OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

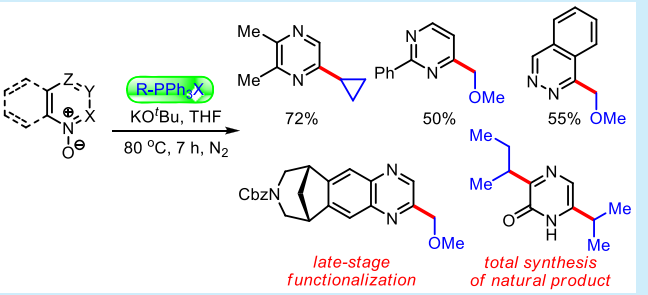
Site-Selective C−H Alkylation of Diazine *N*-Oxides Enabled by Phosphonium Ylides

Prithwish Ghosh,[†] Na Yeon Kwon,[†] Sangil Han, Saegun Kim, Sang Hoon Han, Neeraj Kumar Mishra, Young Hoon Jung, Sang J. Chung,* and In Su Kim*

School of Pharmacy, Sungkyunkwan University, Suwon 16419, Republic of Korea

Supporting Information

ABSTRACT: The synthesis of alkylated diazine derivatives is important for their practical utilization as pharmaceuticals and for other purposes. Herein, we describe the metal-free site-selective C−H alkylation of diazine *N*-oxides using phosphonium ylides that affords a variety of alkylated diazine derivatives with broad functional group tolerance. The utility of this method is showcased by the late-stage functionalization of a commercially available drug such as varenicline. Notably, the sequential C−H alkylation of pyrazine *N*-oxides for the total synthesis of a pyrazine-containing natural product, paenibacillin A, highlights the importance of this method.



The development of effective synthetic methods is important for advancing medicinal, agrochemical, and other chemical industries. The ability to synthesize substituted diazines is of great significance because these motifs are commonly found in biologically relevant molecules.[1] In particular, alkylated diazines are of paramount interest in medicinal chemistry due to their remarkable therapeutic potential. For instance, methoxymethylated, cyclopropylated, and cyclobutylated pyrazine frameworks have been recognized as essential units with potent pharmacological activity (Figure 1).[2]

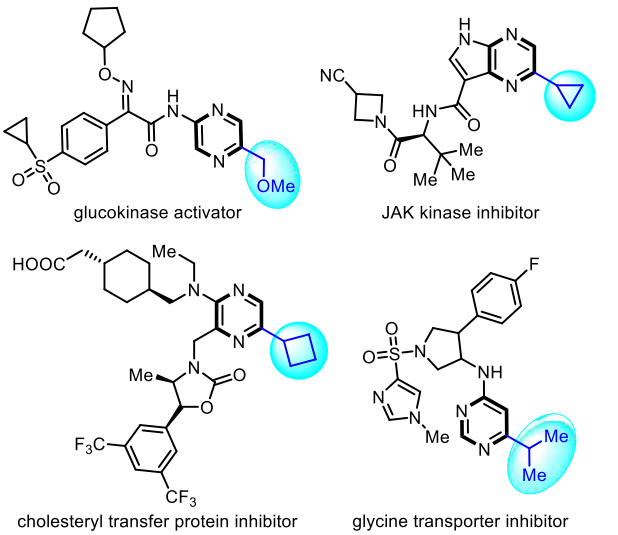
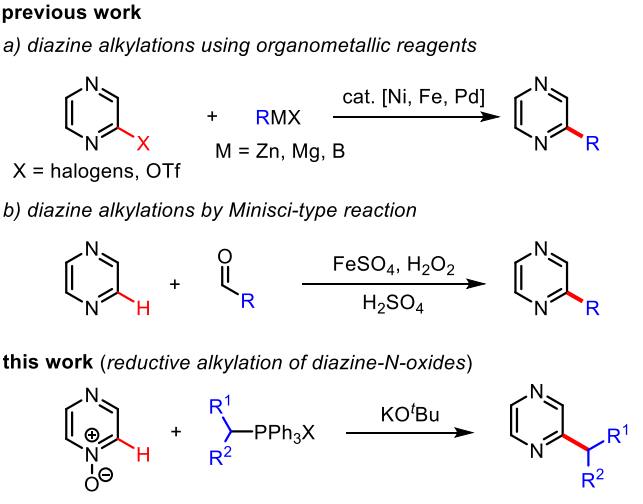


Figure 1. Selected examples of alkylated diazines.

However, the direct installation of these alkyl groups on diazine rings has been rarely explored. The classical approach for the synthesis of alkylated diazines is the transition metal-mediated cross-coupling reaction between functionalized diazines and organometallic reagents (Scheme 1).[3]

The metal-mediated Minisci-type alkylation of diazines in the presence of radical sources has been reported.[4a,b] In addition, the metal-free Minisci-type alkylations of various N-heterocycles were also disclosed.[4c−e] However, the generation of residual metal wastes and regioisomeric impurities remains

Scheme 1. Site-Selective Alkylation of Diazine Heterocycles



Received: July 9, 2019

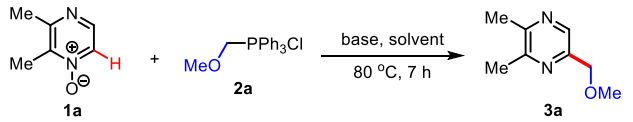
DOI: 10.1021/acs.orglett.9b02365
Org. Lett. XXXX, XXX, XXX−XXX

an obstacle for the pharmaceutical application of alkylated diazines. Therefore, an efficient method for the formation of alkylated diazines under mild and metal-free conditions is highly desirable.

Diazine *N*-oxides have been used as precursors in the synthesis of functionalized diazine derivatives.[5] Halogenation, cyanation, and olefination have been described previously.[6] Additionally, direct lithiation and subsequent alkylation or acylation of pyrazine *N*-oxides were investigated.[7] Phosphonium ylides are conventionally utilized for olefination reaction with carbonyl compounds.[8] Moreover, phosphonium salts have been employed in Michael additions,[9] organocatalytic Mannich reactions,[10] and other alkylation reactions.[11] Recently, our group first demonstrated the metal-free site-selective C−H alkylation of pyridine and quinoline *N*-oxides using Wittig reagents.[12a] Other alkyl sources were also utilized for the metal-free C−H alkylations of heterocyclic *N*-oxides.[12b−d] Due to the widespread relevance of diazine molecules in recent drug discovery, we herein describe the metal-free site-selective alkylation of diazine *N*-oxides using phosphonium ylides to furnish alkylated diazines. Notably, the sequential transformation of diazine *N*-oxides leading to the formation of highly substituted diazines highlights the applicability of the developed methodology.

This investigation was initiated by examining the optimal reaction conditions for the coupling of pyrazine *N*-oxide **1a** with methoxymethyltriphenylphosphonium chloride (**2a**), as shown in Table 1. Screening of various reaction conditions showed that the use of KO^{t}Bu (3 equiv) in a THF solvent at 80 °C with a reaction time of 7 h afforded C2-alkylated pyrazine **3a** in 78% yield (Table 1, entry 2). It should be noted that this reaction was scaled up to 1 g (8.06 mmol) to give 0.95 g of **3a** in 77% yield (Table 1, entry 14).

Table 1. Selected Optimization of Reaction Conditions[a]



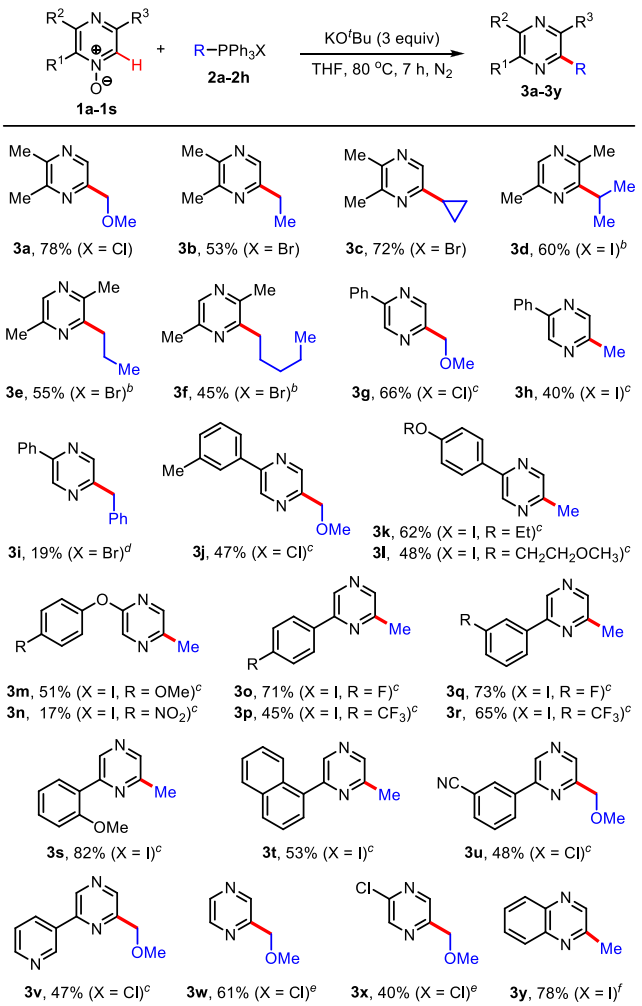
1a 2a 3a

entry	base (equiv)	2a (equiv)	solvent	yield[b]
1	KO^{t}Bu (2)	2	THF	25
2	KO^{t}Bu (3)	3.5	THF	78
3	KO^{t}Bu (3)	5	THF	76
4	NaO^{t}Bu (3)	3.5	THF	8
5	LiO^{t}Bu (3)	3.5	THF	trace
6	KOMe (3)	3.5	THF	6
7	KHMDS (3)	3.5	THF	10
8	DBU (3)	3.5	THF	no reaction
9	KO^{t}Bu (3)	3.5	1,4-dioxane	20
10	KO^{t}Bu (3)	3.5	CPME	72
11	KO^{t}Bu (3)	3.5	MTBE	70
12	KO^{t}Bu (3)	3.5	toluene	74
13[c]	KO^{t}Bu (3)	3.5	THF	51
14[d]	KO^{t}Bu (3)	3.5	THF	77

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (quantity noted), base (quantity noted), solvent (2 mL) at 80 °C for 7 h under a N_2 atmosphere in pressure tubes. Abbreviations: KHMDS, potassium bis(trimethylsilyl)amide; CPME, cyclopentyl methyl ether; MTBE, *tert*-butylmethyl ether. [b]Isolated percent yield determined by flash column chromatography. [c]The reaction was carried out at 60 °C. [d]Gram-scale experiment.

Having determined the optimal reaction conditions, we examined the scope of the reaction with a variety of pyrazine and quinoxaline *N*-oxides and phosphonium salts (Scheme 2).

Scheme 2. Substrate Scope of Pyrazine *N*-Oxides and Phosphonium Salts[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.7 mmol, 3.5 equiv), KO^{t}Bu (3 equiv), THF (2 mL) at 80 °C for 7 h. [b]Reaction conditions: **1** (0.2 mmol), **2** (0.7 mmol, 3.5 equiv), KO^{t}Bu (3.5 equiv), CPME (2 mL) at 90 °C for 10 h. [c]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol, 3 equiv), KO^{t}Bu (2.5 equiv), THF (2 mL) at 80 °C for 6 h. [d]Reaction conditions: **1** (0.2 mmol), **2** (0.7 mmol, 3.5 equiv), KO^{t}Bu (3.5 equiv), THF (2 mL) at 80 °C for 10 h. [e]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol, 3 equiv), KO^{t}Bu (2.5 equiv), THF (2 mL) at 80 °C for 4 h. [f]Reaction conditions: **1** (0.2 mmol), **2** (0.7 mmol, 3.5 equiv), KO^{t}Bu (3.5 equiv), THF (2 mL) at 80 °C for 6 h.

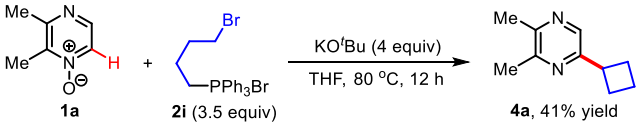
As anticipated, 2,3-dimethylpyrazine *N*-oxide (**1a**) was smoothly coupled with EtPPh$_3$Br (**2b**) and cyclopropyl PPh$_3$Br (**2c**) to afford alkylated pyrazines **3b** (53%) and **3c** (72%), respectively.

To evaluate the steric effect in this process, 2,5-dimethylpyrazine *N*-oxide (**1b**) was coupled with branched or linear alkylphosphonium salts **2d−2f**. Under the modified reaction conditions, the corresponding adducts **3d−3f** were formed in moderate to good yields. In addition, C3-aryl- and C3-oxyaryl-substituted pyrazine *N*-oxides **1c−1h** exclusively underwent C−H alkylation at the less hindered site, affording

DOI: 10.1021/acs.orglett.9b02365
Org. Lett. XXXX, XXX, XXX−XXX

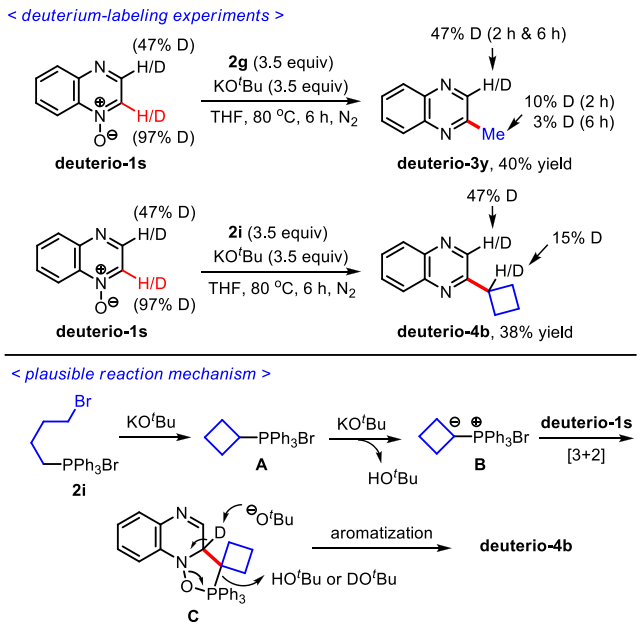
the desired products **3g**−**3n**. Moreover, C2-aryl-substituted pyrazine *N*-oxides **1i**−**1p** also participated in the C6 alkylation reaction to furnish the corresponding products **3o**−**3v**, respectively. The tolerance of this reaction system for NO_2 and CN groups was of interest, as these moieties provide versatile synthetic handles in the products. This reaction proceeded readily with unsubstituted pyrazine *N*-oxide (**1q**) to furnish **3w** in 61% yield. The chloro-substituted pyrazine *N*-oxide **1r** was also compatible, affording the desired product **3x**, which can be further functionalized by nucleophilic aromatic substitution reactions.[13] Furthermore, quinoxaline *N*-oxide (**1s**) also reacted with $MePPh_3I$ (**2g**) to give **3y** in 78% yield. It is known that phosphonium ylide ($CH_3CO_2CH{=}PPh_3$) and phosphonium salts (phenyl PPh_3Br and pyridinyl PPh_3Br) were unsuccessful in this coupling reaction, presumably due to the lower nucleophilicity of the delocalized carbanion and the lack of formation of (hetero)aryl carbanions under the current reaction conditions. Notably, this protocol allows direct incorporation of the cyclobutyl moiety on the diazine frameworks. For example, pyrazine *N*-oxide **1a** was smoothly coupled with 4-bromobutylPPh_3Br (**2i**) to provide the C2-cyclobutylated pyrazine adduct **4a** in 41% yield (Scheme 3).

Scheme 3. Synthesis of the C2-Cyclobutylated Pyrazine Adduct



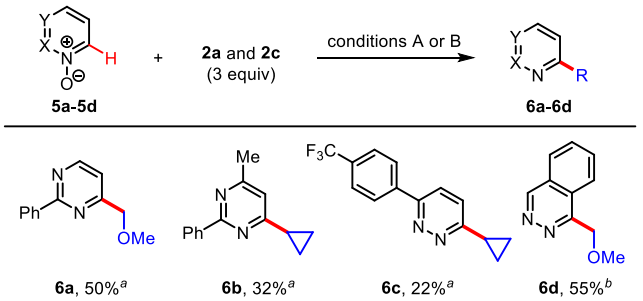
To gain mechanistic insight into this process, we first performed a deuterium labeling experiment using **deuterio-1s** and **2g** for 2 and 6 h, respectively, under otherwise identical reaction conditions (Scheme 4). Partial deuterium incorporation (10% D) at the benzyl position of the product **deuterio-3y** was observed after reaction for 2 h. This result reveals that intramolecular deuterium migration can be excluded in the reaction pathway. Moreover, 3% incorporation of deuterium at the benzyl position was detected after 6 h, indicatve of rapid proton exchange of benzylic deuterium under basic reaction conditions. Furthermore, the deuterium labeling experiment was conducted by using **deuterio-1s** and **2i**, resulting in 15% deuterium incorporation. It should be noted that no exchange of deuterium at the C3 position was observed in any experiment. On the basis of the deuterium labeling experiments, a plausible reaction mechanism was proposed, as outlined in Scheme 4. The initial formation of phosphonium ylide and subsequent intramolecular cyclization afforded cyclobutyl phosphonium salt **A**, which further generated the second ylide intermediate **B** in the presence of KO^{t}Bu. The intermolecular [3+2] annulation reaction between quinoxaline *N*-oxide **deuterio-1s** and phosphonium ylide **B** furnished intermediate **C**, leading to the formation of the C2-cyclobutylated quinoxaline **deuterio-4b** through aromatization by an external base.

Scheme 4. Deuterium Labeling Experiments and Plausible Reaction Mechanism



Pyrimidine and pyridazine *N*-oxides **5a**−**5d** were also employed in the reaction with **2a** and **2c**, as shown in Scheme 5. To our delight, C2-substituted pyrimidine *N*-oxides **5a** and **5b** reacted with phosphonium salts **2a** and **2c**, affording products **6a** and **6b**, respectively. However, the C2-unsubstituted substrate, 5-phenyl pyrimidine *N*-oxide, did not produce any coupling product under the current reaction conditions (data not shown). Moreover, pyridazine *N*-oxide **5c** also participated in the coupling reaction to give **6c**, albeit with slightly decreased reactivity. Phthalazine *N*-oxide (**5d**) was also coupled with **2a** in the presence of KHMDS as a base to furnish phthalazine derivative **6d** in 55% yield. To investigate the relative reactivity of pyrazine *N*-oxides versus pyrimidine *N*-oxides, a competitive intermolecular experiment was performed (see the Supporting Information for details). Exposure of **2a** to equimolar quantities of **1c** and **5a** under otherwise identical conditions provided a mixture of **3g** (60%) and **6a** (31%).

Scheme 5. Substrate Scope of Pyrimidine and Pyridazine *N*-Oxides

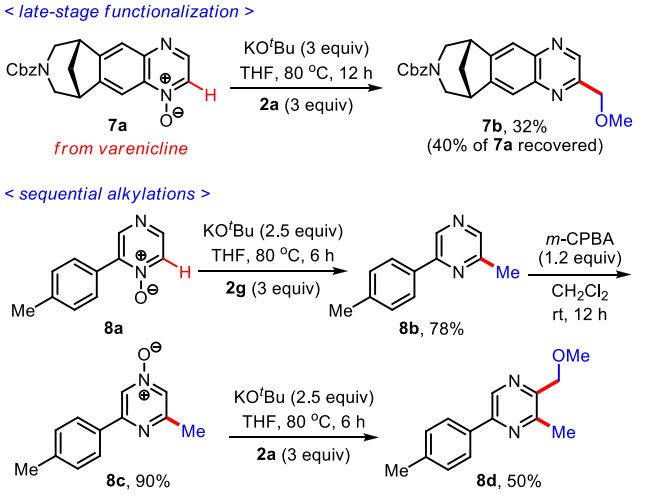


[a]Reaction conditions: **5a**−**5c** (0.2 mmol), **2a** or **2c** (0.6 mmol, 3 equiv), KO^{t}Bu (3 equiv), THF (2 mL) at 80 °C for 6 h under N_2 in reaction tubes. [b]Reaction conditions: **5d** (0.2 mmol), **2a** (0.4 mmol, 2 equiv), KHMDS (1.8 equiv), THF (2 mL) at room temperature for 4 h under N_2 in reaction tubes.

This protocol allows late-stage functionalization and sequential alkylation of complex diazine molecules bearing an *N*-oxide group (Scheme 6). For example, *N*-oxide derivative **7a**, derived from varenicline, a commercial smoking cessation agent, was selectively reacted with **2a** to provide desired product **7b** (32%), with recovery of starting material **7a** (40%).

DOI: 10.1021/acs.orglett.9b02365
Org. Lett. XXXX, XXX, XXX−XXX

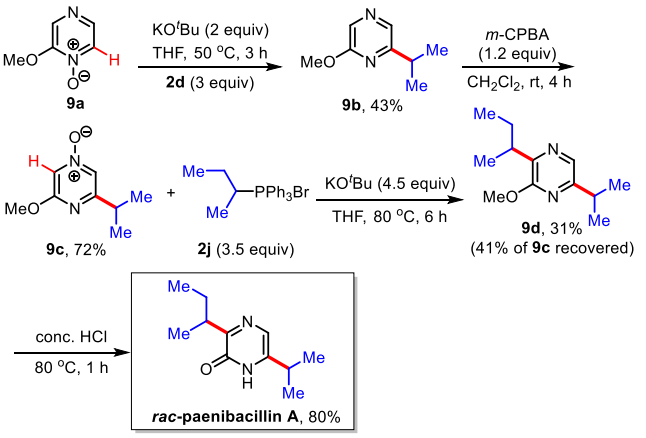
Scheme 6. Late-Stage Functionalization and Sequential Alkylations



Meanwhile, the sequential alkylation of pyrazine *N*-oxide **8a** furnished 2,3-bis-alkylated pyrazine adduct **8d**.

To highlight the utility of this protocol, we first report the total synthesis of racemic paenibacillin A, isolated from *Paenibacillus* sp. XY-2 in 2015,[14] based on the sequential C−H alkylation of pyrazine *N*-oxides (Scheme 7). Treatment of 2-

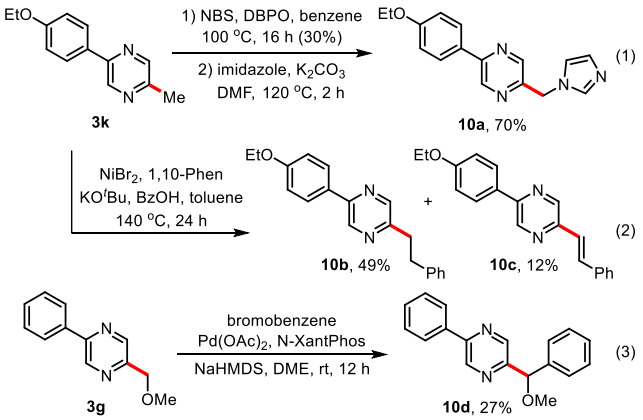
Scheme 7. Total Synthesis of Racemic Paenibacillin A



methoxypyrazine *N*-oxide (**9a**)[15] with **2d** under the developed conditions provided C6-isopropylated pyrazine **9b** in 43% yield, which was subsequently oxidized by *m*-CPBA to afford pyrazine *N*-oxide **9c** in 72% yield. Site-selective alkylation of **9c** was performed using *s*-butylPPh$_3$Br (**2j**), furnishing 3,6-dialkylated pyrazine **9d** (31%), with recovery of starting material **9c** (41%). Hydrolysis of **9d** with concentrated HCl gave racemic paenibacillin A in 80% yield. The spectroscopic data for paenibacillin A were in full agreement with the reported literature values.

To illustrate the applicability of the alkylated diazines, we performed a series of synthetic transformations, as shown in Scheme 8. Benzylic bromination of **3k** and subsequent amination using imidazole afforded **10a** in 70% yield, which is recognized as a pivotal scaffold of a Cushing's syndrome agent (eq 1).[16] The Ni-catalyzed C−H functionalization of **3k** with benzyl alcohol gave alkylated product **10b** (49%) and olefinated product **10c** (12%) (eq 2). Finally, direct C−H

Scheme 8. Synthetic Transformations of Alkylated Diazines



arylation of methoxymethyl pyrazine **3g** was performed to furnish **10d** in 27% yield (eq 3).

In conclusion, a highly efficient protocol for the formation of alkylated diazine derivatives via the metal-free site-selective C−H alkylation of diazine *N*-oxides using phosphonium ylides was developed. The method affords a wide substrate scope, high site selectivity, and broad functional group tolerance. In particular, the sequential C−H alkylation of diazine *N*-oxides and gram-scale reaction demonstrate the utility of the developed method. Furthermore, the late-stage C−H functionalization of a complex molecule and total synthesis of a natural product highlight the great potential of this method for application in drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02365.

Experimental procedures, characterization data, and ^{1}H, ^{13}C, and ^{19}F NMR spectra for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: sjchung@skku.edu.
*E-mail: insukim@skku.edu.

ORCID

Sang J. Chung: 0000-0002-3501-212X
In Su Kim: 0000-0002-2665-9431

Author Contributions

†P.G. and N.Y.K. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF) funded by the Korea government (MSIP) (2017R1A2B2004786 and 2019R1A4A2001451).

■ REFERENCES

(1) Selected reviews: (a) Joule, J. A.; Mills, K. In *Heterocyclic Chemistry*, 5th ed.; Wiley-Blackwell: New York, 2010; pp 249−288. (b) Asif, M. Recent Efforts for the Development of Antitubercular

DOI: 10.1021/acs.orglett.9b02365
Org. Lett. XXXX, XXX, XXX−XXX

Drug Containing Diazine Ring. *Med. Chem.* **2012**, *2*, 151−167. (c) Nikishkin, N. I.; Huskens, J.; Verboom, W. Transition Metal-Catalyzed Functionalization of Pyrazines. *Org. Biomol. Chem.* **2013**, *11*, 3583−3602. (d) Baumann, M.; Baxendale, I. R. An Overview of the Synthetic Routes to the Best Selling Drugs Containing 6-Membered Heterocycles. *Beilstein J. Org. Chem.* **2013**, *9*, 2265−2319. (e) Dolezal, M.; Zitko, J. Pyrazine Derivatives: A Patent Review (June 2012 − present). *Expert Opin. Ther. Pat.* **2015**, *25*, 33−47. (f) Chevallier, F.; Mongin, F. Functionalization of Diazines and Benzo Derivatives through Deprotonated Intermediates. *Chem. Soc. Rev.* **2008**, *37*, 595−609. For selected examples of the C−H functionalization of aza-heterocycles, see: (g) Greßies, S.; Klauck, F. J. R.; Kim, J. H.; Daniliuc, C. G.; Glorius, F. Ligand-Enabled Enantioselective Csp^3−H Activation of Tetrahydroquinolines and Saturated Aza-Heterocycles by Rh^I. *Angew. Chem., Int. Ed.* **2018**, *57*, 9950−9954. (h) Bentley, K. W.; Dummit, K. A.; Van Humbeck, J. F. A Highly Site-Selective Radical sp^3 C−H Amination of Azaheterocycles. *Chem. Sci.* **2018**, *9*, 6440−6445.

(2) (a) Sugawara, K.; Matsudaira, T.; Sugama, H.; Nawano, M.; Ohashi, R. An Oxime Derivative and Preparations Thereof. Intl. Pub. No. WO 2007/007886 A1, 2007. (b) Soth, M.; Hermann, J. C.; Yee, C.; Alam, M.; Barnett, J. W.; Berry, P.; Browner, M. F.; Frank, K.; Frauchiger, S.; Harris, S.; He, Y.; Hekmat-Nejad, M.; Hendricks, T.; Henningsen, R.; Hilgenkamp, R.; Ho, H.; Hoffman, A.; Hsu, P.-Y.; Hu, D.-Q.; Itano, A.; Jaime-Figueroa, S.; Jahangir, A.; Jin, S.; Kuglstatter, A.; Kutach, A. K.; Liao, C.; Lynch, S.; Menke, J.; Niu, L.; Patel, V.; Railkar, A.; Roy, D.; Shao, A.; Shaw, D.; Steiner, S.; Sun, Y.; Tan, S.-L.; Wang, S.; Vu, M. D. 3-Amido Pyrrolopyrazine JAK Kinase Inhibitors: Development of a JAK3 vs JAK1 Selective Inhibitor and Evaluation in Cellular and in Vivo Models. *J. Med. Chem.* **2013**, *56*, 345−356. (c) Park, J. H.; Song, S. H.; Chung, H. K.; Kim, H. J.; Lee, J. H.; Jang, B. J.; Kim, E. J.; Jung, H. H.; Ryu, C. L.; Hwang, J.-S.; Lee, H. K.; Kang, K. K.; Kim, S. H. Novel Oxazolidinone Derivatives as CETP Inhibitors, Its Preparation Method and Pharmaceutical Composition Comprising the Same. Intl. Pub. No. WO 2014/157994 A1, 2014. (d) Amberg, W.; Pohlki, F.; Lange, U.; Wang, Y. X.; Zhao, H. H.; Li, H.-Q.; Brewer, J. T.; Zanze, I.; Dietrich, J.; Vasudevan, A.; Djuric, S. W.; Lao, Y.; Hutchins, C. W. Pyrrolidine Derivatives, Pharmaceutical Compositions Containing Them, and Their Use in Therapy. Int. Pub. No. WO 2014/140310 A1, 2014.

(3) For selected references on diazine alkylations, see: (a) Dickschat, J. S.; Reichenbach, H.; Wagner-Döbler, I.; Schulz, S. Novel Pyrazines from the Myxobacterium *Chondromyces crocatus* and Marine Bacteria. *Eur. J. Org. Chem.* **2005**, *2005*, 4141−4153. (b) Molander, G. A.; Gormisky, P. E. Cross-Coupling of Cyclopropyl- and Cyclobutyltrifluoroborates with Aryl and Heteroaryl Chlorides. *J. Org. Chem.* **2008**, *73*, 7481−7485. (c) Pitchaiah, A.; Hwang, I. T.; Hwang, J.-S.; Kim, H.; Lee, K.-I. Regioselective Synthesis of Trialkylpyrazines via Nickel-Catalyzed Negishi Cross-Coupling of Pyrazine Triflate. *Synthesis* **2012**, *44*, 1631−1636. (d) Petiot, P.; Gagnon, A. Palladium-Catalyzed Cross-Coupling Reaction of Trialkylbismuthines with 2-Haloazines and Diazines. *Heterocycles* **2014**, *88*, 1615−1624. (e) Price, G. A.; Hassan, A.; Chandrasoma, N.; Bogdan, A. R.; Djuric, S. W.; Organ, M. G. Pd-PEPPSI-IPent-SiO_2: A Supported Catalyst for Challenging Negishi Coupling Reactions in Flow. *Angew. Chem., Int. Ed.* **2017**, *56*, 13347−13350.

(4) (a) Bohman, B.; Berntsson, B.; Dixon, R. C. M.; Stewart, C. D.; Barrow, R. A. Alkylations and Hydroxymethylations of Pyrazines via Green Minisci-Type Reactions. *Org. Lett.* **2014**, *16*, 2787−2789. (b) Zhang, L.; Liu, Z.-Q. Molecular Oxygen-Mediated Minisci-Type Radical Alkylation of Heteroarenes with Boronic Acids. *Org. Lett.* **2017**, *19*, 6594−6597. (c) Antonchick, A. P.; Burgmann, L. Direct Selective Oxidative Cross-Coupling of Simple Alkanes with Heteroarenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 3267−3271. (d) Siddaraju, Y.; Lamani, M.; Prabhu, K. R. A Transition Metal-Free Minisci Reaction: Acylation of Isoquinolines, Quinolines, and Quinoxaline. *J. Org. Chem.* **2014**, *79*, 3856−3865. (e) Matsui, J. K.; Primer, D. N.; Molander, G. A. Metal-Free C−H Alkylation of Heteroarenes with Alkyltrifluoroborates: A General Protocol for 1°, 2° and 3° alkylation. *Chem. Sci.* **2017**, *8*, 3512−3522.

(5) (a) Wang, Z.; Li, K.; Zhao, D.; Lan, J.; You, J. Palladium-Catalyzed Oxidative C−H/C−H Cross-Coupling of Indoles and Pyrroles with Heteroarenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 5365−5369. (b) Wang, Z.; Song, F.; Zhao, Y.; Huang, Y.; Yang, L.; Zhao, D.; Lan, J.; You, J. Elements of Regiocontrol in the Direct Heteroarylation of Indoles/Pyrroles: Synthesis of Bi- and Fused Polycyclic Heteroarenes by Twofold or Tandem Fourfold C−H Activation. *Chem. - Eur. J.* **2012**, *18*, 16616−16620. (c) Bering, L.; Antonchick, A. P. Regioselective Metal-Free Cross-Coupling of Quinoline *N*-Oxides with Boronic Acids. *Org. Lett.* **2015**, *17*, 3134−3137. (d) Larionov, O. V. In *Heterocyclic N-Oxide*; Springer: Heidelberg, Germany, 2017.

(6) (a) Landquist, J. K. 567. Quinoxaline *N*-oxides. Part I. The Oxidation of Quinoxaline and Its *Bz*-Substituted Derivatives. *J. Chem. Soc.* **1953**, 2816−2821. (b) Paudler, W. W.; Jovanovic, M. V. Bromination of Some Pyridine and Diazine *N*-Oxides. *J. Org. Chem.* **1983**, *48*, 1064−1069. (c) Akita, Y.; Noguchi, T.; Sugimoto, M.; Ohta, A. Cross-Coupling Reaction of Chloropyrazines with Ethylenes. *J. Heterocycl. Chem.* **1986**, *23*, 1481−1485. (d) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. Palladium-Catalyzed Alkenylation of Quinoline-*N*-oxides via C−H Activation under External-Oxidant-free Conditions. *J. Am. Chem. Soc.* **2009**, *131*, 13888−13889. (e) Wang, D.; Wang, Y.; Zhao, J.; Li, L.; Miao, L.; Wang, D.; Sun, H.; Yu, P. A Highly Practical and Convenient Halogenation of Fused Heterocyclic *N*-Oxides. *Tetrahedron* **2016**, *72*, 5762−5768. (f) Elbert, B. L.; Farley, A. J. M.; Gorman, T. W.; Johnson, T. C.; Genicot, C.; Lallemand, B.; Pasau, P.; Flasz, J.; Castro, J. L.; MacCoss, M.; Paton, R. S.; Schofield, C. J.; Smith, M. D.; Willis, M. C.; Dixon, D. J. C−H Cyanation of 6-Ring *N*-Containing Heteroaromatics. *Chem. - Eur. J.* **2017**, *23*, 14733−14737.

(7) (a) Ohta, A.; Aoyagi, Y.; Maeda, A.; Inoue, M.; Shiraishi, M.; Sakakibara, Y.; Fukui, Y. Efficient Alkylation and Acylation of Pyrazine 1-Oxides. *Heterocycles* **1991**, *32*, 735−748. (b) Itai, T.; Sako, S.; Okusa, G. Potential Anticancer Agents. XIII. Reaction of 3,6-Dimethylpyridazine 1-Oxide and Methylpyridazine 1-Oxides with Benzaldehyde. *Chem. Pharm. Bull.* **1963**, *11*, 1146−1150.

(8) Maryanoff, B. E.; Reitz, A. B. The Wittig Olefination Reaction and Modifications Involving Phosphoryl-Stabilized Carbanions. Stereochemistry, Mechanism, and Selected Synthetic Aspects. *Chem. Rev.* **1989**, *89*, 863−927.

(9) Bestmann, H. J.; Seng, D.-C. F. Reaktion von Triphenylphosphin-Alkylenen Mit Aktivierten Doppelbindungen. *Angew. Chem.* **1962**, *74*, 154−155.

(10) (a) Zhang, Y.; Liu, Y.-K.; Kang, T.-R.; Hu, Z.-K.; Chen, Y.-C. Organocatalytic Enantioselective Mannich-Type Reaction of Phosphorus Ylides: Synthesis of Chiral *N*-Boc-β-Amino-α-Methylene Carboxylic Esters. *J. Am. Chem. Soc.* **2008**, *130*, 2456−2457. (b) Lin, A.; Wang, J.; Mao, H.; Ge, H.; Tan, R.; Zhu, C.; Cheng, Y. Organocatalytic Asymmetric Michael-Type/Wittig Reaction of Phosphorus Ylides: Synthesis of Chiral α-Methylene-δ-Ketoesters. *Org. Lett.* **2011**, *13*, 4176−4179.

(11) Selected references on other alkylation methods: (a) Asunskis, J.; Schechter, H. Reactions of Conjugated Nitro Olefins with Phosphoranes and with Dimethylsulfoxonium Methylide to Give Ylides and Nitrocyclopropanes, Respectively. *J. Org. Chem.* **1968**, *33*, 1164−1168. (b) Von Strandtmann, M.; Cohen, M. P.; Puchalski, C.; Shavel, J. Reaction of Phosphoranes with Mannich Bases. Synthesis of α-Substituted β-Arylacrylic Acids via the Wittig reaction. *J. Org. Chem.* **1968**, *33*, 4306−4309. (c) Connor, D. T.; Von Strandtmann, M. Reaction of (Carbethoxymethylene)triphenylphosphorane with ω-Nitrostyrenes and Isatoic Anhydrides. *J. Org. Chem.* **1973**, *38*, 1047−1049. (d) Kolodiazhnyi, O. I. In *Phosphorus Ylides: Chemistry and Applications in Organic Synthesis*; Wiley-VCH: New York, 1999.

(12) (a) Han, S.; Chakrasali, P.; Park, J.; Oh, H.; Kim, S.; Kim, K.; Pandey, A. K.; Han, S. H.; Han, S. B.; Kim, I. S. Reductive C2-Alkylation of Pyridine and Quinoline *N*-Oxides Using Wittig Reagents. *Angew. Chem., Int. Ed.* **2018**, *57*, 12737−12740. For C2 alkylation of pyridine and quinoline *N*-oxides using other coupling

DOI: 10.1021/acs.orglett.9b02365
Org. Lett. XXXX, XXX, XXX−XXX

partners, see: (b) Jo, W.; Kim, J.; Choi, S.; Cho, S. H. Transition-Metal-Free Regioselective Alkylation of Pyridine *N*-Oxides Using 1,1-Diborylalkanes as Alkylating Reagents. *Angew. Chem., Int. Ed.* **2016**, *55*, 9690−9694. (c) Hwang, C.; Jo, W.; Cho, S. H. Base-Promoted, Deborylative Secondary Alkylation of N-Heteroaromatic *N*-Oxides with Internal *gem*-Bis[(pinacolato)boryl]alkanes: A Facile Derivatization of 2,2′-Bipyridyl Analogues. *Chem. Commun.* **2017**, *53*, 7573−7576. (d) Puthanveedu, M.; Polychronidou, V.; Antonchick, A. P. Catalytic Selective Metal-Free Cross-Coupling of Heteroaromatic *N*-Oxides with Organosilanes. *Org. Lett.* **2019**, *21*, 3407−3411.

(13) (a) Bunnett, J. F.; Zahler, R. E. Aromatic Nucleophilic Substitution Reactions. *Chem. Rev.* **1951**, *49*, 273−412. (b) Bowler, J. T.; Wong, F. M.; Gronert, S.; Keeffe, J. R.; Wu, W. Reactivity in the Nucleophilic Aromatic Substitution Reactions of Pyridinium ions. *Org. Biomol. Chem.* **2014**, *12*, 6175−6180. (c) Chupakhin, O. N.; Charushin, V. N. Recent Advances in the Field of Nucleophilic Aromatic Substitution of Hydrogen. *Tetrahedron Lett.* **2016**, *57*, 2665−2672.

(14) Bian, X.; Shao, M.; Pan, H.; Wang, K.; Huang, S.; Wu, X.; Xue, C.; Hua, H.; Pei, W.; Bai, J. Paenibacillin A, a New 2(1*H*)-Pyrazinone Ring-containing Natural Product from the Endophytic Bacterium *Paenibacillus* sp. Xy-2. *Nat. Prod. Res.* **2016**, *30*, 125−130.

(15) (a) Izquierdo, J.; Landa, A.; Bastida, I.; López, R.; Oiarbide, M.; Palomo, C. Base-Catalyzed Asymmetric α-Functionalization of 2-(Cyanomethyl)azaarene *N*-Oxides Leading to Quaternary Stereocenters. *J. Am. Chem. Soc.* **2016**, *138*, 3282−3285. (b) Butler, M.; Cabrera, G. M. Determination of the Position of the *N*-O Function in Substituted Pyrazine *N*-Oxides by Chemometric Analysis of Carbon-13 Nuclear Magnetic Resonance Data. *J. Mol. Struct.* **2013**, *1043*, 37−42.

(16) Emmerich, J.; Hu, Q.; Hanke, N.; Hartmann, R. W. Cushing's Syndrome: Development of Highly Potent and Selective CYP11B1 Inhibitors of the (Pyridylmethyl)pyridine Type. *J. Med. Chem.* **2013**, *56*, 6022−6032.

DOI: 10.1021/acs.orglett.9b02365
Org. Lett. XXXX, XXX, XXX−XXX