.15 K and \[\Delta G_{RD}^o(XH^{'})\] at 355 K and the activation free energy \[\Delta G_{RD}^a(XH^{'})\] at 298.15 K and \[\Delta G_{RD}^a(XH^{'})\] at 355 K of trifluoromethyl-substituted organic hydride compound radical cations (XH^{'}) releasing trifluoromethyl radical in MeCN with the DFT method. This provides us the precious chance to investigate the relationship of thermodynamics and reactivity between trifluoromethyl-substituted organic hydride compound radical cations (XH^{'}) releasing trifluoromethyl radical and methyl-substituted organic hydride compound radical cations (XH**) releasing methyl radical.

We tried to discover and evaluate the difference in reactivity on XH** and XH^{'}, releasing the methyl or trifluoromethyl radical with the same structure except for the substituent from thermodynamic (\[\Delta G_{RD}^o\]) and kinetic (\[\Delta G_{RD}^a\]) views. Then, we further computed the differences between \[\Delta G_{RD}^o(XH^{'})\] and \[\Delta G_{RD}^o(XH^{'})\] as \[\Delta \Delta G^o = \Delta G_{RD}^o(XH^{'}) - \Delta G_{RD}^o(XH^{'})\] (listed in Table S3), it is obvious that sometimes \[\Delta \Delta G^o\] are the negative values, while sometimes \[\Delta \Delta G^o\] are the positive values. The reason seems probably to be that \[\Delta G_{RD}^o(XH^{'})\] and \[\Delta G_{RD}^o(XH^{'})\] differ to different extents in different skeletal structures. In addition, we also computed the differences between \[\Delta G_{RD}^o(XH^{'})\] and \[\Delta G_{RD}^o(XH^{'})\] as \[\Delta \Delta G^o = \Delta G_{RD}^o(XH^{'}) - \Delta G_{RD}^o(XH^{'})\] (listed in Table S3), which exhibited the same feature as the above Gibbs free energy that sometimes \[\Delta \Delta G^o\] are the negative values, while sometimes \[\Delta \Delta G^o\] are the positive values. In fact, there is indeed a correlation between \[\Delta \Delta G^o\] and \[\Delta \Delta G^2\] (Figure S1a), \[\Delta \Delta G^2 = 0.770 \Delta \Delta G^o - 1.830 (R^2 = 0.75)\] (defined as eq 3), meaning that the \[\Delta \Delta G^o\] values increase with the increase in \[\Delta \Delta G^2\] values. Considering eq 3, it is found that if the \[\Delta \Delta G^o\] is 2.38 kcal/mol, the computed \[\Delta \Delta G^2\] is greater than 0 kcal/mol. That is, if \[\Delta \Delta G^2\] is smaller than 2.38 kcal/mol, the computed \[\Delta \Delta G^2\] value is less than 0 kcal/mol. This means that the difference in thermodynamic driving forces (\[\Delta \Delta G^2\]) between XH** releasing the methyl radical and XH^*' releasing the trifluoromethyl radical is less than 2.38 kcal/mol, and the activation energy of XH** to release the methyl radical is smaller than that of XH^*' releasing the trifluoromethyl radical, i.e., XH** is a better radical donor than XH^*' in kinetics. Besides, there is also no relationship of the sign (negative or positive values) between \[\Delta \Delta G^2\] and \[\Delta \Delta G^o\]. The above phenomenon confused us for a long time to unveil its mystery and reveal the essential reason. Eventually, we found the \[\Delta G_{RD}^o(XH^*)\] and \[\Delta G_{RD}^o(XH^{'})\] values could give us the answer.

Consequently, the relationship between Gibbs free energies \[\Delta G_{RD}^o(XH^*)\] of XH** to release the methyl radical and Gibbs free energies \[\Delta G_{RD}^o(XH^{'})\] of XH^*' releasing the trifluoromethyl radical in MeCN at 298.15 K (Figure 2a) and the relationship between activation free energies \[\Delta G_{RD}^a(XH^*)\] of XH** to release the methyl radical and activation free energies \[\Delta G_{RD}^a(XH^{'})\] of XH^*' releasing the trifluoromethyl radical in MeCN at 355 K (Figure 2b) are presented in Figure 2.

As shown in Figure 2a, \[\Delta G_{RD}^o(XH^*)\] values increase with the increase in \[\Delta G_{RD}^o(XH^{'})\] values with a certain linear equation \[\Delta G_{RD}^o(XH^{'}) = 0.830 \Delta G_{RD}^o(XH^{'}) + 3.773 (R^2 = 0.839, defined as eq 4 in this work). Based on eq 4, it could be deduced that, for the same chemical structure with the trifluoromethyl or methyl substituent (XH** and corresponding XH^*), when the \[\Delta G_{RD}^o(XH^{'})\] value is 22.19 kcal/mol, the \[\Delta G_{RD}^o(XH^{'})\] computed with eq 4 will also be 22.19 kcal/mol. In general, if the \[\Delta G_{RD}^o(XH^{'}) < 22.19\) kcal/mol, the corresponding \[\Delta G_{RD}^a(XH^{'})\] value is smaller than \[\Delta G_{RD}^a(XH^{'})\] values, so the \[\Delta \Delta G^o\] present negative values; if \[\Delta G_{RD}^o(XH^{'}) > 22.19\) kcal/mol, the corresponding \[\Delta G_{RD}^a(XH^{'})\] value would be larger than \[\Delta G_{RD}^a(XH^{'})\] values, so the \[\Delta \Delta G^o\] present positive values. That is, the methyl-radical-releasing ability of XH** could be roughly judged by the thermodynamic data of XH** releasing the trifluoromethyl radical. Specifically, if the thermodynamic driving forces of XH** releasing the trifluoromethyl radical are smaller than 22.19 kcal, the corresponding XH** is a worse methyl radical precursor than XH^*; if the thermodynamic driving forces of XH** releasing the trifluoromethyl radical are more positive than 22.19 kcal, the corresponding XH** is a better methyl radical precursor than XH^*.

Moreover, when eq 5 was compared with eq 4, we were surprised to find that the two equations have almost the same slopes (0.863 vs 0.830) and intercepts (3.324 vs 3.773), indicating that the influence of thermodynamics from XH** releasing the trifluoromethyl radical on that of XH** to release the methyl radical is similar to the influence of kinetics from XH** to release the trifluoromethyl radical on that of XH** to release the methyl radical. Based on the above analysis, the thermodynamic data and kinetic data have inherent and tight connections between XH** releasing the trifluoromethyl radical and XH** releasing the methyl radical. Therefore, the relationship between Gibbs free energies \[\Delta G_{RD}^a(XH^{'})\] of XH** to release the methyl radical in MeCN at 355 K and Gibbs free energies
In summary, the ΔG_Rd^0(X'H^*) of X'H^* releasing the trifluoromethyl radical in MeCN at 298.15 K (Figure S1b), the relationship between activation free energies (∆G^a_Rd^#(X'H^*)) of X'H^* to release the methyl radical in MeCN at 298.15 K and Gibbs free energies (∆G_Rd^0(X'H^*)) of 45 XH^*s releasing the trifluoromethyl radical in MeCN at 298.15 K (Figure S1c), as well as the relationship between activation free energies (∆G^a_Rd^0(X'H^*)) of X'H^* to release the methyl radical in MeCN at 355 K and Gibbs free energies (∆G_Rd^0(X'H^*)) of X'H^* releasing the trifluoromethyl radical in MeCN at 298.15 K (Figure S1d) are examined and displayed in Figure S1. As expected, they all exhibited a good linear relationship to give the corresponding linear equations ∆G_Rd^0(X'H^*) = 0.830∆G_Rd^0(S^0(X'H^*))+1.492 (R^2 = 0.837, eq 6) for Figure S1b, ∆G_Rd^0(X'H^*) = 0.758∆G_Rd^0(X'H^*) + 17.862 (R^2 = 0.804, eq 7) for Figure S1c, and ∆G^a_Rd^0(X'H^*) = 0.754∆G_Rd^0(X'H^*) + 17.694 (R^2 = 0.796, eq 8) for Figure S1d. In other words, if the Gibbs free energy of X'H^* releasing the trifluoromethyl radical in MeCN at 298.15 K is available, the corresponding seven thermodynamic and kinetic data, including the Gibbs free energy of X'H^* releasing the trifluoromethyl radical at 355 K [∆G_Rd^0(X'H^*)], the activation free energy of X'H^* releasing the trifluoromethyl radical at 298.15 K [∆G_Rd^#(X'H^*)], the activation free energy of X'H^* releasing the trifluoromethyl radical at 355 K [∆G_Rd^#(X'H^*)], the Gibbs free energy of X'H^* releasing the methyl radical at 298.15 K [∆G_Rd^0(X'H^*)], the Gibbs free energy of X'H^* to release the methyl radical at 355 K [∆G_Rd^0(X'H^*)], and the activation free energy of X'H^* to release the methyl radical at 355 K [∆G_Rd^#(X'H^*)] could be reasonably computed by employing the corresponding linear equations. The deep relationships reveal the important correlations between methyl and trifluoromethyl-substituted organic hydride compound radical cations (X'H^* and X'H^*), which is expected to guide chemists in better understanding the thermodynamics and reactivity of X'H^* and X'H^* in alkylcation reactions and is worthy of further exploration.

3. CONCLUSIONS

In summary, the ∆G_Rd^0(X'H^*) and ∆G_Rd^#(X'H^*) of 45 classical methyl-substituted organic hydride compound radical cations (X'H^*) releasing the methyl radical are computed with the DFT method. Four XH^*s (1H^*, 3H^*–4H^*, and 44H^*) are found to be excellent methyl radical reagents, while nine XH^*s (5H^*, 6H^*, 9H^*, 10H^*, 12H^*, 13H^*, 15H^*, 39H^*, and 45H^*) are found to be potential methyl reagents in organic synthesis. This work uses the ∆G_Rd^0(X'H^*) and ∆G_Rd^#(X'H^*) to quantitatively measure the reactivity of X'H^* as a methylation reagent and to establish the molecular library and reactivity database of new methylation reagents for synthetic chemists to query and use. From our work, it can be inferred that various 4-substituted-3,4-dihydropyrimidinones can be used as alkyl radical reagents in reactions just like various 4-substituted Hantzsch esters, which offer practical instructions for synthesis chemists to try and realize. Interesting correlations are found between thermodynamic and kinetic data of X'H^* (X'H^*) releasing the methyl radical and the trifluoromethyl radical, which would be helpful in understanding related alkylcation mechanisms and quick estimation of related ∆G^0 and ∆G^# values.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c04556.

Computation methods, Tables S1–S4, Figure S1, coordinate of reactants, coordinate of transition states, coordinate of products, and electron spin density of transition states of each XH^* (PDF)

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Notes

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REFERENCES

(1) Barreiro, E. J.; Kümmel, A. E.; Fraga, C. A. M. The Methylation Effect in Medicinal Chemistry. Chem. Rev. 2011, 111, 5215–5246.
(2) Wienen-Schmidt, B.; Schmidt, D.; Gerber, H.-D.; Heine, A.; Gohlké, H.; Klebe, G. Surprising Non-additivity of Methyl-groups in Drug-kinase Interaction. ACS Chem. Biol. 2019, 14, 2585–2594.
(3) Leung, C. S.; Leung, S. S. F.; Tirado-Rives, J.; Jorgensen, W. L. Methyl Effects on Protein-ligand Binding. J. Med. Chem. 2012, 55, 4489–4500.
(4) Schönheit, H.; Cernák, T. Profound Methyl Effects in Drug Discovery and a Call for New C-H Methylation Reactions. Angew. Chem. Int. Ed. 2013, 52, 12256–12267.
(5) Harris, J. C.; Scheibe, M.; Wongpalee, S. P.; Liu, W.; Cornett, E. M.; Vaughan, R. M.; Li, X.; Chen, W.; Xue, Y.; Zhong, Z.; Yen, L.; Barshop, W. D.; Rayatpisheh, S.; Gallego-Bartolome, J.; Groth, M.; Wang, Z.; Wohlschlege, J. A.; Du, J.; Rothbart, S. B.; Butter, F.; Jacobsen, S. E. A DNA Methylation Reader Complex that Enhances Gene Transcription. Sci. Sin. Chim. 2020, 50, S26–S51.
(7) Ayenitinova, 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.

(8) Huang, J.; Chen, Z.; Wu, J. Recent Progress in Metal-draical-mediated Methylation or Demethylation Reactions. ACS Catal. 2021, 11, 10713–10732.

(9) Du, J.; Chen, Y.; Zuo, Z. Recent Progress of Photocatalytic Methylation of Aromes. Chin. J. Org. Chem. 2020, 40, 3646–3655.

(10) Templ, J.; Schnürch, M. Selective α-Methylation of Aryl Ketones Using Quaternary Ammonium Salts as Solid Methylation Agents. J. Org. Chem. 2022, 87, 4303–4315.

(11) Biswal, P.; Samser, S.; Meher, S. K.; Chandrasekhar, V.; Venkatasubbiah, K. Palladium-catalyzed Synthesis of α-Methyl Ketones from Allylic Alcohols and Methanol. Adv. Synth. Catal. 2022, 364, 413–419.

(12) Maji, S.; Das, A.; Mandal, S. K. Mesionic N-Heterocyclic Olefin Catalysed Reductive Functionalization of CO2 for Consecutive N-Methylation of Amines. Chem. Sci. 2021, 12, 12174–12180.

(13) Washington, J. B.; Assante, M.; Yan, C.; McKinney, D.; Juba, V.; Leach, A. G.; Baillie, S. E.; Reid, M. Trialkylammonium Salt Degradation: Implications for Methylation and Cross-coupling. Chem. Sci. 2021, 12, 6949–6963.

(14) Ni, S.; Hribarsek, M.; Baddigam, S. K.; Ingner, F. J. L.; Orthaber, A.; Gates, P. J.; Pilarski, L. T. Mechanosolvent-Free Caticly Mediated C-H Methylation. Angew. Chem., Int. Ed. 2020, 60, 6600–6606.

(15) Guo, Y.-Q.; Chen, F.; Deng, C.-L.; Zhang, X.-G. Iodine-promoted Ring-opening Methylation of Benzothiazoles with Dimethyl Sulfite. Chem. Commun. 2021, 57, 1923–1926.

(16) Norcott, P. L.; Hammill, C. L.; Noble, B. B.; Robertson, J. C.; Olding, A.; Bissember, A. C.; Coote, M. L. TEMPO-Me: An Electrochemically Activated Methylation Agent. J. Am. Chem. Soc. 2019, 141, 15450–15455.

(17) Novaes, L. F. T.; Ho, J. S. K.; Mao, K.; Liu, K.; Tanwar, M.; Neurock, M.; Villemure, E.; Terrett, J. A.; Lin, S. Exploring Electrochemical C(sp3)-H Oxidation for the Late-stage Methylation of Complex Molecules. J. Am. Chem. Soc. 2022, 144, 1187–1197.

(18) Feng, A.; Liu, Y.; Yang, Y.; Zhu, R.; Zhang, D. Theoretical Insight into the Mechanism and Selectivity in Manganese-catalyzed Oxidative C(sp3)-H Methylation. ACS Catal. 2022, 12, 2290–2301.

(19) Vasilopoulos, A.; Krksa, S. W.; Stahl, S. S. C(sp3)-H Methylation Enabled by Peroxide Photosensitization and Ni-mediated Radical Coupling. Science 2021, 372, 398–403.

(20) Feng, B.; Zhang, G.; Feng, X.; Chen, Y. Palladium-catalysed Decarbonylative Methylation of Aryl Carboxylic Acids. Org. Chem. Front. 2022, 9, 1085–1089.

(21) Paul, B.; Maji, M.; Panja, D.; Kundu, S. Cobalt Catalyzed N-Methylation of Amidines Using Methanol. Asian J. Org. Chem. 2022, 11, No. e202100678.

(22) Gong, P.-X.; Xu, F.; Cheng, L.; Gong, X.; Zhang, J.; Gu, W.-J.; Han, W. Iron-catalyzed Domino Decarboxylation-oxidation of αβ-Unsaturated Carboxylic Acids Enabled Aldehyde C-H Methylation. Chem. Commun. 2021, 57, 5905–5908.

(23) Olivo, G.; Bietti, M. Aliphatic C-H Bond Methylation Enabled by Hydrogen Atom Transfer. Chem. 2021, 7, 1427–1430.

(24) Pan, C.; Yuan, C.; Yu, J.-T. Peroxide-mediated Synthesis of Benzimidazo[2,1-a]isoquinoline-6(5H)-ones via Cascade Methylation/Ethylation and Intramolecular Cyclization. Org. Biomol. Chem., 2021, 19, 619–626.

(25) Kaithal, A.; Hölscher, M.; Leitner, W. Carbon Monoxide and Hydrogen (Syngas) as a C1-Building Block for Selective Catalytic Methylation. Chem. Sci. 2021, 12, 976–982.

(26) Mao, Y.; Jiang, J.; Yuan, D.; Chen, X.; Wang, Y.; Hu, L.; Zhang, Y. Overcoming Peri- and Ortho- Selectivity in C-H Methylation of 1-Naphthaldehydes by a Tunable Transient Ligand Strategy. Chem. Sci. 2022, 13, 2900–2908.