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Ruthenium-Catalyzed Chemoselective N–H Bond Insertion Reactions of 2-Pyridones/7-Azaindoles with Sulfoxonium Ylides

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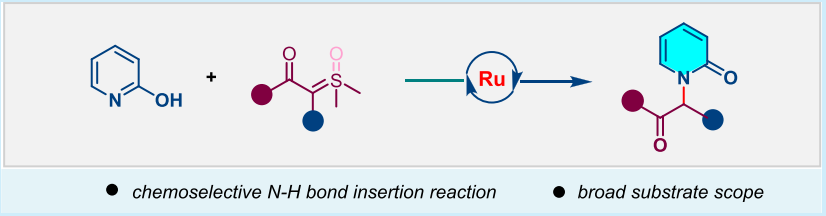
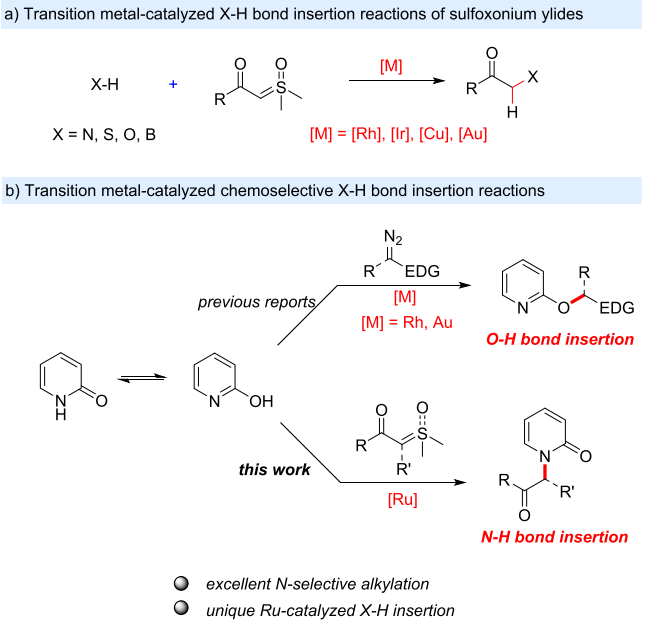


ABSTRACT: A ruthenium-catalyzed highly chemoselective N-alkylation of 2-pyridones has been developed, affording *N*-alkylated 2-pyridone derivatives in good yields and excellent N-selectivity. The key to achieve this unprecedented N–H rather than O–H insertion reaction is the use of $CpRu(PPh_3)_2Cl$ as the catalyst and sulfoxonium ylides as the alkylation reagents. Moreover, this protocol is also amenable to 7-azaindoles by slightly varying the reaction conditions. Furthermore, sulfonium ylides are also suitable alkylation reagents, providing the *N*-alkylated 2-pyridones in good selectivity.

Sulfoxonium ylide derived metal–carbenes have been extensively used in constructing various carbon–carbon and carbon–heteroatom bonds.[1] Typically, compared with traditional carbene precursors, diazo compounds, sulfoxonium ylides are stable, safe, and can be stored for longer time. Therefore, these compounds have been utilized as diazo alternatives in diverse carbene transfer reactions,[2,3] including the formal X–H (X = N, O, S, B) bond insertion reactions.[4−7] Since the pioneering work by Baldwin and co-workers on the rhodium-catalyzed intramolecular N–H bond insertions,[4a4b] to date, a range of X-H insertion reactions have been developed (Scheme 1a). Just recently, Mattson, Burtoloso, and co-workers described an elegant enantioselective S–H bond insertion reaction by using chiral thiourea as the catalyst,[6b] which expanded the applications of sulfoxonium ylides. In continuation of our interest in metal carbene chemistry, we try to use sulfoxonium ylides instead of diazo compounds to develop novel X–H insertion reactions.

N-Alkylated 2-pyridones are important motifs in natural products and biologically active pharmaceuticals.[8] Since the 2-pyridone molecule exists in equilibrium (tautomerism) with 2-hydroxypyridine, the direct alkylation of 2-pyridones remains elusive and often suffers poor chemoselectivity, leading to a mixture of *N*- and *O*-alkylated products. Thus, the highly chemoselective *N*-alkylation of 2-pyridones remains a great challenge.[9] Given that diazo compounds can readily undergo X–H insertion reactions, the alkylation of 2-pyridones with diazo compounds has been previously investigated (Scheme 1b). However, the *O*-alkylation proved to be the dominant insertion reaction under either rhodium[10] or gold catalysis.[11] Recently, using 2-oxypyridines as the substrates, we have

Scheme 1. Previous Reports and Our Protocol



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developed a rhodium-catalyzed synthesis of *N*-alkylated pyridones via a novel *O*-to-*N* acyl rearrangement.[12] Inspired by the pioneering reports and our own interest in metal−carbene chemistry, we envisaged that the reaction of 2-pyridones with stabilized sulfoxonium ylides might occur in the presence of a metal catalyst. In this paper, we wish to report the highly chemoselective *N*-alkylation of 2-pyridones with sulfoxonium ylides under ruthenium catalysis.

We commenced our studies by using 2-pyridone **1a** and sulfoxonium ylide **2a** as model reaction substrates by screening a series of metal catalysts in dichloromethane (DCM) at room temperature (Table 1). Since rhodium catalysts[4a,b] and

Table 1. Optimization of the Reaction Conditions[a]

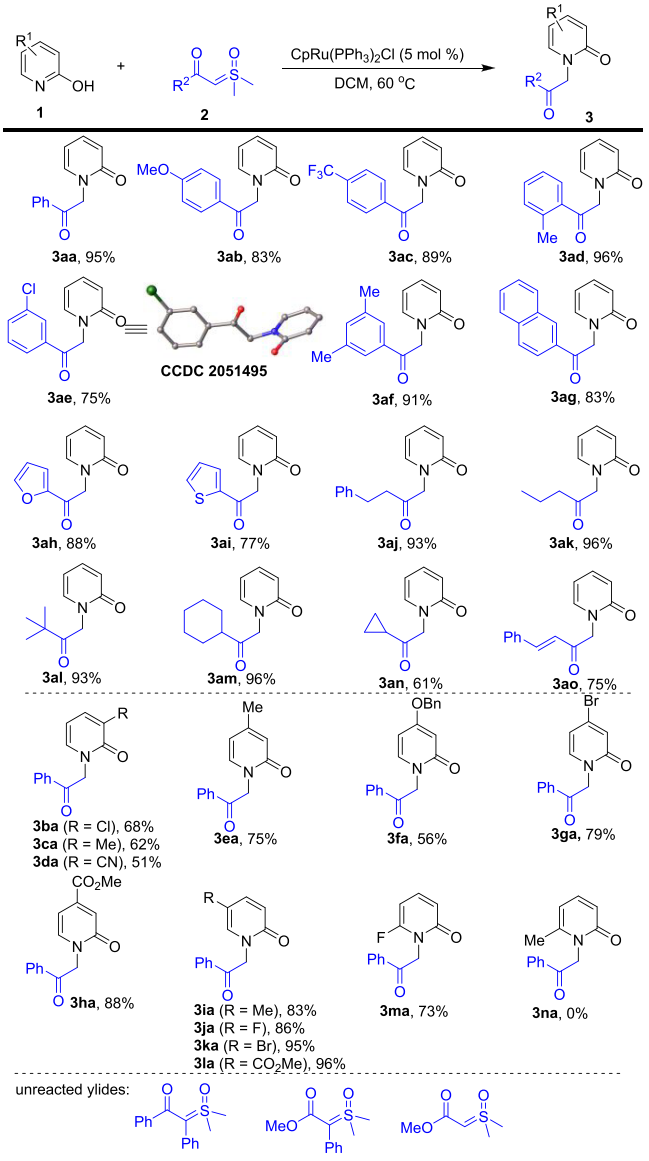
entry	catalyst	solvent	temp (°C)	3aa/3aa′	yield[b] (%)
1	$Rh_2(OAc)_4$	DCM	rt		
2	$Rh_2(TFA)_4$	DCM	rt		
3	$[Ir(COD)Cl]_2$	DCM	rt		
4	$[Ru(p\text{-cymene})Cl_2]_2$	DCM	rt	>19:1	17
5	$[Ru(p\text{-cymene})I_2]_2$	DCM	rt	>19:1	34
6	$CpRu(PPh_3)_2Cl$	DCM	rt	>19:1	65
7	$Cp^*Ru(cod)Cl_2$	DCM	rt		<5
8	$Ru(PPh_3)_3Cl_2$	DCM	rt		<5
9		DCM	rt		
10	$CpRu(PPh_3)_2Cl$	DCM	40	>19:1	74
11	$CpRu(PPh_3)_2Cl$	DCM	60	>19:1	95
12	$CpRu(PPh_3)_2Cl$	MeCN	60	>19:1	58
13	$CpRu(PPh_3)_2Cl$	$CHCl_3$	60	>19:1	79
14	$CpRu(PPh_3)_2Cl$	DCE	60	>19:1	74
15	$CpRu(PPh_3)_2Cl$	toluene	60	>19:1	60
16[c]	$CpRu(PPh_3)_2Cl$	DCM	60	>19:1	74
17[d]	$CpRu(PPh_3)_2Cl$	DCM	60	>19:1	52

[a]Reaction conditions: To a solution of **1a** (0.2 mmol) and **2a** (0.4 mmol) in 2.0 mL of solvent was added 5 mol % of catalyst. Then the mixture was stirred at the corresponding reaction temperature for 4 h in a sealed tube. The ratio of **3aa**/**3aa′** was determined by crude NMR analysis. [b]Yield of isolated products. [c]2.5 mol % catalyst. [d]1 mol % of catalyst.

$[Ir(COD)Cl]_2$[4c−e] have been successfully used to accomplish several X−H insertion reactions, we first tested these catalysts. Unfortunately, no reaction occurred under either rhodium or iridium catalysis (entries 1−3). We then attempted to explore other catalysts. When $[Ru(p\text{-cymene})Cl_2]_2$[13] (5 mol %) was used, the *N*-alkylated product **3aa** was isolated in 17% yield with no detection of the O-alkylated product **3aa′** (entry 4). The use of $[Ru(p\text{-cymene})I_2]_2$ slightly improved the yield of **3aa** to 34% (entry 5). To our delight, the yield of **3aa** was increased to 65% when $CpRu(PPh_3)_2Cl$ was used (entry 6). In contrast, $Cp^*Ru(cod)Cl_2$ and $Ru(PPh_3)_3Cl_2$ were almost inactive in promoting the alkylation reaction (entries 7 and 8). Moreover, no reaction occurred in the absence of a catalyst (entry 9). It should be noted that a higher reaction temperature was beneficial to the formation of **3aa**. Performing the reaction at 40 °C provided **3aa** in 74% yield (entry 10), which was further increased to 95% at 60 °C (entry 11). Several solvents were then screened. The use of acetonitrile (MeCN), chloroform, 1,2-dichloroethane (DCE), and toluene furnished **3aa** in moderate yields (entries 12−15). Reducing the catalyst loading to 2.5 mol % delivered 74% yield of **3aa** (entry 16), and 1 mol % of $CpRu(PPh_3)_2Cl$ provided **3a** in 52% yield (entry 17).

Under the optimized reaction conditions, the scope of this reaction was examined (Scheme 2). Initially, the scope with

Scheme 2. Scope for N-Alkylation of 2-Pyridones[a,b]



[a]Reaction conditions: To a solution of **1** (0.2 mmol) and **2** (0.4 mmol) in 2.0 mL of DCM was added 5 mol % of $CpRu(PPh_3)_2Cl$. The reaction was stirred at 60 °C for 4 h. [b]Yield of isolated products.

respect to sulfoxonium ylides was investigated. Various functional groups at the phenyl ring of ylides such as methoxy (**3ab**), trifluoromethyl (**3ac**), methyl (**3ad**, **3af**), chloro (**3ae**), and naphthyl (**3ag**) were all tolerated, providing the corresponding products in good yields. The sulfoxonium ylides containing a heteroaryl groups were also suitable substrates, and the desired products (**3ah** and **3ai**) were obtained in good yields too. For alkyl-substituted sulfoxonium ylides, the corresponding products (**3aj**−**3am**) were obtained in excellent yields. The ylide bearing a cyclopropane group

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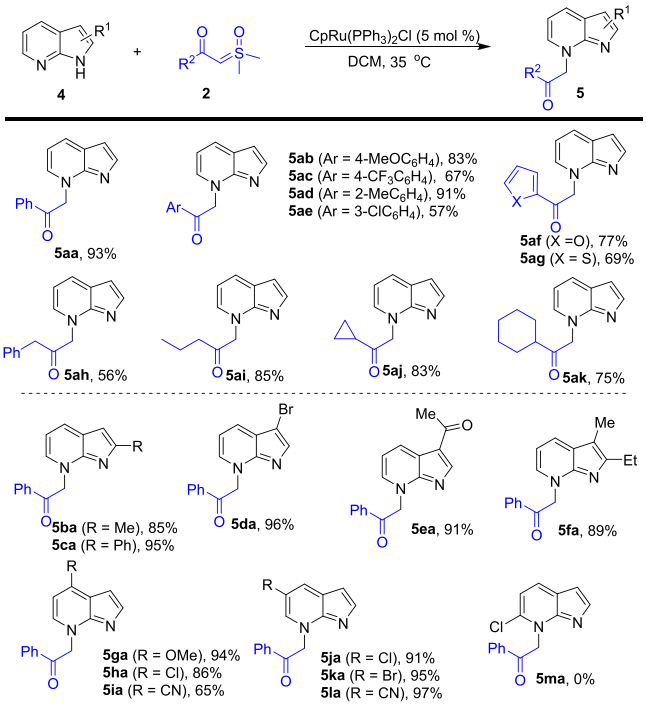
afforded the alkylated product (**3an**) in 61% yield. Moreover, this reaction was also amenable to an alkenyl ylide, which gave **3ao** in 75% yield. The molecular structure of **3ae** was elucidated by X-ray diffraction studies.

Next, the scope of 2-pyridones was evaluated. Generally, both electron-donating and electron-withdrawing substituents at the C3, C4, and C5 positions of the pyridone ring were all tolerated, delivering the corresponding *N*-alkylated pyridones in moderate to good yields. 2-Pyridones bearing chloro (**3ba**), methyl (**3ca**), and strong electron-withdrawing cyano (**3da**) groups at the C3 position led to moderate yields of the desired products. Likewise, the C4-substituted with methyl (**3ea**), benzyloxy (**3fa**), bromo (**3ga**), and ester (**3ha**) were all tolerated. Comparatively, 2-pyridones bearing either electron-donating or electron-withdrawing groups at the C5 position gave the corresponding products (**3ia**−**3la**) in excellent yields. Typically, this protocol was also applicable to sterically hindered 5-fluoro-2-pyridone, which gave the desired product (**3ma**) in 73% yield. However, 5-methyl substrate failed to give the corresponding product (**3na**), indicating the increased steric hindrance at that position would stop the reaction. It should be noted that the ylides bearing a substituent at the ylide carbon atom, and the ester substituted sulfoxonium ylide did not work.

Similar with indoles, it was reported that the reaction of 7-azaindoles with diazo compounds resulted in diverse reaction modes upon different metal catalysts.[14] However, the selective N-7 alkylation of azaindoles with sulfoxonium ylides has not been reported. Upon the successful *N*-alkylation of 2-pyridones, we then focused on using this protocol to achieve the selective alkylation of 7-azaindoles with sulfoxonium ylides. Using $CpRu(PPh_3)_2Cl$ (5 mol %) as the catalyst, the reaction of unsubstituted 7-azaindole with **2a** at 35 °C furnished **5aa** in 93% yield. Then the scope of this reaction was investigated (Scheme 3). With respect to sulfoxonium ylides, similar to Scheme 2, the substrates containing either electron-donating or electron-withdrawing substituents at different positions of the phenyl ring were all tolerated, providing the corresponding *N*7-alkylated products (**5ab**−**5ae**) in yields of 57−91%. The heteroaryl- (**5af**−**5ag**) and alkyl-substituted (**5ah**−**5ak**) sulfoxonium ylides were also tolerated. With respect to the scope of 7-azaindoles, the substituents at the C2, C3, C4, and C5 positions, including electron-donating and electron-withdrawing groups, were all applicable, leading to the corresponding products (**5ba**−**5la**) in excellent yields (85%−97%) except **5ia**, which was obtained in 65% yield. However, 6-chloro-7-azaindole was totally unreactive in this reaction.

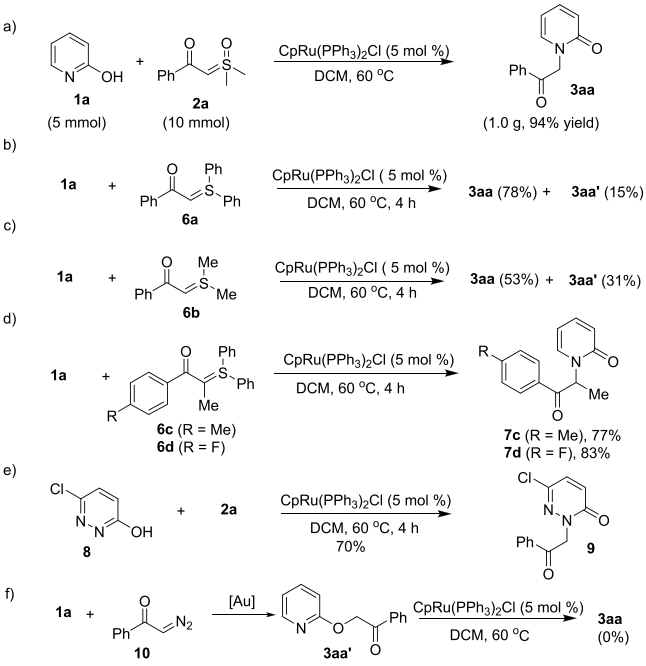
A gram-scale synthesis was conducted with 5 mmol of **1a** and 10 mmol of **2a**, affording **3aa** in 94% yield (1.0 g) (Scheme 4a). Considering the similar reactivity of sulfonium ylides to sulfoxonium ylides,[15] we next investigated the use of sulfonium ylides in this reaction. Subjected **1a** to 2 equiv of **6a** afforded 78% yield of **3aa** together with 15% yield of O-alkylated product **3aa′** (Scheme 4b). Using dimethyl ylide **6b** instead, **3aa** and **3aa′** were isolated in 53% and 31% yield, respectively (Scheme 4c). Next, the sulfonium ylides bearing a substitution at the ylide carbon were tested. The reaction of **1a** with **6c** and **6d** delivered N-substituted products **7c** and **7d** in 77% and 83% yield, respectively (Scheme 4d). Moreover, reaction of pyridazine **8** with **2a** led to 70% yield of *N*-alkylated product **9** (Scheme 4e). To gain insight into the alkylation process, compound **3aa′** was prepared according to our previous gold-catalyzed O-alkylation reaction (Scheme 4f).[11]

Scheme 3. Scope for *N*7-Alkylation of 7-Azaindoles[a,b]



[a]Reaction conditions: To a solution of **4** (0.2 mmol) and **2** (0.2 mmol) in 2 mL of DCM was added 5 mol % of $CpRu(PPh_3)_2Cl$. The reaction was stirred at 35 °C for 4 h. [b]Yield of isolated products.

Scheme 4. Application and Elaboration



No *O*-to-*N* migration reaction occurred in the presence of a ruthenium catalyst, which excluded the possibility that the previous formation of *O*-alkylation product followed by *O*-to-*N* rearrangement to give the *N*-alkylated 2-pyridones.

The exact reaction mechanism for the selective *N*-alkylation reaction is not clear at this moment. Based on the literature reports[1] and our own observations, we proposed the possible reaction pathways in Scheme 5. The left catalytic cycle

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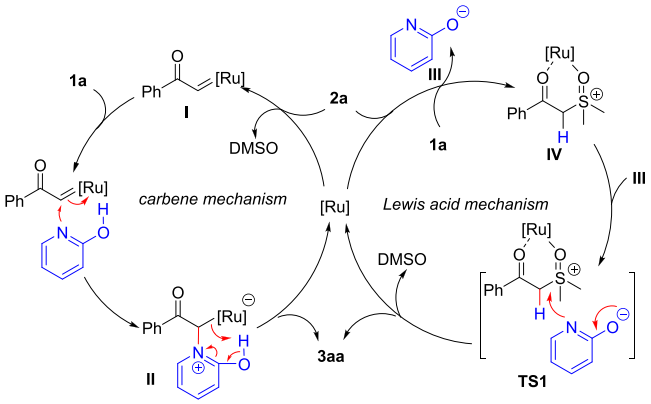
Scheme 5. Proposed Reaction Mechanism



represents carbene mechanism. The reaction of sulfoxonium ylide **2a** with ruthenium catalyst leads to ruthenium carbene species **I**. Nucleophilic attack of nitrogen atom in **1a** to carbene carbon atom generates zwitteronic intermediate **II**. Subsequently intramolecular proton transfer affords **3aa** and regenerates the ruthenium catalyst. The other possibility is the Lewis acid mechanism. The deprotonation of **1a** by **2a** happens at first place to generate anion **III**. The ruthenium catalyst may work as a Lewis acid to activate the carbonyl group or coordinate with the two oxygen atoms of sulfoxonium ylide (right cycle of Scheme 5). Subsequent substitution of **IV** with **III** via transition state **TS1**produces **3aa** and DMSO molecule while releasing the ruthenium catalyst.

In summary, we have developed a ruthenium-catalyzed selective N−H rather than O−H insertion reaction of 2-pyridones by using safe and stable sulfoxonium ylides as the alkylating reagents, which is different from the use of diazo compounds. The use of ruthenium catalyst is the key to achieve the unique *N*-selectivity. Likewise, this alkylation protocol is also amenable to 7-azaindoles, affording the dearomative *N*7-alkylated chemoisomer as the single product. Moreover, using sulfonium ylides bearing a substitution at the ylide carbon atom as the substrates, the ruthenium-catalyzed selective N-alkylation also works well to give the *N*-alkylated 2-pyridones in good yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04229.

Experimental procedures along with characterization data and copies of NMR spectra (PDF)

Accession Codes

CCDC 2051495 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Burtoloso, A. C. B.; Dias, R. M. P.; Leonarczyk, I. A. Sulfoxonium and Sulfonium Ylides as Diazocarbonyl Equivalents in Metal-Catalyzed Insertion Reactions. *Eur. J. Org. Chem.* **2013**, *2013*, 5005−5016. (b) Wu, X.; Sun, S.; Yu, J. T.; Cheng, J. Recent Applications of α-Carbonyl Sulfoxonium Ylides in Rhodium- and Iridium-Catalyzed C-H Functionalizations. *Synlett* **2019**, *30*, 21−29. (c) Bisag, G. D.; Ruggieri, S.; Fochi, M.; Bernardi, L. Sulfoxonium Ylides: Simple Compounds with Chameleonic Reactivity. *Org. Biomol. Chem.* **2020**, *18*, 8793−8809. (d) Vaitla, J.; Bayer, A. Sulfoxonium Ylide Derived Metal Carbenoids in Organic Synthesis. *Synthesis* **2019**, *51*, 612−628.

(2) For selected examples of C−H functionalization, see: (a) Xu, Y.; Zhou, X.; Zheng, G.; Li, X. Sulfoxonium Ylides as a Carbene Precursor in Rh(III)-Catalyzed C-H Acylmethylation of Arenes. *Org. Lett.* **2017**, *19*, 5256−5259. (b) Liang, Y. F.; Yang, L.; Rogge, T.; Ackermann, L. Ruthenium(IV) Intermediates in C−H Activation/Annulation by Weak O-Coordination. *Chem. - Eur. J.* **2018**, *24*, 16548−16552. (c) Wu, X.; Xiong, H.; Sun, S.; Cheng, J. Rhodium-Catalyzed Relay Carbenoid Functionalization of Aromatic C-H Bonds toward Fused Heteroarenes. *Org. Lett.* **2018**, *20*, 1396−1399. (d) Wu, X.; Xiao, Y.; Sun, S.; Yu, J. T.; Cheng, J. Rhodium-Catalyzed Reaction of Sulfoxonium Ylides and Anthranils toward Indoloindolones via a (4 + 1) Annulation. *Org. Lett.* **2019**, *21*, 6653−6657. (e) Wang, P.; Xu, Y.; Sun, J.; Li, X. Rhodium(III)-Catalyzed Chemo-Divergent Couplings of Sulfoxonium Ylides with Oxa/Azabicyclic Olefins. *Org. Lett.* **2019**, *21*, 8459−8463. (f) Lou, J.; Wang, Q.; Zhou, Y. G.; Yu, Z. Rhodium(III)-Catalyzed Annulative Coupling of Sulfoxonium Ylides and Allenoates: An Arene C-H Activation/Cyclopropanation Cascade. *Org. Lett.* **2019**, *21*, 9217−9222. (g) Kommagalla, Y.; Ando, S.; Chatani, N. Rh(III)-Catalyzed Reaction of α-Carbonyl Sulfoxonium Ylides and Alkenes: Synthesis of Indanones via [4 + 1] Cycloaddition. *Org. Lett.* **2020**, *22*, 1375−1379. (h) Zhou, P.; Yang, W. T.; Rahman, A. U.; Li, G.; Jiang, B. Rh(III)-Catalyzed [3 + 3] Annulation Reaction of Cyclopropenones and Sulfoxonium Ylides toward Trisubstituted 2-Pyrones. *J. Org. Chem.* **2020**, *85*, 360−366. (i) Caiuby, C. A. D.; De Jesus, M. P.; Burtoloso, A. C. B. α-Imino Iridium Carbenes from Imidoyl Sulfoxonium Ylides: Application in the One-Step Synthesis of Indoles. *J. Org. Chem.* **2020**, *85*, 7433−7445. (j) Kona, C. N.; Nishii, Y.; Miura, M. Thioether-Directed C4-Selective C-H Acylmethylation of Indoles Using α-Carbonyl Sulfoxonium Ylides. *Org. Lett.* **2020**, *22*, 4806−4811.

(3) For selected examples, see: (a) Talero, A. G.; Martins, B. S.; Burtoloso, A. C. B. Coupling of Sulfoxonium Ylides with Arynes: A Direct Synthesis of Pro-Chiral Aryl Ketosulfoxonium Ylides and Its Application in the Preparation of α-Aryl Ketones. *Org. Lett.* **2018**, *20*, 7206−7211. (b) Vaitla, J.; Bayer, A.; Hopmann, K. H. Iron-Catalyzed Carbenoid-Transfer Reactions of Vinyl Sulfoxonium Ylides: An Experimental and Computational Study. *Angew. Chem., Int. Ed.* **2018**, *57*, 16180−16184. (c) Yuan, Y.; Wu, X. F. Direct Access to 1,1-Dicarbonyl Sulfoxonium Ylides from Aryl Halides or Triflates: Palladium-Catalyzed Carbonylation. *Org. Lett.* **2019**, *21*, 5310−5314. (d) Clare, D.; Dobson, B. C.; Inglesby, P. A.; Aïssa, C. Chemospecific Cyclizations of α-Carbonyl Sulfoxonium Ylides on Aryls and Heteroaryls. *Angew. Chem., Int. Ed.* **2019**, *58*, 16198−16202.

(4) For selected examples on N-H insertion reactions, see: (for Rh catalysis) (a) Baldwin, J. E.; Adlington, R. M.; Godfrey, C. R. A.; Gollins, D. W.; Vaughan, J. G. A Novel Entry to Carbenoid Species via β-Ketosulfoxonium Ylides. *J. Chem. Soc., Chem. Commun.* **1993**, 1434−1435. (b) Baldwin, J. E.; Adlington, R. M.; Godfrey, C. R.; Gollins, D. W.; Smith, M. L.; Russel, A. T. A New Approach to the Synthesis of γ-Keto-α-Amino Acids: Synthesis of Optically Pure 5-Hydroxy-4-oxo-L-norvaline, L-HON. *Synlett* **1993**, 51. (for Ir catalysis) (c) Mangion, I. K.; Nwamba, I. K.; Shevlin, M.; Huffman, M. A. Iridium-Catalyzed X-H Insertions of Sulfoxonium Ylides. *Org. Lett.* **2009**, *11*, 3566−3569. (d) Vaitla, J.; Bayer, A.; HopmannHopmann, K. H. Synthesis of Indoles and Pyrroles Utilizing Iridium Carbenes Generated from Sulfoxonium Ylides. *Angew. Chem., Int. Ed.* **2017**, *56*, 4277−4281. (e) Phelps, A. M.; Chan, V. S.; Napolitano, J. G.; Krabbe, S. W.; Schomaker, J. M.; Shekhar, S. Ligand-Controlled Synthesis of Azoles via Ir-Catalyzed Reactions of Sulfoxonium Ylides with 2-Amino Heterocycles. *J. Org. Chem.* **2016**, *81*, 4158−4169. (for Cu catalysis) (f) Furniel, L. G.; Burtoloso, A. C. B. Copper-Catalyzed N−H Insertion Reactions from Sulfoxonium Ylides. *Tetrahedron* **2020**, *76*, 131313.

(5) For O−H insertion reactions, see: Mangion, I. K.; Weisel, M. Gold (I) Catalysis of X-H Bond Insertions. *Tetrahedron Lett.* **2010**, *51*, 5490−5492.

(6) For S−H insertion reactions, see: (a) Dias, R. M. P.; Burtoloso, A. C. B. Catalyst-Free Insertion of Sulfoxonium Ylides into Aryl Thiols. A Direct Preparation of β-Keto Thioethers. *Org. Lett.* **2016**, *18*, 3034−3037. (b) Momo, P. B.; Leveille, A. N.; Farrar, E. H. E.; Grayson, M. N.; Mattson, A. E.; Burtoloso, A. C. B. Enantioselective S−H Insertion Reactions of α-Carbonyl Sulfoxonium Ylides. *Angew. Chem., Int. Ed.* **2020**, *59*, 15554−15559.

(7) For B−H insertion reactions, see: (a) Li, J.; He, H.; Huang, M.; Chen, Y.; Luo, Y.; Yan, K.; Wang, Q.; Wu, Y. Iridium-Catalyzed B-H Bond Insertion Reactions Using Sulfoxonium Ylides as Carbene Precursors toward α-Boryl Carbonyls. *Org. Lett.* **2019**, *21*, 9005−9008. (b) Zhang, S. S.; Xie, H.; Shu, B.; Che, T.; Wang, X. T.; Peng, D.; Yang, F.; Zhang, L. Iridium-Catalyzed B-H Insertion of Sulfoxonium Ylides and Borane Adducts: A Versatile Platform to α-Boryl Carbonyls. *Chem. Commun.* **2020**, *56*, 423−426.

(8) For selected recent examples, see: (a) Li, L.; Jiang, X.; Huang, S.; Ying, Z.; Zhang, Z.; Pan, C.; Li, S.; Wang, X.; Zhang, Z. Discovery of Highly Potent 2-Sulfonyl-Pyrimidinyl Derivatives for Apoptosis Inhibition and Ischemia Treatment. *ACS Med. Chem. Lett.* **2017**, *8*, 407−412. (b) Namasivayam, V.; Vanangamudi, M.; Kramer, V. G.; Kurup, S.; Zhan, P.; Liu, X.; Kongsted, J.; Byrareddy, S. N. The Journey of HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) from Lab to Clinic. *J. Med. Chem.* **2019**, *62*, 4851−4883. (c) Cox, R. M.; Toots, M.; Yoon, J. J.; Sourimant, J.; Ludeke, B.; Fearns, R.; Bourque, E.; Patti, J.; Lee, E.; Vernachio, J.; Plemper, R. K. Development of an Allosteric Inhibitor Class Blocking RNA Elongation by the Respiratory Syncytial Virus Polymerase Complex. *J. Biol. Chem.* **2018**, *293*, 16761−16777. (d) Ettari, R.; Cerchia, C.; Maiorana, S.; Guccione, M.; Novellino, E.; Bitto, A.; Grasso, S.; Lavecchia, A.; Zappalà, M. Development of Novel Amides as Noncovalent Inhibitors of Immunoproteasomes. *ChemMedChem* **2019**, *14*, 842−852. (e) Wang, Z.; Yu, Z.; Kang, D.; Zhang, J.; Tian, Y.; Daelemans, D.; De Clercq, E.; Pannecouque, C.; Zhan, P.; Liu, X. Design, Synthesis and Biological Evaluation of Novel Acetamide-Substituted Doravirine and Its Prodrugs as Potent HIV-1 NNRTIs. *Bioorg. Med. Chem.* **2019**, *27*, 447−456. (f) Dorich, S.; Cox, J. H.; Burch, J. D.; Chagnon, F.; Chen, B.; Léger, S.; St-Onge, M.; Fader, L. D. Novel Pyridone EP4 Agonists Featuring Allylic Alcohol ω-Chains. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 127104.

(9) For represent examples on *N*-alkylation of 2-pyridones, see: (a) Fang, Y. Q.; Bio, M. M.; Hansen, K. B.; Potter, M. S.; Clausen, A. Magnesium Coordination-Directed N-Selective Stereospecific Alkylation of 2-Pyridones, Carbamates, and Amides Using α-Halocarboxylic Acids. *J. Am. Chem. Soc.* **2010**, *132*, 15525−15527. (b) Yeung, C. S.; Hsieh, T. H. H.; Dong, V. M. Ru-Catalyzed Activation of Sp^3 C-O Bonds: O- to N-Alkyl Migratory Rearrangement in Pyridines and Related Heterocycles. *Chem. Sci.* **2011**, *2*, 544−551. (c) Li, C.; Kahny, M.; Breit, B. Rhodium-Catalyzed Chemo-, Regio-, and Enantioselective Addition of 2-Pyridones to Terminal Allenes. *Angew. Chem., Int. Ed.* **2014**, *53*, 13780−13784. (d) Zhang, X.; Yang, Z. P.; Huang, L.; You, S. L. Highly Regio- And Enantioselective Synthesis of N-Substituted 2-Pyridones: Iridium-Catalyzed Intermolecular Asymmetric Allylic. *Angew. Chem., Int. Ed.* **2015**, *54*, 1873−1876. (e) Cheng, L. J.; Brown, A. P. N.; Cordier, C. J. Enantioselective Propargylic [1,3]-Rearrangements: Copper-Catalyzed: O-to-N Migrations toward C-N Bond Formation. *Chem. Sci.* **2017**, *8*, 4299−4305. (f) Wu, Y. C.; Jhong, Y.; Lin, H. J.; Swain, S. P.; Tsai, H. H. G.; Hou, D. R. Organocatalyzed Enantioselective Michael Addition of 2-Hydroxypyridines and α,β-Unsaturated 1,4-Dicarbonyl Compounds. *Adv. Synth. Catal.* **2019**, *361*, 4966−4982. (g) Hao, X.; Xu, Z.; Lu, H.; Dai, X.; Yang, T.; Lin, X.; Ren, F. Mild and Regioselective N-Alkylation of 2-Pyridones in Water. *Org. Lett.* **2015**, *17*, 3382−3385. (h) Feng, B.; Li, Y.; Li, H.; Zhang, X.; Xie, H.; Cao, H.; Yu, L.; Xu, Q. Specific N-Alkylation of Hydroxypyridines Achieved by a Catalyst- and Base-Free Reaction with Organohalides. *J. Org. Chem.* **2018**, *83*, 6769−6775. (i) Gurak, J. A.; Tran, V. T.; Sroda, M. M.; Engle, K. M. N-Alkylation of 2-Pyridone Derivatives via Palladium(II)-Catalyzed Directed Alkene Hydroamination. *Tetrahedron* **2017**, *73*, 3636−3642.

(10) Busch-Petersen, J.; Corey, E. J. A Rhodium(II) Catalytic Approach to the Synthesis of Ethers of a Minor Component in a Tautomeric Set. *Org. Lett.* **2000**, *2*, 1641−1643.

(11) (a) Huang, D.; Xu, G.; Peng, S.; Sun, J. Gold-Catalyzed Highly Regio- and Enantioselective Vinylcarbene Insertion into O-H Bonds of 2-Pyridones. *Chem. Commun.* **2017**, *53*, 3197−3200. (b) Xu, G.; Liu, K.; Dai, Z.; Sun, J. Gold/Silver-Catalyzed Controllable Regioselective Vinylcarbene Insertion into O-H Bonds. *Org. Biomol. Chem.* **2017**, *15*, 2345−2348.

(12) (a) Xu, G.; Chen, P.; Liu, P.; Tang, S.; Zhang, X.; Sun, J. Access to N-Substituted 2-Pyridones by Catalytic Intermolecular Dearomatization and 1,4-Acyl Transfer. *Angew. Chem., Int. Ed.* **2019**, *58*, 1980−1984. (b) Xu, G.; Shao, Y.; Tang, S.; Chen, Q.; Sun, J. Dearomative Migratory Rearrangement of 2-Oxypyridines Enabled by α-Imino Rhodium Carbene. *Org. Lett.* **2020**, *22*, 9303−9307.

(13) For Ru-catalyzed transformations of sulfoxonium ylides, see: (a) Neuhaus, J. D.; Bauer, A.; Pinto, A.; Maulide, N. A Catalytic Cross-Olefination of Diazo Compounds with Sulfoxonium Ylides. *Angew. Chem., Int. Ed.* **2018**, *57*, 16215−16218. (b) Wen, S.; Lv, W.; Ba, D.; Liu, J.; Cheng, G. Ruthenium(II)-Catalyzed Chemoselective Deacylative Annulation of 1,3-Diones with Sulfoxonium Ylides: Via C-C Bond Activation. *Chem. Sci.* **2019**, *10*, 9104−9108.

(14) Liu, J.; Xu, G.; Tang, S.; Chen, Q.; Sun, J. Site-Selective Functionalization of 7-Azaindoles via Carbene Transfer and Isolation of N -Aromatic Zwitterions. *Org. Lett.* **2020**, *22*, 9376−9380. See also references cited therein.

(15) (a) Neuhaus, J. D.; Oost, R.; Merad, J.; Maulide, N. Sulfur-Based Ylides in Transition-Metal-Catalysed Processes. *Top. Curr. Chem.* **2018**, *376*, 15. (b) Lu, L. Q.; Li, T. R.; Wang, Q.; Xiao, W. J. Beyond Sulfide-Centric Catalysis: Recent Advances in the Catalytic Cyclization Reactions of Sulfur Ylides. *Chem. Soc. Rev.* **2017**, *46*, 4135−4149. (c) Kaiser, D.; Klose, I.; Oost, R.; Neuhaus, J.; Maulide, N. Bond-Forming and -Breaking Reactions at Sulfur(IV): Sulfoxides, Sulfonium Salts, Sulfur Ylides, and Sulfinate Salts. *Chem. Rev.* **2019**,

https://dx.doi.org/10.1021/acs.orglett.0c04229
Org. Lett. 2021, 23, 1038−1043

119, 8701−8780. (d) Guo, W.; Luo, Y.; Sung, H. H. Y.; Williams, I. D.; Li, P.; Sun, J. Chiral Phosphoric Acid Catalyzed Enantioselective Synthesis of α-Tertiary Amino Ketones from Sulfonium Ylides. *J. Am. Chem. Soc.* **2020**, *142*, 14384−14390.

https://dx.doi.org/10.1021/acs.orglett.0c04229
Org. Lett. 2021, 23, 1038−1043