

# Sulfoxonium ylides for direct methylation of *N*-heterocycles in water

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## Article

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# Abstract

The direct methylation of N-heterocycles is an important transformation for the advancement of pharmaceuticals, agrochemicals, functional materials, and other chemical entities. Herein, the unprecedented C(sp<sup>2</sup>)-H methylation of iminoamido N-heterocycles as nucleoside base analogues is described. Notably, trimethylsulfoxonium salt was employed as a methylating agent under aqueous conditions. A wide substrate scope and excellent level of functional group tolerance were attained. Moreover, this method can be readily applied to the site-selective methylation of azauracil nucleosides. The feasibility of gram-scale reactions and various transformations of the products highlight the synthetic potential of the developed method. Combined deuterium-labeling experiments aided the elucidation of a plausible reaction mechanism.

## Introduction

Methylation is one of vital processes in biological systems because DNA and histone methylation is responsible for gene expression without affecting the gene sequence<sup>1-2</sup>. For example, the C(sp<sup>2</sup>)-H methylation of uracil of deoxyuridine-5'-monophosphate (dUMP) by thymidylate synthase is a well-known metabolic process for DNA biosynthesis and RNA post-translational modification<sup>3-4</sup>. In addition, methylation of cysteine can affect signaling pathways by disrupting ubiquitin-chain sensing in NF-κB activation<sup>5</sup>. Methylation is also an important modification in medicinal chemistry and drug discovery, as physical and pharmacological properties of lead candidates can be favorably or adversely affected with the mere addition of a methyl group<sup>6</sup>. To address this challenge, number of synthetic strategies have been explored to install methyl and alkyl groups on N-heterocyclic molecules<sup>7-9</sup>. In particular, alkylation beyond monoazines, i.e., that of diazines and triazines, has emerged as a hot topic in this area due to the relevance of a number of bioactive molecules<sup>10-14</sup>.

The conventional approach is the transition-metal-catalyzed cross-coupling reactions between halogenated N-heterocycles and organometallic reagents (Fig. 1a)<sup>15-16</sup>. Minisci-type alkylations using alkyl radicals<sup>17-22</sup> and metal-catalyzed C-H alkylations<sup>23-30</sup> of N-heterocycles constitute the current established protocols. Alternative routes including the metal-free C-H alkylations of preactivated N-heterocycles have been also developed<sup>31-34</sup>. Recently, our group described the reductive C2-alkylation of heterocyclic N-oxides using phosphonium ylides (Fig. 1b)<sup>35-36</sup>. In this reaction, a concerted [3+2] cycloaddition between a 1,3-dipolar fragment of pyridine N-oxides and zwitterionic phosphonium ylides provides aza-oxaphospholane intermediates, which subsequently undergo aromatization to afford C2-alkylated pyridines. A key driving force might be the formation of a strong P=O bond (bond dissociation energy of Ph<sub>3</sub>P=O = 529 kJ/mol).

Since the landmark discovery by Johnson, Corey, and Chaykovsky in the 1960s<sup>37–39</sup>, sulfoxonium ylides have been widely employed as methylene surrogates in epoxidations, cyclopropanations, and aziridinations via intermolecular nucleophilic addition into electron-deficient  $\pi$ -unsaturated compounds, such as carbonyls,  $\alpha,\beta$ -unsaturated compounds, and imines<sup>40–43</sup>. However, there are no reports on the direct alkylation of *N*-heterocyclic compounds using alkyl sulfoxonium ylides. Moreover, previous reports related to sulfoxonium ylides predominantly rely on the use of organic solvents, which preclude them as environmentally benign processes<sup>44–48</sup>. Herein, we describe the unprecedented C(sp<sup>2</sup>)-H alkylation of iminoamido diazines and triazines as nucleoside base analogues with alkyl sulfoxonium salts. Of particular importance is the unconventional mechanistic pathway for the imino alkylation in aqueous media, which can provide novel insights into Corey-Chaykovsky reagents (Fig. 1c). Moreover, the amenability of this protocol to the pharmaceutical industry is attributed to the use of H<sub>2</sub>O as the greenest solvent and KOH as an economical reagent.

## Results

**Investigation of reaction conditions.** Optimization of reaction conditions commenced with the coupling between pyrazinone **1a** and trimethylsulfoxonium iodide (**2a**), as shown in Table 1. The formation of C3-methylated pyrazinone **3a** was achieved with the use of KO<sup>t</sup>Bu in THF at 100 °C (entry 1). This reaction could likewise be performed in protic solvents, such as MeOH (entry 3). Surprisingly, aqueous media accelerated the coupling reaction between **1a** and **2a** to afford **3a** in 84% yield within 2 h (entry 4). It should be noted that the aziridine compound generated from the imine functionality by the Corey-Chaykovsky aziridination was not observed in all cases, suggesting that the reaction pathways of the Corey-Chaykovsky reaction and the C(sp<sup>2</sup>)-H methylation reported herein are distinct. More importantly, this reaction was successful with the use of KOH, a cost-efficient base, to provide **3a** in 91% yield (entry 5). Screening of other bases yielded inferior results (entries 6 and 7). Control experiments revealed that the loading amount of KOH and reaction temperature were crucial for increasing the yield of **3a** (entries 8 and 9) (see Table 1 in the Supplementary Files).

**Substrate scope with respect to pyrazinones.** With the optimized reaction conditions in hand, the substrate scope of pyrazinones was examined (Table 2). A wide range of *N*-alkylated and *N*-benzylated pyrazinones **1b–1f** were found to be suitable substrates for this transformation, providing the corresponding C3-methylated pyrazinones **3b–3f** in high yields. Substrates **1c–1f** produced the corresponding products in low yields in H<sub>2</sub>O, presumably due to the presence of hydrophobic substituents. After careful screening of reaction conditions, it was established that protic solvents, such as EtOH and *i*-PrOH, resulted in higher levels of conversion. Notably, *N*-tetrahydropyranyl and *N*-benzyl groups are readily removable via conventional protocols for further elaboration of the free-(NH)-amido group. In addition, we observed the successful methylation of *N*-arylated pyrazinones **1g–1l**. Halogen-substituted and electron-rich *N*-aryl groups (**1g** and **1j**) displayed good reactivity, whereas electron-deficient *N*-aryl groups (**1h**, **1i**, **1k** and **1l**) were relatively less reactive. The electronic effect on this transformation was likewise observed for the C4-arylated pyrazinones **1m–1p**. The tolerance of cyano

and bromo groups presents valuable opportunities for further versatile synthetic transformation. Moreover, tri-substituted pyrazinone adduct **3q** was formed smoothly in 73% yield. Furthermore, the site-selective methylation of **1r–1t** was successfully achieved under the standard reaction conditions, affording the corresponding products **3r–3t** in high yields. (see Table 2 in the Supplementary Files)

**Substrate scope with respect to sulfoxonium salts.** Having established the broad scope of pyrazinones, the scope of sulfoxonium salts **2b–2e** was then evaluated. In the case of ethylation and propylation, trialkyl sulfoxonium chlorides were employed as alkylating agents to afford the corresponding products **3u** (70%) and **3v** (77%). The current protocol could be implemented using Johnson's sulfoxonium salts<sup>49</sup> **2d** and **2e** to furnish cyclopropylated pyrazinone **3w** (45%) and methylated pyrazinone **3a** (35%), respectively.

**Substrate scope with respect to quinoxalinones.** Meanwhile, the scope of quinoxalinones **4a–4l** was explored (Table 3). *N*-Alkylated quinoxalinones **4a–4c** and *N*-benzylated quinoxalinone **4d** were successfully reacted with **2a** to provide C3-methylated quinoxalinone adducts **5a–5d** in excellent yields. Additionally, quinoxalinones **4e** and **4f** were coupled with **2a** to afford **5e** (94%) and **5f** (32%), respectively. The reaction also readily proceeded with *N*-arylated quinoxalinones **4g–4k**, furnishing the corresponding products **5g–5k**. Notably, the electronic property of the quinoxalinone or *N*-aryl rings had a profound effect on this transformation. For example, the methylation of highly electron-deficient quinoxalinone derivatives **4f**, **4h** and **4k** was less efficient. Finally, pyrido-pyrazinone **4l** also participated in the methylation reaction to provide **5l** in 78% yield. (see Table 3 in the Supplementary Files)

**Substrate scope with respect to azauracils and azauracil nucleosides.** Azauracil, an azapyrimidinone analogue of uracil, is of interest in medicinal chemistry due to its potential to inhibit various species of microorganisms. The ribonucleosides of 6-azauracil have been shown to display diverse biological profiles such as antiviral, antitumor, and antifungal activities<sup>50–53</sup>. Based on the methylation of uracil in nature, we envisioned the direct alkylation of 6-azauracils and 6-azauracil nucleosides (Scheme 4). *N*-Substituted azauracil **6a** was smoothly alkylated with **2a–2c** to afford the corresponding products **7a–7c** in satisfactory yields. In addition, triazinones **6b–6e** were compatible with this process. It is noteworthy that hydroxyl and 2-pyranosyl groups in **7e** and **7g** were also tolerable. Direct C(sp<sup>2</sup>)-H methylation of 2'-deoxy-6-azauridine nucleoside **6f** was successfully achieved by using K<sub>3</sub>PO<sub>4</sub> as a base, providing **7h** in 94% yield. Moreover, azauracil ribonucleoside **6g** was also methylated with **2a** to afford **7i** in 91% yield.

**Mechanistic investigation and proposed reaction mechanism.** To garner mechanistic insights into this process, a series of deuterium-labeling experiments were performed (Fig. 2a). Treatment of **1a** with KOH in the presence of D<sub>2</sub>O resulted in 45% and 94% deuterium incorporation at the C3 and C6 positions, respectively. Partial deuteration (20%) on the *N*-Me group was also observed. These results indicate that a hydroxide anion possibly undergo nucleophilic addition onto imino functionality of pyrazinone **1a** to generate a nitrogen anion intermediate, which can undergo a deuteration/deprotonation equilibrium reaction at the C3 and C6 positions (see the Supporting Information for the proposed mechanism). The reaction of **1a** with **2a** in the presence of D<sub>2</sub>O under otherwise identical reaction conditions provided 93%

deuteration at the benzylic CH<sub>3</sub> moiety as well as 73% deuteration at the C6 position, suggesting C3-methylation by sulfoxonium ylide on **1a** followed by subsequent deproto-deuteration at the benzylic position. Benzylic deuteration was further confirmed by the reaction of **3a** in aqueous KOH solution. To evaluate the unique reactivity of pyrazinones as cyclic iminoamides, control experiments were performed with *N*-aryl 2-pyridone and 2*H*-benzo[*b*][1,4]oxazin-2-one. No formation of methylated adducts under the standard reaction conditions was observed, revealing that the cyclic iminoamide backbone is crucial for the C(sp<sup>2</sup>)-H methylation (see the Supporting Information for the details). Based on the deuterium-labeling experiment results and previous literature related to sulfoxonium ylides,<sup>8</sup> we propose a plausible reaction mechanism (Fig. 2b). Sulfoxonium ylide **A**, derived from **2a** and KOH, undergoes nucleophilic addition onto the imine moiety of **1a**, generating intermediate **B**. Under basic aqueous conditions, protonation of the nitrogen anion and E2 elimination of intermediate **B** spontaneously occur to deliver intermediate **C** and DMSO. The release of DMSO was detected by GC-MS analysis of the crude reaction mixture. Finally, protonation of the exo-olefin in **C** occurs to afford the C3-methylated pyrazinone **3a**.

**Synthetic applications.** To illustrate the synthetic potential of the developed protocol, gram-scale experiments were first performed (Fig. 3a). The reaction of pyrazinone **1a** (2 g, 10.8 mmol) with **2a** afforded **3a** in 90% yield. In addition, a gram-scale reaction of quinoxalinone **4d** was also successfully performed, providing **5d** in 95% yield. It is noteworthy that both products **3a** and **5d** were isolated by simple filtration instead of column chromatography, indicating the capability of the developed method in process chemistry. Next, various transformations of the synthesized C3-methylated products were performed (Fig 3b). The Ni(II)-catalyzed cross-coupling reaction between **3a** and benzyl alcohol gave **8a** in 82% yield. Benzylic oxidation of **3a** with SeO<sub>2</sub> followed by reductive amination with 1-adamantylamine provided **8b** in 40% yield. In addition, benzylic bromination of **5a** and subsequent *O*-nucleophilic substitution with estrone furnished **8c** in 50% yield. To demonstrate the utility of the *N*-protecting group, the tetrahydropyranyl group on **3d** was removed under acidic conditions to provide the free-(NH)-pyrazinone adduct in 90% yield, which further reacted with arylsulfonyl chloride to deliver **8d** in 60% yield.

**Synthesis of tetra-substituted pyrazine.** To further demonstrate the utility of the developed methodology, the sequential transformation of *N*-benzylated pyrazinone **9a** was performed (Fig. 4). Pyrazinone **9a** was smoothly methylated with **2a** to provide **9b** in 82% yield. Removal of the benzyl group of **9b** followed by treatment with PhPOCl<sub>2</sub> afforded chloropyrazine **9c** in 79% yield. Finally, Suzuki cross-coupling reaction between **9c** and 2-thiophene boronic acid under Pd(II) catalysis provided tetra-substituted pyrazine **9d** in 70% yield.

## Discussion

In conclusion, we presented an unprecedented protocol for the direct C-H alkylation of *N*-heterocycles, including pyrazinones, quinoxalinones, and azauracils, using sulfoxonium salts as the alkylating agents. The use of aqueous solvent in the coupling reaction and the selective methylation of azauracil nucleosides under the developed reaction conditions are noteworthy. The synthetic applicability of this

method was demonstrated by successful gram-scale reactions and valuable synthetic transformations of the methylated products, as well as by the synthesis of a tetra-substituted pyrazine via sequential transformations. The findings of this study are expected to be of significant interest to organic and medicinal chemists because of the synthetic simplicity, broad substrate scope, high efficiency, excellent chemoselectivity, and environmentally benign nature of the developed methodology.

## Methods

**General methods.** For the synthetic procedure and  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  NMR spectra of all compounds in this manuscript, see Supplementary Informations.

**General procedure for the methylation of 3a.** To an oven-dried sealed tube charged with 1-methyl-5-phenylpyrazinone (**1a**) (37.6 mg, 0.2 mmol, 1.0 equiv.), KOH (33.6 mg, 0.6 mmol, 3.0 equiv.), and trimethylsulfonium iodide (**2a**) (132.0 mg, 0.6 mmol, 3.0 equiv.) was added  $\text{H}_2\text{O}$  (1 mL) at room temperature under air. The reaction mixture was allowed to stir at 100 °C for 2 h. The reaction mixture was cooled to room temperature and filtered through a bed of  $\text{Na}_2\text{SO}_4$ . The solid bed was washed with a mixture of  $\text{CH}_2\text{Cl}_2$  and MeOH (9:1). The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography ( $\text{CH}_2\text{Cl}_2/\text{acetone} = 97:3$ ) to afford 36.0 mg of **3a** in 90% yield.

## Declarations

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### Author Contributions

I.S.K. conceived and designed the experiments. I.S.K. and P.G. wrote the manuscript. P.G., N.Y.K., S.K. and S.H. performed experiments and prepared the Supplementary Information. S.H.L., W.A., N.K.M. and S.B.H. helped collecting some starting materials. P.G. and N.Y.K. contributed equally on this work. All authors discussed the results and commented on the manuscript.

### Competing Interests

The authors declare no competing interests.

### Additional Information

**Supplementary Information** is available for this paper at <https://>

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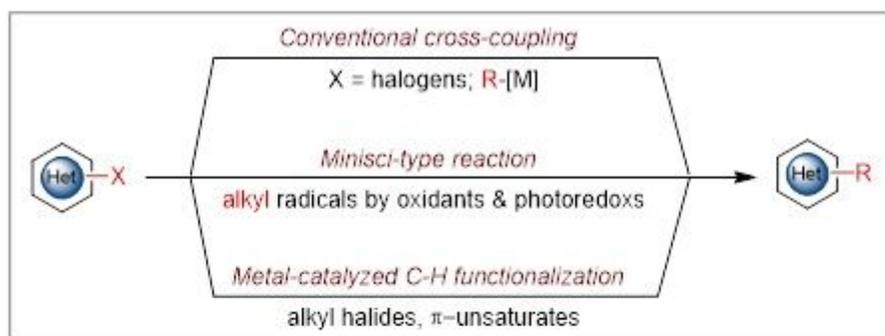
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## Tables

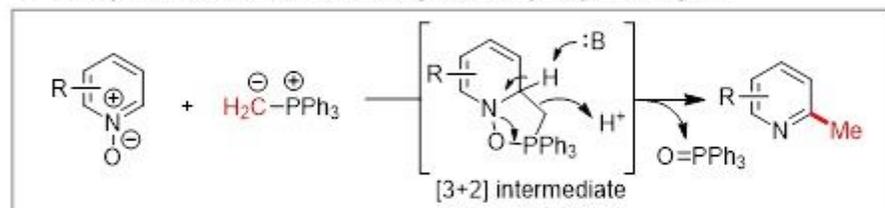
Due to technical limitations the Tables are available as a download in the Supplementary Files.

## Figures

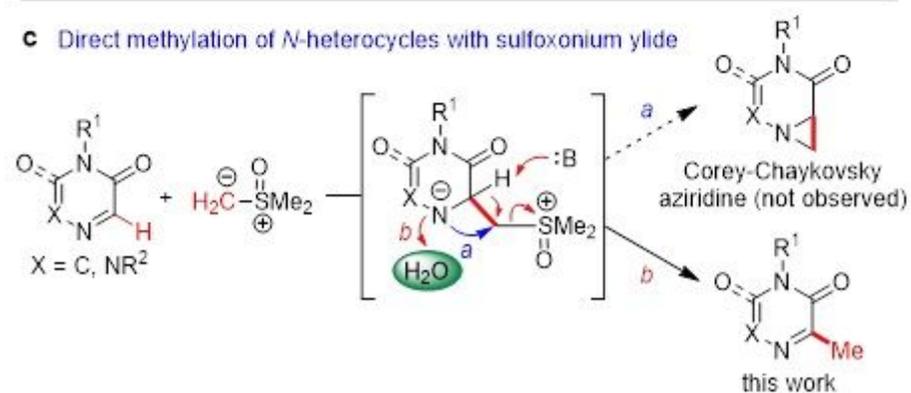
**a** Classification of *N*-heterocycle alkylations



**b** Methylation of activated *N*-heterocycles with phosphonium ylide

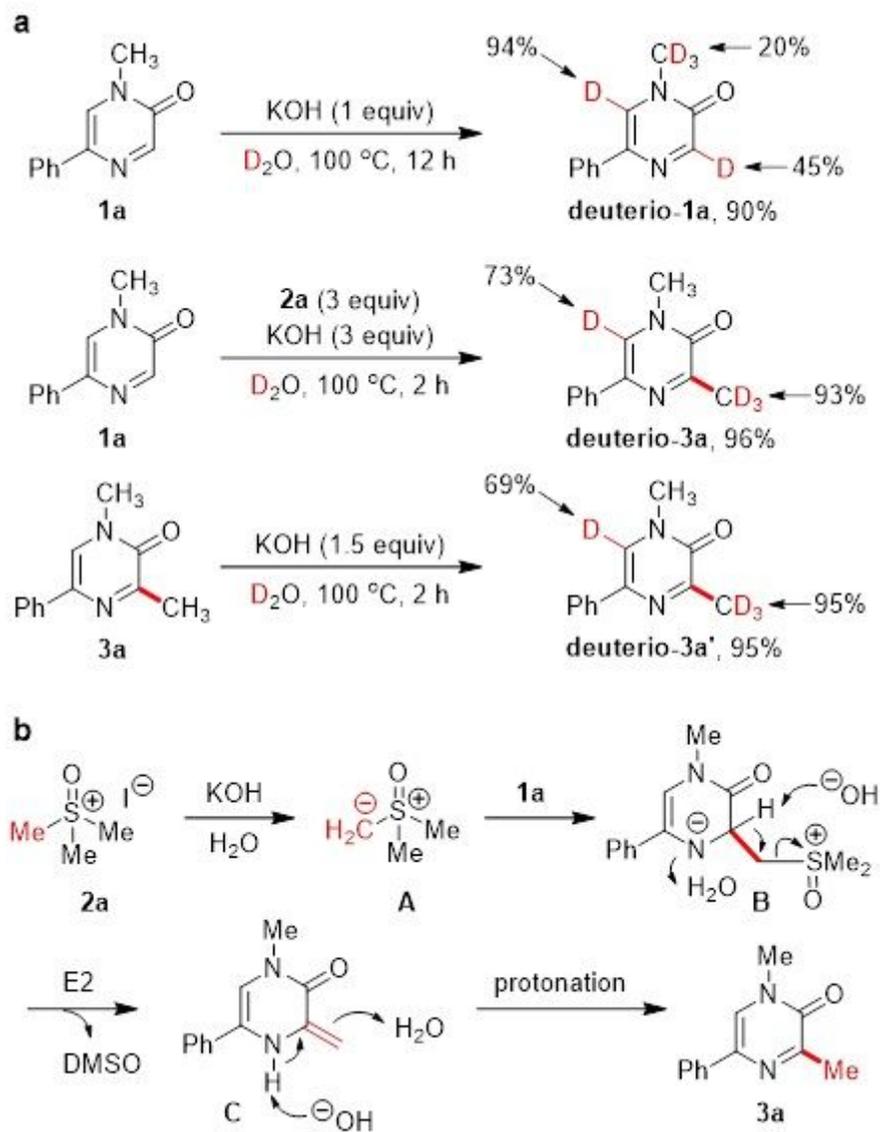


**c** Direct methylation of *N*-heterocycles with sulfoxonium ylide



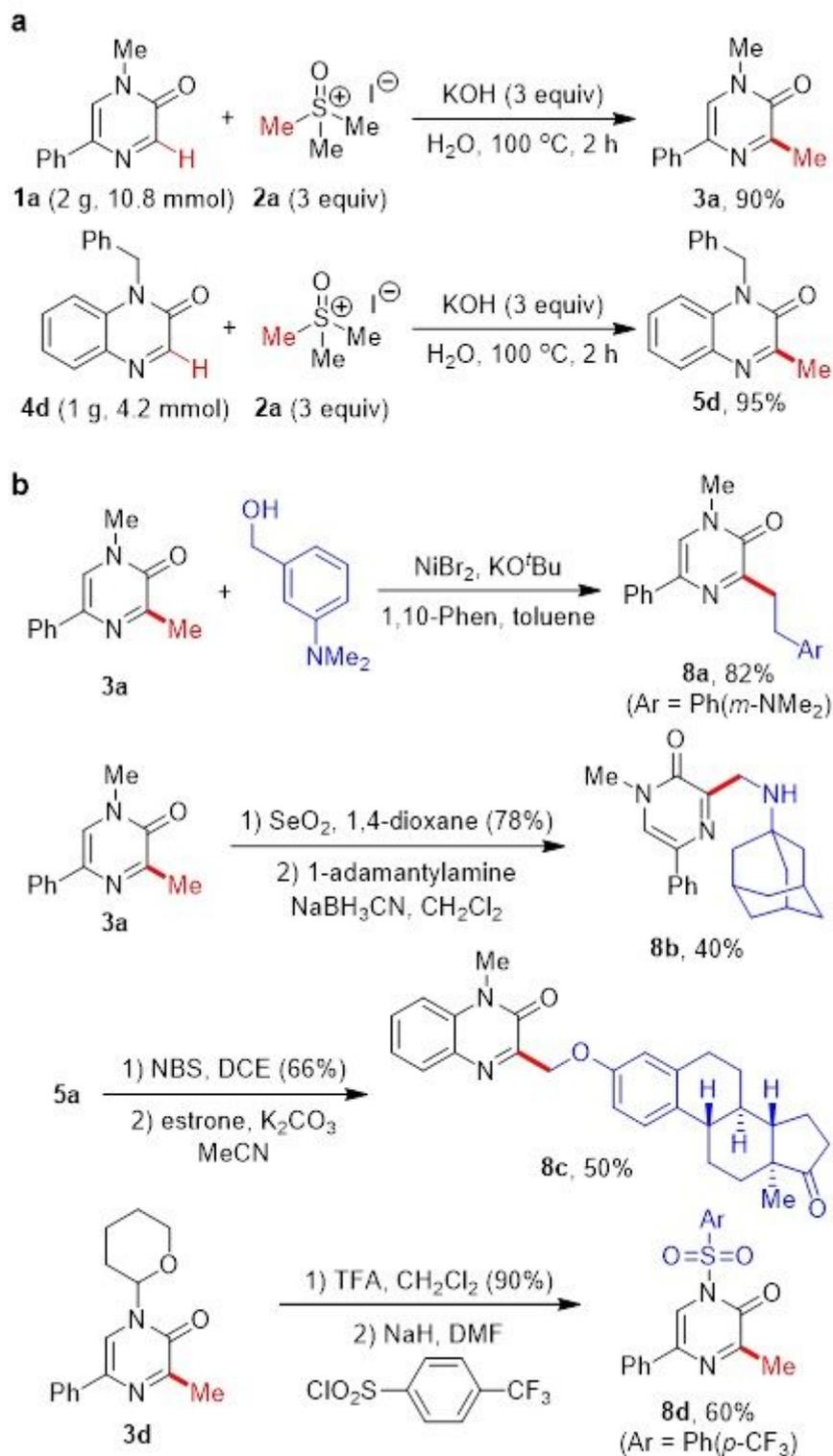
**Figure 1**

Direct C(sp<sup>2</sup>)-H alkylations. a Classification of *N*-heterocycle alkylations. b Methylation of activated *N*-heterocycles with phosphonium ylide. c Direct methylation of *N*-heterocycles with sulfoxonium ylide.



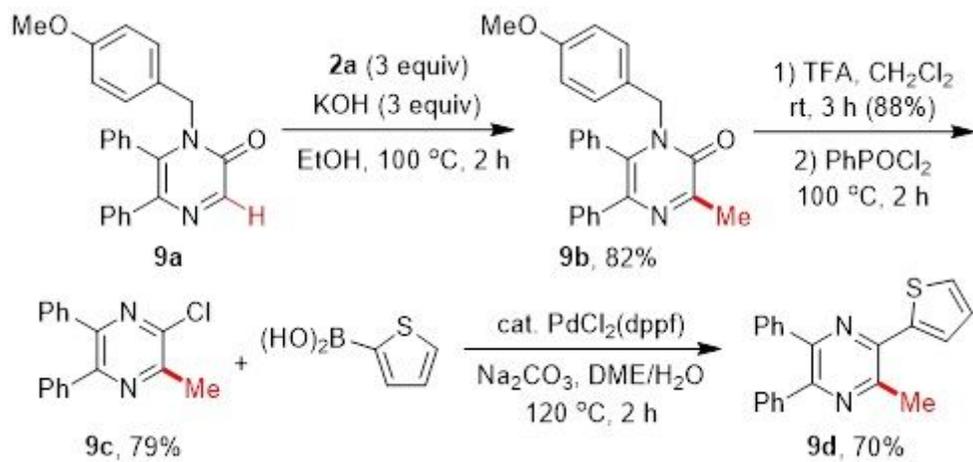
**Figure 2**

Insight into the reaction mechanism. a Mechanistic investigations using deuterium-labeling experiments. b Proposed reaction mechanism.



**Figure 3**

Synthetic applications. a Gram-scale reactions. b Synthetic transformations.



**Figure 4**

Synthesis of tetra-substituted pyrazine.

## Supplementary Files

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