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Three-Component Coupling of Aldehydes, Aminopyrazoles, and Sulfoxonium Ylides via Rhodium(III)-Catalyzed Imidoyl C−H Activation: Synthesis of Pyrazolo[1,5-*a*]pyrimidines

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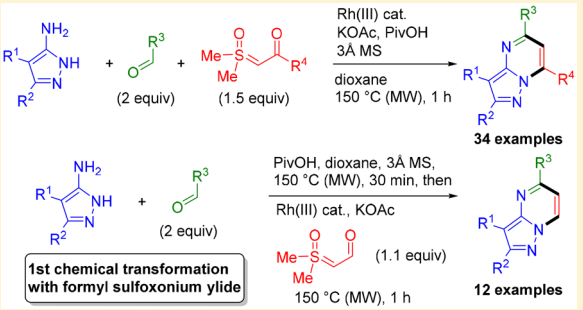
Supporting Information

ABSTRACT: An efficient, three-component strategy for Rh(III)-catalyzed annulation of readily available 3-aminopyrazoles, aldehydes, and sulfoxonium ylides to give diverse pyrazolo[1,5-*a*]pyrimidines is disclosed. The reactions were performed under straightforward benchtop conditions using microwave heating with short reaction times. Good yields were obtained for many substituted aminopyrazoles and a very large variety of aromatic and heteroaromatic aldehydes, including those incorporating electron-withdrawing, electron-donating, basic nitrogen, halide and acidic functionality. Ester and methoxy functionalities could also be directly installed on the pyrimidine ring by employing ethyl glyoxylate and trimethyl orthoformate in place of the aldehyde, respectively. In addition, a range of sulfoxonium ylides provided products in good yields to establish that aryl, heteroaryl, and branched and unbranched alkyl substituents can be introduced with this reagent. Finally, the first use of a formyl sulfoxonium ylide in a chemical transformation enabled the preparation of products with only a single substituent on the pyrimidine ring as introduced by the aldehyde coupling partner. For the formyl ylide, a one-pot, stepwise reaction sequence was used to prevent competitive condensation of the formyl group with the aminopyrazole.



INTRODUCTION

Fused [5,6]-bicyclic bridgehead nitrogen heterocycles are privileged pharmacophores in drug discovery. The azolopyrimidines are the most prevalent subclass and are featured in many USFDA-approved drugs and even more clinical candidates.[1,2] We have recently reported the first examples of imidoyl C−H activation via Rh(III)-catalyzed two-component annulations of *N*-azolo imines **1** with alkynes, diazoketones and sulfoxonium ylides to give azolopyrimidines **2** (Scheme 1A).[3,4] Moreover, annulations with 1,4,2-dioxazol-5-one amidating reagents afforded a wide range of azolo[1,3,5]-triazines **3**.[5,6] A particularly attractive feature of the aforementioned approach is the large number of diverse *N*-azolo imines **1** that can readily be prepared from commercially available aminoazoles and aldehydes.

Multicomponent reactions enable access to complex structures from simple precursors. In work relevant to *N*-fused [5,6]-bicyclic heterocycle synthesis, the Groebke−Blackburn−Bienaymé (GBBR) reaction is a popular and efficient approach (Scheme 1B).[7] In this three-component reaction, imines formed in situ couple with isocyanides to afford a wide range of fused imidazole bridgehead nitrogen heterocycles **4**.

Herein, we report the multicomponent synthesis of pyrazolopyrimidines **8** (Scheme 1C), which are found in more approved drugs and clinical candidates than any other subclass of [5,6]-bicyclic bridgehead nitrogen heterocycles.[1] In this three-component coupling reaction, imines that are formed in situ from readily available aldehydes **5** and aminoazoles **6** undergo Rh-catalyzed annulation with sulfoxonium ylides **7**, which are stable, crystalline carbene equivalents that are increasingly used in Rh(III)-catalyzed C−H functionalization.[8,9] The rapid preparation of diverse pyrazolopyrimidines **8** is further facilitated by the use of a commercially available and air-stable Rh(III) catalyst, convenient benchtop setup, and short reaction times with microwave heating.

High functional group compatibility is an important aspect of this three-component reaction, with unhindered basic heterocycle nitrogens, amides, esters, secondary and tertiary carbamates, halides, carboxylic acids and acidic secondary anilides all successfully incorporated. Ester and methoxy functionalities can be directly installed on the pyrimidine ring by employing ethyl glyoxylate and trimethyl orthoformate in place of the aldehyde, respectively.

We also report the efficient preparation of pyrazolopyrimidines **8** with only a single substituent on the pyrimidine ring (bottom of Scheme 1C). In a one-pot reaction, stepwise formation of *N*-azolo imines is followed by the addition of formyl ylide **7i** and the Rh(III) catalyst. To our knowledge,

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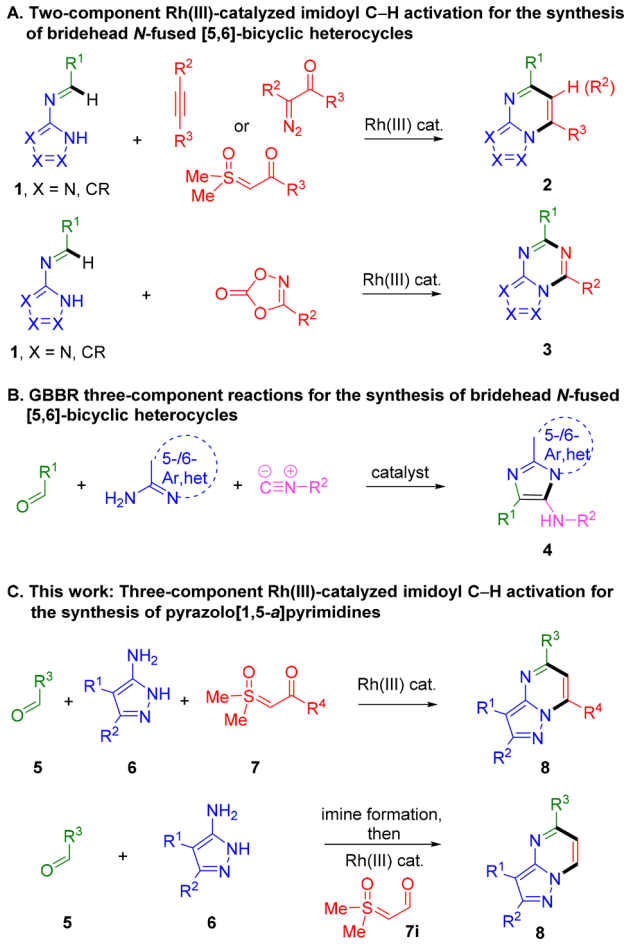
Scheme 1. Fused [5,6]-Bicyclic Bridgehead Nitrogen Heterocycle Synthesis

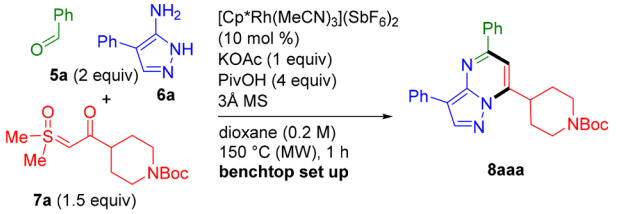


this is the first chemical transformation of a formyl sulfoxonium ylide.

RESULTS AND DISCUSSION

A large variety of reaction parameters were first examined for coupling benzaldehyde (**5a**), aminopyrazole **6a**, and sulfoxonium ylide **7a** to give pyrazolopyrimidine **8aaa** (Table 1). This investigation established that good yields of **8aaa** could be obtained by benchtop setup using the commercially available and air-stable cationic catalyst $[Cp^*Rh(MeCN)_3](SbF_6)_2$ with KOAc, pivalic acid (PivOH), and 3 Å sieves as additives in dioxane (0.2 M) under microwave (MW) conditions at 150 °C for 1 h (Table 1, entry 1). When the halide was not abstracted from $[Cp^*RhCl_2]_2$, a slight reduction in yield of the product was observed (Table 1, entry 2). As expected, when a Rh(III) catalyst was not added, no product was obtained (Table 1, entry 3). NaOAc was found to be less effective than KOAc (Table 1, entry 4), and completely removing the base led to a further reduction in the yield (Table 1, entry 5). Removing the PivOH also resulted in a significantly lower yield (Table 1, entry 6). Increasing the temperature to 160 °C did not improve the yield, indicating that more forcing conditions are not necessary (Table 1, entry 7). Chlorobenzene, which is a typical solvent for microwave reactions, was tested and determined to be less effective (Table 1, entry 8). Reducing the amount of sulfoxonium ylide (1.1 equiv) only led to a slightly lower yield (Table 1, entry 9). In comparison to

Table 1. Reaction Parameters for Annulation to Pyrazolopyrimidine 8[a]



entry	variation	yield[b] (%)
1	none	75
2	$[Cp^*RhCl_2]_2$ (5%)	61
3	no Rh	0
4	NaOAc instead of KOAc	60
5	no KOAc	39
6	no PivOH	27
7	160 °C	73
8	chlorobenzene as solvent	57
9	ylide **7a** (1.1 equiv)	67
10	$[Cp^*IrCl_2]_2$ (5%) and $AgSbF_6$ (20%)	28
11	$[Cp^*Co(MeCN)_3](SbF_6)_2$ (10%)	21
12	0.1 M	62
13	**0.4 M**	**85 (82)**[c]
14	0.4 M, no sieves	75
15	0.4 M, $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5%)	77
16	0.4 M, $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (2.5%)	38
17	0.4 M, conventional heating, 100 °C, 16 h	82

[a]Conditions: **5a** (0.20 mmol), **6a** (0.10 mmol), **7a** (0.15 mmol). [b]Yield determined by ^1H NMR relative to 1,3,5-trimethoxybenzene as external standard. [c]Isolated yield of a 0.30 mmol scale (see Scheme 2).

Cp*Rh(III) catalysis, Cp*Ir(III) and Cp*Co(III) catalysts were much less effective (Table 1, entries 10 and 11).

Concentration is important, as might be expected for a multicomponent reaction (Table 1, entries 12 and 13), with a higher concentration (0.4 M), resulting in an appreciable increase in yield (Table 1, entry 13). We did not explore further increases in the concentration, because of the amount of 3 Å sieves used (ca. 100 mg per 0.1 mmol of limiting reagent), although it should be noted that only a modest reduction in yield was observed when 3 Å sieves were not added (Table 1, entry 14).

Consistent with our goal to provide access to diverse pyrazolopyrimidines **8** at short reaction times, we chose 10 mol % catalyst loading for evaluating the substrate scope. However, 5 and 2.5 mol % catalyst loadings did afford significant amounts of the desired product (Table 1, entries 15 and 16). Therefore, lower catalyst loadings are likely to be applicable to many starting material combinations (vide infra), as well as by employing more forcing reaction conditions. Finally, an 82% yield for this three-component reaction was observed by employing conventional heating for 16 h at 100 °C, which is a temperature lower than the boiling point of the dioxane solvent (Table 1, entry 17).

Using the optimal reaction conditions (i.e., Table 1, entry 13), we first explored aldehyde scope for three-component coupling with aminopyrazole **6a** and sulfoxonium ylide **7a** (Scheme 2). Benzaldehydes with electron-withdrawing and electron-donating groups at the *para*-position gave pyrazolopyrimidines **8baa** and **8caa** in 78% and 80% yields, respectively, establishing that the reaction is effective,

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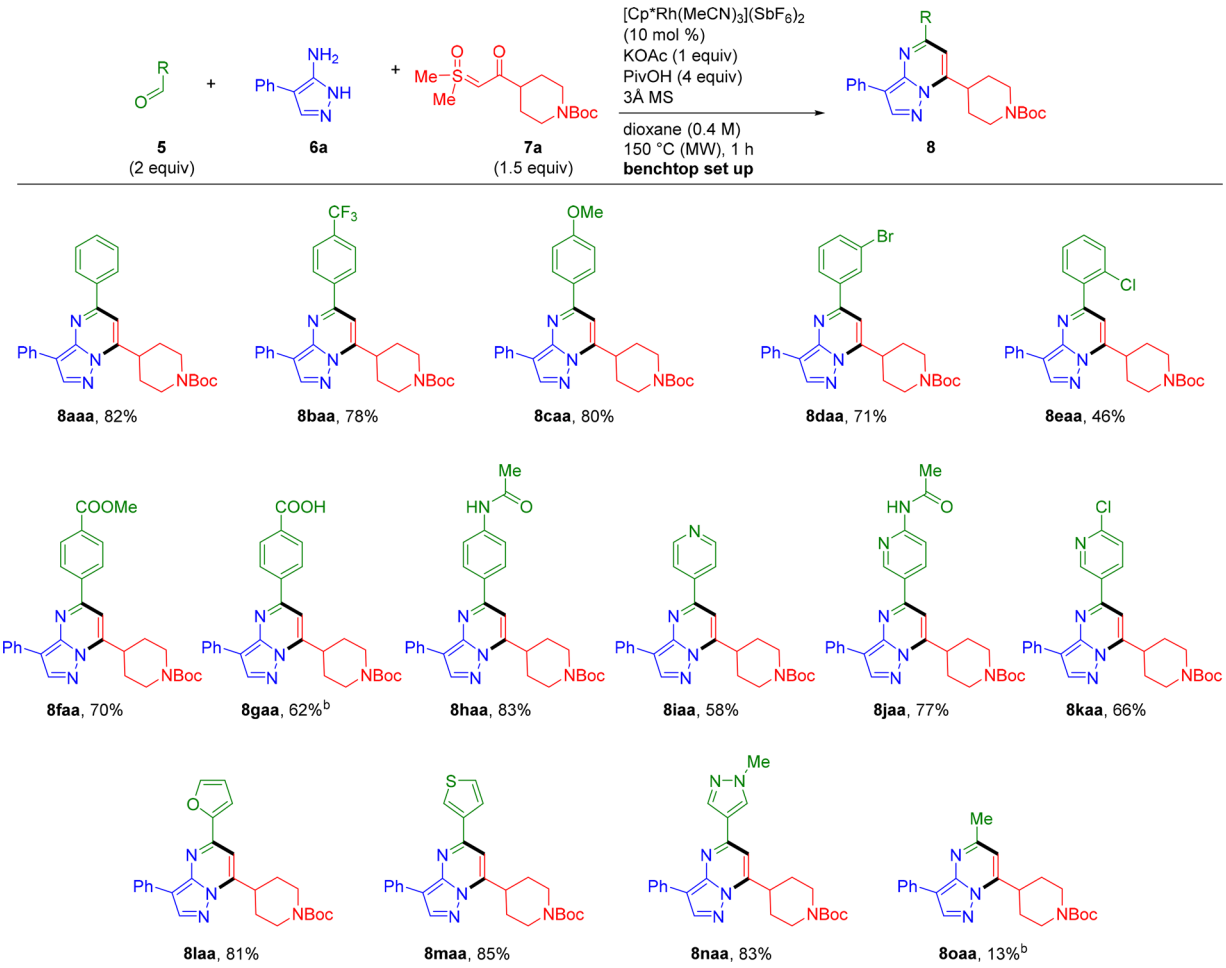
Scheme 2. Aldehyde Scope for Three-Component Synthesis of Pyrazolopyrimidines 8[a]



[a]Standard conditions with **5** (0.60 mmol), **6a** (0.30 mmol), and **7a** (0.45 mmol). [b]0.2 M.

regardless of the electronic properties of the aldehyde input. Benzaldehydes substituted at the *meta*- and *ortho*-positions were also effective coupling partners, as exemplified by the halo-substituted products **8daa** and **8eaa**, respectively. However, a moderate reduction in yield was observed for ortho-substituted product **8eaa**.

Benzaldehydes bearing a large variety of useful functional groups were effective inputs. For example, good yields were obtained for pyrazolopyrimidine products displaying ester (**8faa**), carboxylic acid (**8gaa**), and acidic secondary anilide (**8haa**) functionality. Pyridinecarboxaldehydes were also effective inputs. Notably, unhindered basic heterocyclic nitrogens do not interfere with this directed C−H functionalization reaction, as demonstrated by the incorporation of 4-pyridinecarboxaldehyde to give **8iaa** in 58% yield. The 4-acetamido- and 4-chloro-substituted 3-pyridinecarboxaldehydes also coupled effectively to give **8jaa** and **8kaa** in 77% and 66% yields, respectively. The chloropyridine substituent in **8kaa**, as well as the bromophenyl substituent in **8daa**, provide versatile sites for incorporating additional functionality. These examples highlight the compatibility of haloarene functionality with the three-component reaction conditions. This outcome contrasts with methods to elaborate pyrazolopyrimidine frameworks by using cross-coupling to introduce aromatic substituents, which inherently rely on reactions that proceed via aryl halide oxidative addition.[10]

Five-membered furancarboxaldehydes, thiophenecarboxaldehydes, and pyrazolecarboxaldehydes provided **8laa**−**8naa** in excellent yields (81%−85%). Notably, the *N*-alkyl pyrazolyl motif in **8naa** is incorporated into several approved kinase inhibitor drugs and drug candidates with [5,6]-bicyclic nitrogen heterocycle pharmacophores, such as the approved janus kinase inhibitor drugs ruxolitinib and baricitinib.[11] Lastly, enolizable aldehydes provide the desired pyrazolopyrimidines **8** in poor yields, as exemplified by **8oaa** obtained in 13% yield from acetaldehyde.

We next investigated the scope for the sulfoxonium ylides **7** (Scheme 3). Significantly, these ylides can readily be prepared by straightforward one-step protocols from trimethylsulfoxonium iodide and acid chlorides or activated esters.[8,9] In addition to employing *N*-Boc-piperidine ylide **7a**, another example of the incorporation of an α-branched substituent is provided by the isopropyl substituted pyrazolopyrimidine product **8aab**, which was obtained in 79% yield. Methyl, β-branched and *N*-Boc-ethyl substituted products **8aac**−**8aae** were also obtained in excellent yields (80%−94%). Electron-rich and electron-poor aryl-substituted ylides efficiently coupled to give **8aaf** (89%) and **8aag** (87%), respectively. These results, when considered along with the successful incorporation of electron-poor and electron-rich benzaldehydes, such as **8baa** and **8caa** (Scheme 2), clearly establish that the regiospecific introduction of aromatic substituents,

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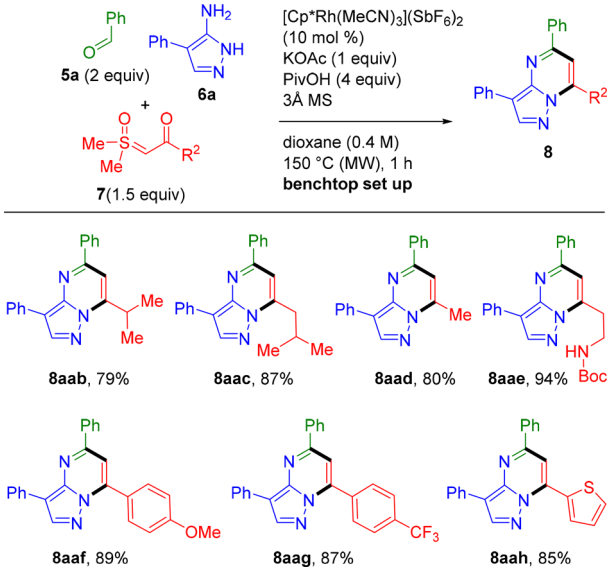
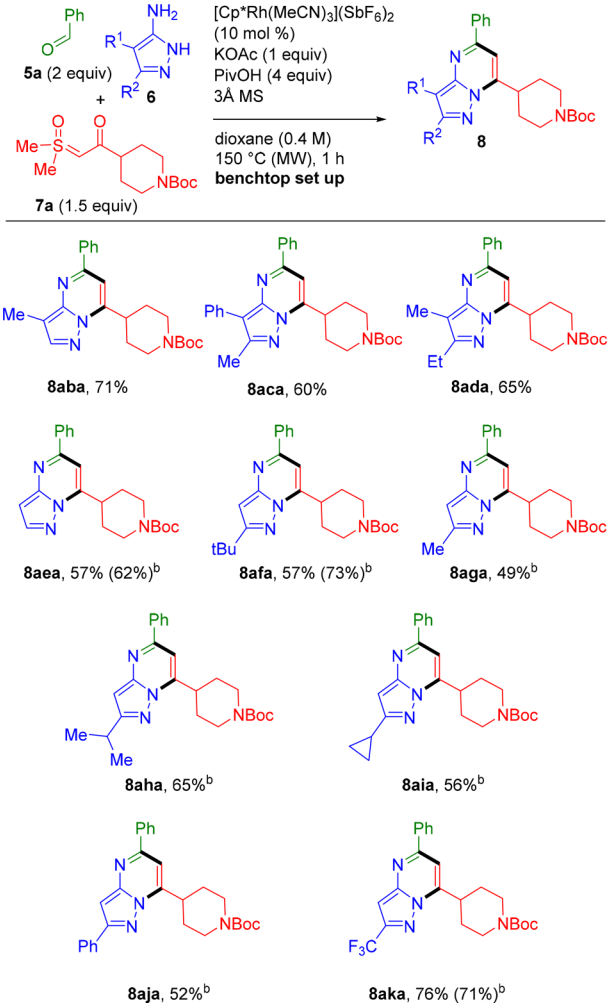
Scheme 3. Sulfoxonium Ylide Scope for Three-Component Synthesis of Pyrazolopyrimidines 8[a]



[a]Standard conditions with **5a** (0.60 mmol), **6a** (0.30 mmol), and **7** (0.45 mmol).

Scheme 4. Aminopyrazole Scope for Three-Component Synthesis of Pyrazolopyrimidines 8[a]



[a]Standard conditions with **5a** (0.60 mmol), **6** (0.30 mmol), and **7a** (0.45 mmol). [b]0.2 M.

regardless of electronic properties, can be achieved. In contrast, while the efficient preparation of pyrazolopyrimidines can be accomplished by condensations of 3-aminopyrazole with symmetrical 1,3-dicarbonyl compounds, this approach generally provides mixtures of regioisomers when unsymmetrical diketones are employed.[12] Finally, the effective incorporation of a heteroaryl-substituted ylide was demonstrated by the preparation of thiophenyl-substituted **8aah** in 85% yield.

As depicted in Scheme 4, we next evaluated the scope for the aminopyrazoles, many of which are commercially available or straightforward to prepare in high yields.[13] Using standard conditions for 4-phenyl-substituted 3-aminopyrazole (**6a**), 4-methyl-substituted 3-aminopyrazole efficiently provided pyrazolopyrimidine **8aba** in 71% yield. Disubstituted aminopyrazoles also coupled efficiently to give **8aca** and **8ada**. Unsubstituted and 5-*tert*-butyl-substituted aminopyrazoles were also effective inputs providing **8aea** in 62% and **8afa** in 73% yields, respectively. Note that, for these inputs, modest improvements in the product yields were achieved by lowering the concentration to 0.2 M. Therefore, 0.2 M was chosen for the evaluation of other 5-substituted-3-aminopyrazoles, including those with methyl, isopropyl, cyclopropyl, and phenyl substituents, which gave **8aga**–**8aja** in reasonable yields (49%–65%). In addition, electron-deficient 5-trifluoromethyl-3-aminopyrazole (**6k**) efficiently underwent standard coupling reaction conditions at both concentrations (0.4 and 0.2 M), affording bicyclic product **8aka** in good yield (76% and 71%, respectively). In contrast, 2-aminoimidazoles are not effective coupling partners, presumably because more forcing conditions are required for aldehyde condensation to give imines. However, we have previously reported that imines from 2-aminoimidazoles can be prepared using $Ti(OEt)_4$ as an acid catalyst and water scavenger. After isolation, the imines can then be subjected to Rh(III)-catalyzed coupling with sulfoxonium ylides to give imidazopyrimidines in high yields.[3]

In some drug discovery efforts, pyrazolopyridimines with only a single substituent on the pyrimidine ring might be desired. Therefore, we explored formyl sulfoxonium ylide **7i** as a potential input to give pyrazolopyrimidines **8** having only one pyrimidine ring substituent, as introduced by the aldehyde (Scheme 5). To the best of our knowledge, formyl sulfoxonium ylides have never previously been employed in a chemical transformation.

Under the optimized one-step three-component reaction conditions, we found that the aldehyde functionality in formyl ylide **7i** effectively competes with the aldehyde input for condensation with the aminopyrazoles. To circumvent this side reaction, a two-step one-pot sequence was implemented instead. The aldehyde **5** and aminopyrazole **6** are first condensed by microwave heating at 150 °C for 30 min in the presence of molecular sieves and PivOH. Formyl ylide **7i**, KOAc, and $[Cp^*Rh(MeCN)_3](SbF_6)_2$ are then added, followed by microwave heating at 150 °C for 1 h. Note that PivOH is added in the first step to catalyze imine formation. In addition, the use of only 1.1 equiv rather than 1.5 equiv of formyl ylide **7i** resulted in moderately higher yields, because it minimized competitive imine exchange during the annulation step.

The effect of reaction concentration on this two-step, one-pot protocol was evaluated for the preparation of pyrazolopyr-

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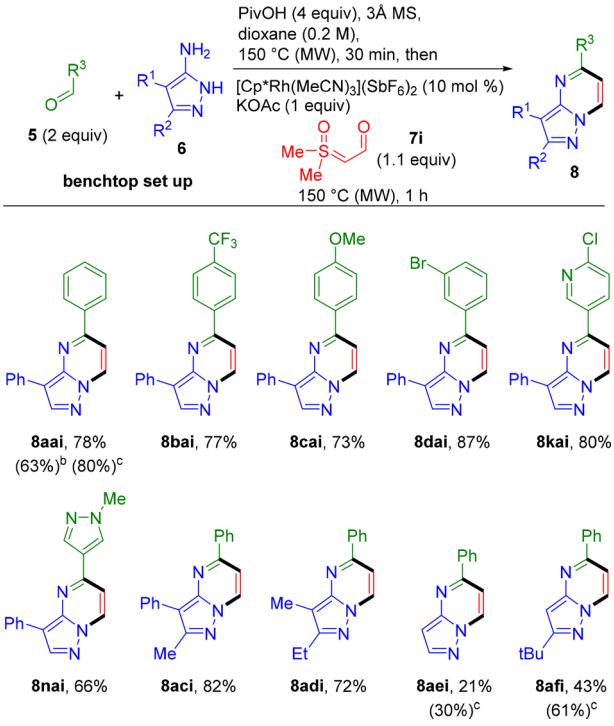
Scheme 5. Annulations with Formyl Ylide To Give Pyrazolopyrimidines 8[a]



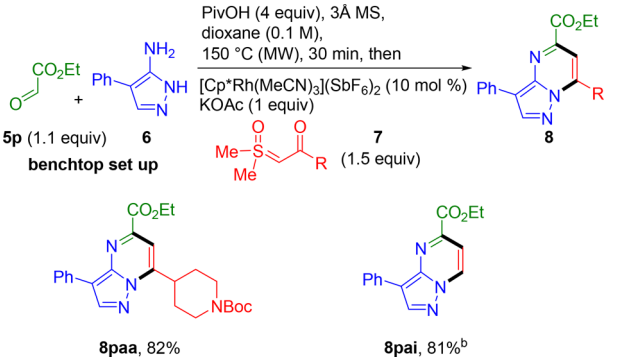
[a]Standard conditions **5** (0.60 mmol), **6** (0.30 mmol), **7i** (0.33 mmol). [b]0.4 M. [c]0.1 M.

imidine **8aai** from benzaldehyde (**5a**), 4-phenyl-3-aminopyrazole (**6a**), and formyl ylide **7i**. At concentrations of 0.1 and 0.2 M, comparable 80% and 78% yields were obtained, respectively. However, in contrast to the higher yield obtained at higher concentrations for the three-component reaction of *β*-keto sulfoxonium ylide **7a** (see Table 1, entries 12 and 13), at 0.4 M, a significantly lower 63% yield was observed. Therefore, we used a reaction concentration of 0.2 M for evaluating the coupling of formyl ylide **7i** with 4-phenyl-3-aminopyrazole **6a** and different aldehydes **5**. Good yields of pyrazolopyrimidines were obtained for benzaldehydes incorporating the electron-deficient trifluoromethyl (**8bai**), electron-rich methoxy (**8cai**), and bromo (**8dai**) functionality. In addition, pyrazolopyrimidine **8kai** was obtained from 6-chloronicotinaldehyde in 80% yield, and pyrazolopyrimidine **8nai** was obtained from *N*-methyl-4-pyrazolecarboxaldehyde in 66% yield. Disubstituted aminopyrazoles also gave **8aci** and **8adi** in 82% and 72%, respectively.

Unsubstituted aminopyrazole and 5-substituted aminopyrazoles gave higher yields at lower concentrations. At a concentration of 0.1 M, pyrazolopyrimidines **8aei** and **8afi** were obtained in 30% and 61% yields, respectively.

To directly install an ester group onto the pyrimidine ring of the product, we sought to employ ethyl glyoxylate (**5p**) as the aldehyde input (Scheme 6). The standard one-step three-component conditions provided the desired pyrazolopyrimidine **8paa**, but in <15% yield. Because of the reactive nature of ethyl glyoxylate, we speculated that a two-step, one-pot procedure for imine formation followed by Rh(III)-catalyzed annulation might be more successful. Indeed, pyrazolopyrimidine **8paa** was obtained in 82% yield by employing this stepwise approach using only a slight excess of ethyl glyoxylate

Scheme 6. Ethyl Glyoxylate as the Aldehyde[a]

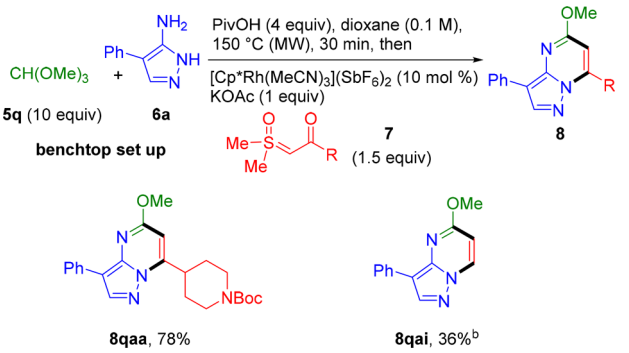


[a]**5p** (0.60 mmol), **6a** (0.30 mmol), **7** (0.45 mmol). [b]**7i** (1.1 equiv).

(1.1 equiv). Note that the reaction was completely shut down at high glyoxylate loading (5 equiv). In addition, this stepwise approach was successfully applied to formyl sulfoxonium ylide **7i** to give pyrazolopyrimidine **8pai** in 81%.

To directly install a methoxy group onto the pyrimidine ring, trimethyl orthoformate (**5q**) was used in place of the aldehyde input **5** (Scheme 7). For this transformation, a one-pot

Scheme 7. Methoxy Group Introduction[a]



[a]**5q** (3.0 mmol), **6a** (0.30 mmol), **7** (0.45 mmol). [b]**7i** (1.1 equiv).

stepwise approach was also the most effective. Consistent with the use of trimethyl orthoformate as a low-cost dehydrating agent, the highest yields were achieved by employing 10 equiv of trimethyl orthoformate without the addition of sieves. Under these conditions, pyrazolopyridimines **8qaa** and **8qai** were obtained in 78% and 36% yields, respectively.

Finally, pyrazolopyrimidine **8naa** was prepared on a 3-fold larger 1 mmol scale with a benchtop setup and a lower catalyst loading of 5 mol % (Scheme 8). Note that this lower catalyst loading resulted in only a slight reduction in the yield to 77% at a standard reaction temperature of 150 °C and a time of 1 h.

A plausible mechanism for this three-component coupling reaction is depicted in Scheme 9. In accordance to our publication on Rh(III)-catalyzed two-component annulations of *N*-azolo imines with alkynes, diazoketones, and sulfoxonium ylides,[3] we propose that imine **A**, formed *in situ* from aldehyde **5** and aminopyrazole **6**, undergoes concerted metalation–deprotonation to give rhodacycle **B**. In this publication, we reported the X-ray structural characterization of a catalytically competent neutral rhodacycle analogous to **B**.[3] Carbene insertion of sulfoxonium ylide **7** with the release of dimethyl sulfoxide (DMSO) then provides the six-membered rhodacycle **C**. Proto-demetalation releases ketone **D** to regenerate the

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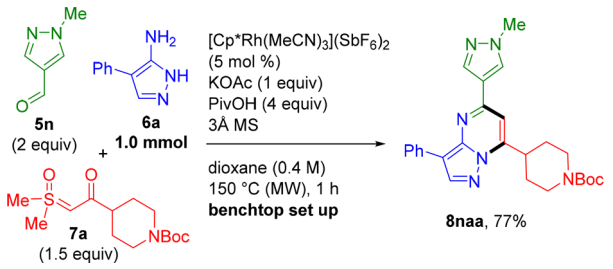
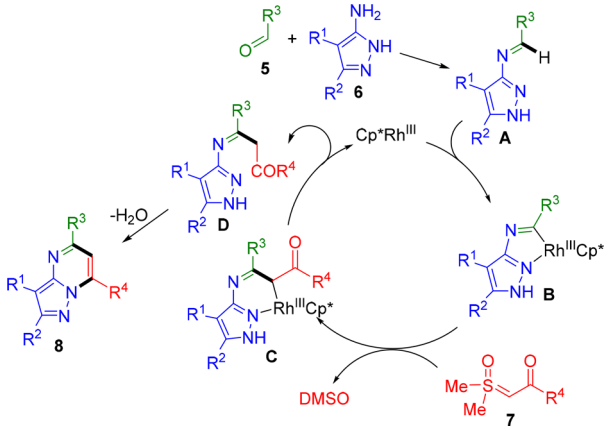
Scheme 8. Benchtop Reaction Setup at 1 mmol Scale



Scheme 9. Proposed Mechanism for Annulation



active Rh(III) catalyst. Finally, under the reaction conditions, ketone **D** undergoes cyclodehydration to afford the pyrazolopyrimidine **8**.

In conclusion, we have reported the Rh(III)-catalyzed three-component coupling of aldehydes **5**, aminopyrazoles **6**, and sulfoxonium ylides **7** to generate diverse pyrazolopyrimidines **8**. This method is operationally convenient with benchtop setup and a short reaction time with microwave heating. Many aromatic and heteroaromatic aldehydes **5** displaying diverse functionality are effective inputs, as are numerous aminopyrazole derivatives **6**. The reaction also proceeds in good yields for a range of aryl, heteroaryl, and alkyl ylides **7**. In addition, the first examples of the application of a formyl sulfoxonium ylide in a metal-catalyzed transformation were implemented for the preparation of pyrazolopyrimidines **8** with only a single substituent on the pyrimidine ring. Ester and methoxy functionalities were also installed directly onto the pyrimidine ring of the bicyclic product by employing ethyl glyoxylate and trimethyl orthoformate in place of the aldehyde input, respectively.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all commercially available reagents were purchased and used as received. Solvents including 1,4-dioxane, tetrahydrofuran (THF), and dichloromethane (CH_2Cl_2) were deoxygenated by sparging with argon. Chlorobenzene was purified by passing through a plug of alumina before use. Microwave reactions were performed using a microwave reactor with an external IR sensor and in a closed reaction vessel. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on 400 or 600 MHz spectrometers. Chemical shifts [δ (ppm)], coupling constants [J (Hz)], multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, m = multiplet, br = broad), and integration are reported. Chemical shifts for ^{1}H and ^{13}C NMR are reported relative to residual undeuterated solvent in $CDCl_3$ (7.24 ppm for ^{1}H NMR and 76.99 ppm for ^{13}C NMR) and $(CD_3)_2SO$ (2.47 ppm for ^{1}H NMR and 39.94 ppm for ^{13}C NMR). Flash chromatography was performed with silica gel with a particle size of 40−63 μm and 230−400 mesh. Partial data are provided for infrared (IR) spectra. Melting points are reported uncorrected. High-resolution mass spectroscopy (HRMS) spectra were obtained using electrospray ionization (ESI) on a time-of-flight (TOF) mass spectrometer (Yale University) or electron ionization (EI) that was performed at the University of Illinois SCS Mass Spectrometry Laboratory.

Preparation of Catalysts and Reactants. All aldehydes **5** and aminopyrazoles **6** were purchased and used as received. $[Cp^*Rh(MeCN)_3](SbF_6)_2$ was synthesized according to literature procedures.[14] Sulfoxonium ylides **7a**−**7d** and **7f**−**7h** were synthesized according to literature procedures.[9f] Sulfoxonium ylides **7e** and **7i** were prepared according to a literature procedure used for a related compound, with slight modifications.[9f]

*tert-Butyl (4-(dimethyl(oxo)-λ^6-sulfaneylidene)-3-oxobutyl)-carbamate (**7e**).* Ylide **7e** was prepared from a literature procedure for a related compound with slight modification.[9f] A mixture of trimethylsufoxonium iodide (3.52 g, 16.0 mmol, 3.2 equiv) and potassium *tert*-butoxide (1.68 g, 15.0 mmol, 3.0 equiv) in THF (125 mL) was heated to reflux (67 °C) for 2 h under nitrogen. After cooling to room temperature (rt), a solution of 4-nitrophenyl 3-((*tert*-butoxycarbonyl)amino)propanoate (1.55 g, 5.00 mmol, 1.00 equiv) in THF (25 mL) was slowly added to the above mixture. The resulting mixture was stirred at rt for 2 h, filtered through a pad of Celite, washed thoroughly with CH_2Cl_2 and concentrated under reduced pressure. Purification by silica gel column chromatography (5% MeOH/CH_2Cl_2) afforded ylide **7e** (591 mg, 45%) as a yellow solid. Melting point (mp): 114−116 °C. FTIR (neat): 3369, 3001, 1682, 1553, 1523, 1391, 1364, 1276, 1170, 1033, 990, 848, 449 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.22 (s, 1H), 4.43 (s, 1H), 3.39 (s, 6H), 3.36 (q, J = 6.1 Hz, 2H), 2.37 (t, J = 6.1 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 189.2, 156.1, 79.0, 70.2, 42.3, 40.0, 37.3, 28.5. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{22}NO_4S^+$, 264.1264; found 264.1278.

*2-(Dimethyl(oxo)-λ^6-sulfaneylidene)acetaldehyde (**7i**).* Ylide **7i** was prepared from a literature procedure for a related compound with slight modification.[9f] A mixture of trimethylsufoxonium iodide (10.6 g, 48.0 mmol, 3.2 equiv) and potassium *tert*-butoxide (5.05 g, 45.0 mmol, 3.0 equiv) in THF (100 mL) was heated at reflux (67 °C) for 2 h under nitrogen. After cooling to rt, to the above mixture was slowly added a solution of ethyl formate (1.11 g, 15.0 mmol, 1.0 equiv) in THF (10 mL). The resulting mixture was stirred at rt for 1 h, filtered through a pad of Celite, washed thoroughly with CH_2Cl_2, and concentrated under reduced pressure. Purification by silica gel column chromatography (10% MeOH/CH_2Cl_2) afforded formyl ylide **7i** as a 97:3 cis/trans ratio of stereoisomers (1.12 g, 62%) as a white solid. mp: 71−73 °C. Fourier transform infrared (FTIR) spectroscopy (neat): 3394, 3082, 3005, 2914, 2788, 1565, 1309, 1296, 1162, 1028, 949, 833, 466 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.09 (trans, d, J = 9.6 Hz, 0.03H), 8.61 (cis, d, J = 2.6 Hz, 1H), 4.61 (trans, d, J = 9.6 Hz, 0.03H), 4.35 (cis, d, J = 2.6 Hz, 1H), 3.41 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.1, 71.9, 42.5. ^{1}H NMR in $(CD_3)_2SO$ was also obtained to provide a different ratio of sulfoxonium ylide cis/trans isomers (0.74:0.26), which also equilibrated slowly on the NMR time scale as has previously been noted by Kondo and Tunemoto:[15] ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.84 (trans, d, J = 9.9 Hz, 0.24H), 8.46 (cis, d, J = 2.6 Hz, 0.64H), 4.70 (cis, d, J = 2.3 Hz, 0.74H), 4.53 (trans, d, J = 9.9 Hz, 0.26H), 3.47 (s, 6H). HRMS (EI): m/z $[M]^+$ calcd for $C_4H_8O_2S$, 120.0245; found 120.0244.

General Procedure for Three-Component Reaction of Aminopyrazoles, Aldehydes, and β-Keto Sulfoxonium Ylides (0.3 mmol scale). Aminopyrazole (0.300 mmol, 1.00 equiv), aldehyde (0.600 mmol, 2.00 equiv), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (10 mol %, 0.030 mmol, 25 mg), PivOH (1.20 mmol, 4.00 equiv, 123 mg), KOAc (0.30 mmol, 1.0 equiv, 29 mg), 3 Å molecular sieves (~300 mg), sulfoxonium ylide (0.450 mmol, 1.50 equiv) and dioxane (0.400 M, 0.750 mL) were added to a flame-dried 2−5 mL Biotage microwave vial (No. 351521) charged with a stir bar on the benchtop.

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The vial was capped with a Teflon-lined cap, flushed with nitrogen for ~2 min, and then heated with a Biotage Initiator+ (No. 356007), which employs an external IR sensor and a closed reaction vessel. The resultant mixture was stirred in the microwave reactor for 1 h at 150 °C, using the following settings (absorption level, low; vial type, 2−5 mL; prestirring, 0; initial power, 0; dynamic deflector optimization, ON; pressure: OFF; power, OFF; fixed hold time, ON; stir rate, 600). After cooling to rt, the crude mixture was transferred to a separatory funnel with CH_2Cl_2 (50 mL). PivOH was removed by extracting with saturated $NaHCO_3$ (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with saturated $NaHSO_3$ (10 wt %, 100 mL) to remove the remaining aldehyde.[16] The organic layer was dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. The product was purified by silica gel column chromatography.

*tert-Butyl 4-(3,5-diphenylpyrazolo[1,5-a]pyrimidin-7-yl)-piperidine-1-carboxylate (**8aaa**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (10%−30% Et_2O/hexanes) afforded **8aaa** (112 mg, 82%) as a yellow solid. ^1H and ^{13}C NMR spectra matched with previously reported literature.[3] ^1H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 8.22−8.09 (m, 4H), 7.59−7.39 (m, 5H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.12 (s, 1H), 4.51−4.14 (m, 2H), 3.78 (tt, *J* = 12.2, 3.4 Hz, 1H), 2.98 (m, 2H), 2.32−2.11 (m, 2H), 1.86−1.65 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.9, 154.6, 152.1, 145.1, 142.3, 137.5, 132.3, 130.4, 128.9, 128.7, 127.3, 126.2, 126.1, 110.7, 101.4, 79.8, 43.7, 36.6, 29.4, 28.5.

*tert-Butyl 4-(3-phenyl-5-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidin-7-yl)piperidine-1-carboxylate (**8baa**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 82.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5b**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (10%−30% Et_2O/hexanes) afforded **8baa** (123 mg, 78%) as a yellow foam. FTIR (neat): 1681, 1422, 1314, 1237, 1157, 1113, 1063, 768, 725, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 8.26 (d, *J* = 8.2 Hz, 2H), 8.18−8.09 (m, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.52−7.43 (m, 2H), 7.32−7.26 (m, 1H), 7.12 (s, 1H), 4.51−4.17 (m, 2H), 3.79 (tt, *J* = 12.1, 3.3 Hz, 1H), 3.10−2.87 (m, 2H), 2.28−2.15 (m, 2H), 1.85−1.69 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.6, 154.2, 152.6, 144.9, 142.6, 140.8, 132.0, 131.9 (q, *J* = 32.6 Hz), 128.8, 127.6, 126.34, 126.30, 125.8 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.2 Hz), 111.3, 101.3, 79.9, 43.7, 36.7, 29.3, 28.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.8. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{30}F_3N_4O_2^+$, 523.2315; found 523.2291.

*tert-Butyl 4-(5-(4-methoxyphenyl)-3-phenylpyrazolo[1,5-a]-pyrimidin-7-yl)piperidine-1-carboxylate (**8caa**).* The reaction was performed according to the general procedure, employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 73.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5c**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (10%−30% Et_2O/hexanes) afforded **8caa** (116 mg, 80%) as a yellow solid. mp: 191−193 °C. FTIR (neat): 1693, 1602, 1426, 1388, 1250, 1173, 1128, 1032, 945, 823, 699, 563, 509 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.23−8.05 (m, 4H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.11−6.90 (m, 3H), 4.49−4.17 (m, 2H), 3.88 (s, 3H), 3.75 (tt, *J* = 12.2, 3.4 Hz, 1H), 2.98 (broad t, *J* = 10.6 Hz, 2H), 2.28−2.15 (m, 2H), 1.86−1.64 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.6, 155.5, 154.7, 151.9, 145.1, 142.2, 132.5, 130.0, 128.8, 128.7, 126.2, 125.9, 114.3, 110.3, 100.9, 79.8, 55.4, 43.8, 36.6, 29.4, 28.5. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{33}N_4O_3^+$, 485.2547; found 485.2547.

*tert-Butyl 4-(5-(3-bromophenyl)-3-phenylpyrazolo[1,5-a]-pyrimidin-7-yl)piperidine-1-carboxylate (**8daa**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 70.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5d**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (10%−40% Et_2O/hexanes) afforded **8daa** (114 mg, 71%) as a yellow solid. mp: 168−171 °C. FTIR (neat): 1682, 1563, 1429, 1234, 1166, 1126, 1078, 946, 795, 760, 623, 533 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.44 (s, 1H), 8.26 (t, *J* = 1.8 Hz, 1H), 8.16−8.11 (m, 2H), 8.09 (ddd, *J* = 7.9, 1.8, 1.0 Hz, 1H), 7.61 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.31−7.25 (m, 1H), 7.06 (s, 1H), 4.55−4.20 (m, 2H), 3.78 (tt, *J* = 12.1, 3.4 Hz, 1H), 3.15−2.77 (m, 2H), 2.28−2.16 (m, 2H), 1.84−1.66 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.6, 154.2, 152.5, 144.9, 142.6, 139.5, 133.2, 132.1, 130.4, 130.3, 128.8, 126.3, 126.3, 125.9, 123.1, 111.1, 101.2, 79.8, 43.9, 36.7, 29.3, 28.5. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{30}BrN_4O_2^+$, 533.1547; found 533.1573.

*tert-Butyl 4-(5-(2-chlorophenyl)-3-phenylpyrazolo[1,5-a]-pyrimidin-7-yl)piperidine-1-carboxylate (**8eaa**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 67.6 μL (0.600 mmol, 2.00 equiv) of aldehyde **5e**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (5%−20% EtOAc/hexanes) afforded **8eaa** (67.5 mg, 46%) as a yellow solid. mp: 194−196 °C. FTIR (neat): 1688, 1609, 1564, 1425, 1231, 1163, 1126, 946, 758, 696, 516 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 8.14−8.05 (m, 2H), 7.81−7.74 (m, 1H), 7.55−7.47 (m, 1H), 7.46−7.37 (m, 4H), 7.26−7.20 (m, 1H), 7.10 (s, 1H), 4.49−4.20 (m, 2H), 3.79 (tt, *J* = 12.1, 3.3 Hz, 1H), 3.08−2.89 (m, 2H), 2.30−2.17 (m, 2H), 1.80−1.65 (m, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.1, 154.7, 151.1, 144.9, 142.2, 137.8, 132.3, 132.1, 131.8, 130.6, 130.4, 128.7, 127.2, 126.3, 126.2, 111.3, 106.0, 79.8, 43.8, 36.5, 29.2, 28.4. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{30}ClN_4O_2^+$, 489.2052; found 489.2042.

*tert-Butyl 4-(5-(4-(methoxycarbonyl)phenyl)-3-phenylpyrazolo-[1,5-a]pyrimidin-7-yl)piperidine-1-carboxylate (**8faa**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 98.5 mg (0.600 mmol, 2.00 equiv) of aldehyde **5f**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (2%−10% EtOAc/CH_2Cl_2) afforded **8faa** (108 mg, 70%) as a yellow solid. mp: >240 °C. FTIR (neat): 1716, 1692, 1406, 1274, 1233, 1166, 1119, 1109, 947, 767, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 8.26−8.12 (m, 6H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.14 (s, 1H), 4.49−4.22 (m, 2H), 3.95 (s, 3H), 3.78 (tt, *J* = 12.1, 3.4 Hz, 1H), 3.09−2.86 (m, 2H), 2.29−2.16 (m, 2H), 1.86−1.68 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6, 154.6, 154.5, 152.5, 144.9, 142.6, 141.4, 132.1, 131.5, 130.1, 128.8, 127.2, 126.3, 111.3, 101.4, 79.8, 52.3, 43.8, 36.7, 29.3, 28.5. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{33}N_4O_4^+$, 513.2496; found 513.2520.

*4-(7-(1-(tert-Butoxycarbonyl)piperidin-4-yl)-3-phenylpyrazolo-[1,5-a]pyrimidin-5-yl)benzoic acid (**8gaa**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 90.1 mg (0.600 mmol, 2.00 equiv) of aldehyde **5g**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a** with slight modification in reaction concentration (0.200 M, 1.50 mL of dioxane) and workup procedure; the reaction mixture after diluting with CH_2Cl_2 was washed with citric acid monohydrate (1 wt %, 100 mL) instead of saturated $NaHCO_3$. Purification by silica gel column chromatography (10%−50% EtOAc/CH_2Cl_2) afforded **8gaa** (92.7 mg, 62%) as a yellow solid. mp: >240 °C. FTIR (neat): 1716, 1615, 1439, 1366, 1243, 1163, 1131, 1113, 787, 692, 663, 515, 526 cm^{-1}. ^1H NMR (600 MHz, $(CD_3)_2SO$): δ 13.12 (br s, 1H), 8.76 (s, 1H), 8.43 (d, *J* = 8.5 Hz, 2H), 8.23−8.16 (m, 2H), 8.08 (d, *J* = 8.5 Hz, 2H), 7.62 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.26−7.21 (m, 1H), 4.27−4.05 (m, 2H), 3.72 (tt, *J* = 12.1, 3.4 Hz, 1H), 3.08−2.73 (m, 2H), 2.13−1.99 (m, 2H), 1.89−1.72 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (151 MHz, $(CD_3)_2SO$): δ 167.4, 154.8, 154.1, 153.2, 144.6, 143.1, 141.0, 132.7, 132.5, 130.2, 129.2, 128.0, 126.4, 126.2, 110.2, 102.8, 79.2, 44.2, 43.2, 36.7, 29.0, 28.6. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{31}N_4O_4^+$, 499.2340; found 499.2358.

*tert-Butyl 4-(5-(4-acetamidophenyl)-3-phenylpyrazolo[1,5-a]-pyrimidin-7-yl)piperidine-1-carboxylate (**8haa**).* The reaction was

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performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 97.9 mg (0.600 mmol, 2.00 equiv) of aldehyde **5h**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (10%−40% EtOAc/CH_2Cl_2) afforded **8haa** (128 mg, 83%) as a yellow solid. mp: 130−133 °C. FTIR (neat): 1667, 1596, 1522, 1387, 1366, 1235, 1161, 1124, 945, 768, 693, 507 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.16−8.06 (m, 4H), 7.73 (br s, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.44 (t, J = 7.8 Hz, 2H), 7.24 (t, J = 7.4 Hz, 1H), 7.02 (s, 1H), 4.45−4.19 (m, 2H), 3.71 (tt, J = 12.2, 3.4 Hz, 1H), 3.07−2.81 (m, 2H), 2.21 (s, 3H), 2.25−2.14 (m, 2H), 1.82−1.62 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6, 155.0, 154.7, 152.0, 145.0, 142.2, 140.0, 132.9, 132.3, 128.7, 128.1, 126.1, 126.0, 119.7, 110.5, 101.0, 79.9, 43.9, 36.6, 29.3, 28.5, 24.7. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{30}H_{34}N_5O_3^+$, 512.2656; found 512.2661.

*tert-Butyl 4-(3-phenyl-5-(pyridin-4-yl)pyrazolo[1,5-a]pyrimidin-7-yl)piperidine-1-carboxylate (**8iaa**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 56.5 μL (0.600 mmol, 2.00 equiv) of aldehyde **5i**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (10%−40% EtOAc/CH_2Cl_2) afforded **8iaa** (78.8 mg, 58%) as a yellow solid. mp: 169−171 °C. FTIR (neat): 1682, 1604, 1566, 1428, 1387, 1295, 1234, 1166, 1129, 942, 817, 768, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, J = 5.6 Hz, 2H), 8.47 (s, 1H), 8.16−8.08 (m, 2H), 8.06−7.96 (m, 2H), 7.47 (t, J = 7.8 Hz, 2H), 7.33−7.24 (m, 1H), 7.12 (s, 1H), 4.51−4.22 (m, 2H), 3.80 (tt, J = 12.1, 3.3 Hz, 1H), 3.10−2.89 (m, 2H), 2.30−2.19 (m, 2H), 1.86−1.68 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.6, 153.0, 152.9, 150.7, 144.8, 144.4, 142.8, 131.8, 128.8, 126.5, 126.4, 121.1, 111.7, 101.0, 79.9, 43.8, 36.7, 29.3, 28.4. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{27}H_{30}N_5O_2^+$, 456.2394; found 456.2401.

*tert-Butyl 4-(5-(6-acetamidopyridin-3-yl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)piperidine-1-carboxylate (**8jaa**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 98.5 mg (0.600 mmol, 2.00 equiv) of aldehyde **5j**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (10%−40% EtOAc/CH_2Cl_2) afforded **8jaa** (118 mg, 77%) as a yellow solid. mp: >240 °C. FTIR (neat): 1696, 1598, 1520, 1384, 1364, 1305, 1232, 1167, 1122, 9945, 767, 691, 509 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.07 (d, J = 1.8 Hz, 1H), 8.47 (s, 1H), 8.46−8.40 (m, 2H), 8.39−8.31 (m, 1H), 8.15−8.07 (m, 2H), 7.45 (t, J = 7.8 Hz, 2H), 7.29−7.22 (m, 1H), 7.04 (s, 1H), 4.47−4.18 (m, 2H), 3.77 (tt, J = 12.1, 3.3 Hz, 1H), 3.06−2.88 (m, 2H), 2.26 (s, 3H), 2.29−2.17 (m, 2H), 1.82−1.66 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8, 154.6, 152.9, 152.6, 152.6, 147.1, 144.9, 142.5, 137.1, 132.1, 129.1, 128.7, 126.3, 126.2, 113.5, 110.9, 100.5, 79.8, 43.7, 36.7, 29.3, 28.5, 24.8. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{29}H_{33}N_6O_3^+$, 513.2609; found 513.2619.

*tert-Butyl 4-(5-(6-chloropyridin-3-yl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)piperidine-1-carboxylate (**8kaa**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 84.9 mg (0.600 mmol, 2.00 equiv) of aldehyde **5k**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (2%−10% EtOAc/CH_2Cl_2) afforded **8kaa** (96.3 mg, 66%) as a yellow solid. mp: 199−202 °C. FTIR (neat): 1692, 1567, 1426, 1235, 1164, 1129, 1105, 945, 826, 771, 692, 497, 474 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.11 (d, J = 2.1 Hz, 1H), 8.45 (s, 1H), 8.43 (dd, J = 8.3, 2.5 Hz, 1H), 8.14−8.05 (m, 2H), 7.52−7.40 (m, 3H), 7.32−7.25 (m, 1H), 7.05 (s, 1H), 4.49−4.20 (m, 2H), 3.78 (tt, J = 12.1, 3.3 Hz, 1H), 3.09−2.83 (m, 2H), 2.31−2.13 (m, 2H), 1.84−1.68 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.6, 153.1, 153.0, 152.0, 148.5, 144.8, 142.7, 137.3, 132.0, 131.8, 128.77, 126.5, 126.3, 124.5, 111.4, 100.6, 79.9, 43.7, 36.8, 29.2, 28.4. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{27}H_{29}ClN_5O_2^+$, 490.2004; found 490.2022.

*tert-Butyl 4-(5-(furan-2-yl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)piperidine-1-carboxylate (**8laa**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 49.7 μL (0.600 mmol, 2.00 equiv) of aldehyde **5l**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (10%−40% Et_2O/hexanes) afforded **8laa** (108 mg, 81%) as a yellow solid. mp: 201−203 °C. FTIR (neat): 1681, 1610, 1426, 1292, 1229, 1167, 1005, 937, 765, 743, 515 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.15−8.07 (m, 2H), 7.59 (dd, J = 1.8, 0.8 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.31 (dd, J = 3.5, 0.8 Hz, 1H), 7.29−7.20 (m, 1H), 7.10 (s, 1H), 6.59 (dd, J = 3.5, 1.8 Hz, 1H), 4.48−4.21 (m, 2H), 3.74 (tt, J = 12.1, 3.4 Hz, 1H), 3.06−2.86 (m, 2H), 2.27−2.13 (m, 2H), 1.84−1.64 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.6, 152.5, 152.3, 147.7, 144.9, 144.5, 142.3, 132.3, 128.7, 126.2, 126.1, 112.7, 111.5, 110.4, 100.1, 79.7, 43.8, 36.5, 29.3, 28.5. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{29}N_4O_3^+$, 445.2240; found 445.2263.

*tert-Butyl 4-(3-phenyl-5-(thiophen-3-yl)pyrazolo[1,5-a]pyrimidin-7-yl)piperidine-1-carboxylate (**8maa**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 52.6 μL (0.600 mmol, 2.00 equiv) of aldehyde **5m**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (5%−25% EtOAc/hexanes) afforded **8maa** (117 mg, 85%) as a yellow solid. mp: 182−185 °C. FTIR (neat): 1691, 1672, 1608, 1418, 1366, 1291, 1237, 1163, 1134, 1068, 762, 691, 515 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.17−8.09 (m, 2H), 8.03 (dd, J = 3.0, 1.3 Hz, 1H), 7.84 (dd, J = 5.1, 1.3 Hz, 1H), 7.50−7.40 (m, 3H), 7.30−7.22 (m, 1H), 6.96 (s, 1H), 4.50−4.17 (m, 2H), 3.75 (tt, J = 12.1, 3.4 Hz, 1H), 3.08−2.84 (m, 2H), 2.27−2.17 (m, 2H), 1.83−1.64 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.7, 152.1, 151.9, 144.9, 142.3, 140.9, 132.4, 128.7, 126.7, 126.7, 126.2, 126.0, 125.9, 110.5, 101.7, 79.8, 43.8, 36.5, 29.4, 28.5. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{29}N_4O_2S^+$, 461.2006; found 461.2000.

*tert-Butyl 4-(5-(1-methyl-1H-pyrazol-4-yl)-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)piperidine-1-carboxylate (**8naa**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 66.1 mg (0.600 mmol, 2.00 equiv) of aldehyde **5n**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (5%−30% EtOAc/CH_2Cl_2) afforded **8naa** (114 mg, 83%) as a light yellow solid. mp: >240 °C. FTIR (neat): 1684, 1616, 1551, 1427, 1235, 1168, 1126, 999, 863, 767, 751, 695, 516 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.12−8.09 (m, 2H), 8.07 (s, 1H), 8.05 (s, 1H), 7.47−7.43 (m, 2H), 7.30−7.21 (m, 1H), 6.78 (s, 1H), 4.51−4.14 (m, 2H), 3.99 (s, 3H), 3.73 (tt, J = 12.2, 3.4 Hz, 1H), 3.12−2.86 (m, 2H), 2.27−2.15 (m, 2H), 1.79−1.65 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 154.6, 152.0, 150.9, 145.1, 142.2, 138.4, 132.5, 130.1, 128.7, 126.1, 125.9, 122.5, 109.7, 101.4, 79.8, 44.1, 43.4, 39.4, 36.4, 29.4, 28.5. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{31}N_6O_2^+$, 459.2503; found 459.2507.

*tert-Butyl 4-(5-methyl-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)-piperidine-1-carboxylate (**8oaa**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 26.5 mg (0.600 mmol, 2.00 equiv) of aldehyde **5o** and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a** with slight modification in reaction concentration (0.200 M, 1.50 mL of dioxane) and in order of addition; after nitrogen flush, acetaldehyde was added in one portion as a solution in dioxane (1.50 mL) via syringe. Purification by preparative TLC plate (UV_{254}, 20 cm × 20 cm, 1000 μm; 20:80:1 EtOAc/hexanes/Et_3N) afforded **8oaa** (15.2 mg, 13%) as a white solid. mp: 194−196 °C. FTIR (neat): 1679, 1605, 1566, 1441, 1427, 1365, 1289, 1234, 1156, 1125, 864, 771, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.10−7.95 (m, 2H), 7.41 (t, J = 7.8 Hz, 2H), 7.27−7.18 (m, 1H), 6.51 (s, 1H), 4.45−4.15 (m, 2H), 3.69 (tt, J = 12.1, 3.4 Hz, 1H), 2.94 (t, J = 13.2 Hz, 2H), 2.61 (s, 3H), 2.21−2.10 (m, 2H), 1.69−1.58 (m, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.1, 154.6, 151.3, 144.9, 141.9, 132.4, 128.7, 126.2, 126.0, 109.6, 105.1, 79.8, 43.7, 36.2, 29.3, 28.4, 25.2. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{29}N_4O_2^+$, 393.2285; found 393.2289.

*7-Isopropyl-3,5-diphenylpyrazolo[1,5-a]pyrimidine (**8aab**).* The reaction was performed according to the general procedure employing

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47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 78.8 mg (0.486 mmol, 1.5 equiv) of ylide **7b**. Purification by silica gel column chromatography (25%−50% CH_2Cl_2/hexanes) afforded **8aab** (74.1 mg, 79%) as a yellow solid. mp: 105−107 °C. FTIR (neat): 1606, 1564, 1523, 1492, 1386, 1253, 1201, 1176, 828, 763, 692, 657, 603 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 8.48 (s, 1H), 8.23−8.20 (m, 4H), 7.58−7.47 (m, 5H), 7.29 (tt, *J* = 7.3, 1.2 Hz, 1H), 7.20 (s, 1H), 3.95 (hept, *J* = 6.9 Hz, 1H), 1.54 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 155.9, 155.2, 145.2, 142.3, 137.7, 132.6, 130.2, 128.9, 128.7, 127.4, 126.2, 126.0, 110.5, 100.9, 28.7, 20.1. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{20}N_3^+$, 314.1652; found 314.1654.

*7-Isobutyl-3,5-diphenylpyrazolo[1,5-a]pyrimidine (**8aac**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 80.1 mg (0.454 mmol, 1.5 equiv) of ylide **7c**. Purification by silica gel column chromatography (25%−50% CH_2Cl_2/hexanes) afforded **8aac** (85.0 mg, 87%) as a yellow solid. mp: 114−116 °C. FTIR (neat): 1607, 1564, 1523, 1389, 1197, 763, 685, 643, 595, 516 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 8.47 (s, 1H), 8.24−8.18 (m, 4H), 7.59−7.46 (m, 5H), 7.31−7.26 (m, 1H), 7.16 (s, 1H), 3.12 (d, *J* = 7.3 Hz, 2H), 2.54−2.43 (m, 1H), 1.09 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 155.6, 149.1, 145.4, 142.6, 137.7, 132.7, 130.4, 129.0, 128.8, 127.5, 126.3, 126.1, 110.6, 104.9, 40.2, 26.0, 22.8. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{22}N_3^+$, 328.1808; found 328.1803.

*7-Methyl-3,5-diphenylpyrazolo[1,5-a]pyrimidine (**8aad**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 65.2 mg (0.486 mmol, 1.5 equiv) of ylide **7d**. Purification by silica gel column chromatography (50% CH_2Cl_2/hexanes) afforded **8aad** (68.5 mg, 80%) as a yellow solid. mp: 142−144 °C. FTIR (neat): 1605, 1563, 1369, 1200, 765, 692, 640, 596, 515 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 8.23−8.10 (m, 4H), 7.56−7.41 (m, 5H), 7.31−7.22 (m, 1H), 7.17 (s, 1H), 2.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.5, 146.0, 145.0, 142.5, 137.4, 132.5, 130.3, 128.9, 128.7, 127.3, 126.2, 126.0, 110.6, 105.0, 17.5. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{16}N_3^+$, 286.1339; found 286.1338.

*tert-Butyl (2-(3,5-diphenylpyrazolo[1,5-a]pyrimidin-7-yl)ethyl)-carbamate (**8aae**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 129 mg (0.488, 1.5 equiv mmol) of ylide **7e**. Purification by silica gel column chromatography (25% EtOAc/hexanes) afforded **8aae** (118 mg, 94%) as a yellow solid. mp: 153−155 °C. FTIR (neat): 1698, 1565, 1530, 1271, 1160, 1137, 765, 685, 596, 495 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 8.44 (s, 1H), 8.25−8.13 (m, 4H), 7.56−7.45 (m, 5H), 7.31−7.26 (m, 2H), 4.93 (br s, NH, 1H), 3.76 (q, *J* = 6.6 Hz, 2H), 3.46 (t, *J* = 6.8 Hz, 2H), 1.42 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 155.9, 155.7, 146.6, 145.1, 142.5, 137.2, 132.3, 130.4, 128.9, 128.7, 127.4, 126.2, 126.1, 110.8, 104.9, 79.6, 37.5, 31.6, 28.3. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{27}N_4O_2^+$, 415.2129; found 415.2138.

*7-(4-Methoxyphenyl)-3,5-diphenylpyrazolo[1,5-a]pyrimidine (**8aaf**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 107 mg (0.473 mmol, 1.5 equiv) of ylide **7f**. Purification by silica gel column chromatography (25%−50% CH_2Cl_2/hexanes) afforded **8aaf** (101 mg, 89%) as a yellow solid. ^1H and ^{13}C NMR spectra matched with previously reported literature.[3] ^1H NMR (600 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.28−8.20 (m, 4H), 8.13−8.07 (m, 2H), 7.58−7.47 (m, 5H), 7.38 (s, 1H), 7.32−7.27 (m, 1H), 7.15−7.09 (m, 2H), 3.92 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 161.9, 156.0, 146.9, 146.2, 143.0, 137.7, 132.7, 131.1, 130.5, 129.1, 128.9, 127.5, 126.5, 126.2, 123.8, 114.3, 110.6, 104.5, 55.7.

*3,5-Diphenyl-7-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-a]-pyrimidine (**8aag**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 124 mg (0.469 mmol, 1.5 equiv) of ylide **7g**. Purification by silica gel column chromatography (25%−50% CH_2Cl_2/hexanes) afforded **8aag** (109 mg, 87%) as a yellow solid. ^1H, ^{13}C, and ^{19}F NMR spectra matched with previously reported literature.[3] ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 8.27−8.16 (m, 6H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.60−7.47 (m, 5H), 7.39 (s, 1H), 7.32 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.0, 146.0, 145.5, 143.2, 137.2, 135.0, 132.9 (q, *J* = 32.9 Hz), 132.2, 130.8, 129.9, 129.2, 128.9, 127.5, 126.6, 126.5, 125.9 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 272.5 Hz), 111.3, 105.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.0.

*3,5-Diphenyl-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidine (**8aah**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 91.1 mg (0.450, 1.50 equiv mmol) of ylide **7h**. Purification by silica gel column chromatography (25%−50% CH_2Cl_2/hexanes) afforded **8aah** (89.8 mg, 85%) as a red solid. mp: 162−164 °C. FTIR (neat): 1603, 1554, 1529, 1494, 1380, 820, 763, 715, 690, 668, 491 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.39−8.37 (m, 1H), 8.26−8.19 (m, 4H), 7.74−7.71 (m, 1H), 7.69 (s, 1H), 7.59−7.47 (m, 5H), 7.33−7.27 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 155.4, 146.1, 142.6, 140.2, 137.6, 132.5, 132.1, 131.9, 131.3, 130.4, 129.0, 128.8, 127.7, 127.4, 126.5, 126.2, 110.7, 101.7. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{16}N_3S^+$, 354.1059; found 354.1063.

*tert-Butyl 4-(3-methyl-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)-piperidine-1-carboxylate (**8aba**).* The reaction was performed according to the general procedure employing 29.2 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6b**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (2%−5% EtOAc/CH_2Cl_2) afforded **8aba** (83.6 mg, 71%) as a light yellow solid. mp: 150−152 °C. FTIR (neat): 1673, 1616, 1430, 1381, 1238, 1162, 1125, 968, 773, 690, 639, 538 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.10−8.04 (m, 2H), 7.95 (s, 1H), 7.53−7.41 (m, 3H), 7.01 (s, 1H), 4.47−4.15 (m, 2H), 3.73 (tt, *J* = 12.1, 3.3 Hz, 1H), 3.07−2.83 (m, 2H), 2.42 (s, 3H), 2.27−2.14 (m, 2H), 1.80−1.61 (m, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.6, 154.6, 151.5, 146.5, 144.5, 137.9, 130.0, 128.8, 127.2, 106.2, 100.8, 79.7, 43.7, 36.4, 29.3, 28.5, 7.7. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{29}N_4O_2^+$, 393.2285; found 393.2298.

*tert-Butyl 4-(2-methyl-3,5-diphenylpyrazolo[1,5-a]pyrimidin-7-yl)piperidine-1-carboxylate (**8aca**).* The reaction was performed according to the general procedure employing 52.0 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6c**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (5%−20% acetone/hexanes) afforded **8aca** (84.4 mg, 60%) as a light yellow solid. mp: 156−158 °C. FTIR (neat): 1680, 1606, 1420, 1364, 1233, 1165, 1125, 745, 768, 696, 621 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 8.11 (d, *J* = 6.7 Hz, 2H), 7.85 (d, *J* = 6.8 Hz, 2H), 7.53−7.40 (m, 5H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.06 (s, 1H), 4.50−4.20 (s, 2H), 3.80 (tt, *J* = 12.2, 3.4 Hz, 1H), 3.12−2.89 (bs, 2H), 2.68 (s, 3H), 2.35−2.16 (m, 2H), 1.82−1.70 (m, 2H), 1.50 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 155.6, 154.7, 152.2, 151.4, 146.3, 137.6, 132.8, 130.1, 128.8, 128.8, 128.4, 127.2, 126.0, 109.4, 100.9, 79.8, 44.2, 43.4, 36.3, 29.4, 28.5, 14.7. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{33}N_4O_2^+$, 469.2598; found 469.2601.

*tert-Butyl 4-(2-ethyl-3-methyl-5-phenylpyrazolo[1,5-a]-pyrimidin-7-yl)piperidine-1-carboxylate (**8ada**).* The reaction was performed according to the general procedure employing 37.6 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6d**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (5%−20% EtOAc/hexanes) afforded **8ada** (82.0 mg, 65%) as a light yellow solid. mp: 120−122 °C. FTIR (neat): 1689, 1617, 1425, 1364, 1292, 1232,

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1165, 1119, 770, 688 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 8.13−8.01 (m, 2H), 7.53−7.38 (m, 3H), 6.92 (s, 1H), 4.50−4.14 (m, 2H), 3.74 (tt, J = 12.1, 3.4 Hz, 1H), 3.08−2.90 (m, 2H), 2.85 (q, J = 7.6 Hz, 2H), 2.36 (s, 3H), 2.26−2.13 (m, 2H), 1.80−1.63 (m, 2H), 1.48 (s, 9H), 1.33 (t, J = 7.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 158.4, 154.7, 154.3, 151.2, 147.0, 138.2, 129.8, 128.8, 127.1, 102.9, 99.9, 79.7, 44.1, 43.4, 36.2, 29.3, 28.5, 21.0, 13.7, 7.0. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{33}N_4O_2^+$, 421.2598; found 421.2604.

*tert-Butyl 4-(5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)piperidine-1-carboxylate (**8aea**).* The reaction was performed according to the general procedure employing 25.0 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6e**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a** with slight modification in reaction concentration (0.200 M, 1.50 mL of dioxane). Purification by silica gel column chromatography (5%−20% EtOAc/CH_2Cl_2) afforded **8aea** (69.9 mg, 62%) as an off-white foam. FTIR (neat): 1670, 1613, 1432, 1240, 1163, 1129, 1002, 903, 771, 693, 640, 540 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 2.4 Hz, 1H), 8.08−7.97 (m, 2H), 7.54−7.40 (m, 3H), 7.06 (s, 1H), 6.71 (d, J = 2.3 Hz, 1H), 4.47−4.21 (m, 2H), 3.77 (tt, J = 12.2, 3.2 Hz, 1H), 3.06−2.87 (m, 2H), 2.27−2.16 (m, 2H), 1.81−1.66 (m, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.2, 154.6, 152.0, 148.9, 144.6, 137.6, 130.2, 128.9, 127.2, 101.5, 97.1, 79.7, 43.7, 36.6, 29.3, 28.4. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{27}N_4O_2^+$, 379.2129; found 379.2131.

*tert-Butyl 4-(2-(tert-butyl)-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)piperidine-1-carboxylate (**8afa**).* The reaction was performed according to the general procedure employing 41.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6f**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a** with slight modification in reaction concentration (0.200 M, 1.50 mL of dioxane). Purification by silica gel column chromatography (2%−5% EtOAc/CH_2Cl_2) afforded **8afa** (95.0 mg, 73%) as a white foam. FTIR (neat): 2961, 1690, 1610, 1533, 1449, 1364, 1233, 1164, 1120, 771, 692, 591 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.10−7.92 (m, 2H), 7.54−7.38 (m, 3H), 6.96 (s, 1H), 6.54 (s, 1H), 4.46−4.19 (m, 2H), 3.73 (tt, J = 12.1, 3.4 Hz, 1H), 3.06−2.86 (m, 2H), 2.28−2.16 (m, 2H), 1.82−1.65 (m, 2H), 1.48 (s, 9H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.7, 155.5, 154.7, 151.5, 149.2, 138.0, 129.9, 128.8, 127.1, 100.5, 92.9, 79.7, 43.9, 36.7, 32.9, 30.4, 29.0, 28.5. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{35}N_4O_2^+$, 435.2755; found 435.2760.

*tert-Butyl 4-(2-methyl-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)-piperidine-1-carboxylate (**8aga**).* The reaction was performed according to the general procedure employing 29.2 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6g**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a** with slight modification in reaction concentration (0.200 M, 1.50 mL of dioxane). Purification by silica gel column chromatography (2%−10% EtOAc/CH_2Cl_2) afforded **8aga** (57.6 mg, 49%) as an off-white solid. mp: 165−167 °C. FTIR (neat): 1685, 1610, 1533, 1470, 1415, 1364, 1235, 1156, 999, 867, 772, 695, 586 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.05−7.99 (m, 2H), 7.52−7.41 (m, 3H), 6.97 (s, 1H), 6.48 (s, 1H), 4.48−4.13 (m, 2H), 3.76 (tt, J = 12.2, 3.4 Hz, 1H), 3.12−2.84 (m, 2H), 2.52 (s, 3H), 2.25−2.15 (m, 2H), 1.80−1.62 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.9, 154.9, 154.7, 151.5, 149.7, 137.9, 130.0, 128.8, 127.2, 100.6, 96.4, 79.7, 43.8, 36.4, 29.4, 28.5, 14.8. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{29}N_4O_2^+$, 393.2285; found 393.2286.

*tert-Butyl 4-(2-isopropyl-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)-piperidine-1-carboxylate (**8aha**).* The reaction was performed according to the general procedure employing 37.6 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6h**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a** with slight modification in reaction concentration (0.200 M, 1.50 mL of dioxane). Purification by silica gel column chromatography (10%−40% Et_2O/hexanes) afforded **8aha** (81.7 mg, 65%) as a white solid. mp: 100−102 °C. FTIR (neat): 2957, 1704, 1613, 1554, 1417, 1365, 1232, 1170, 1124, 766, 683, 439 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.06−7.96 (m, 2H), 7.51−7.41 (m, 3H), 6.97 (s, 1H), 6.51 (s, 1H), 4.43−4.17 (m, 2H), 3.75 (tt, J = 12.1, 3.4 Hz, 1H), 3.17 (hept, J = 6.9 Hz, 1H), 3.02−2.92 (m, 2H), 2.27−2.16 (m, 2H), 1.81−1.64 (m, 2H), 1.48 (s, 9H), 1.37 (d, J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.2, 155.7, 154.7, 151.6, 149.4, 137.9, 129.9, 128.8, 127.2, 100.6, 93.3, 79.7, 43.9, 36.4, 29.2, 28.8, 28.5, 22.9. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{33}N_4O_2^+$, 421.2598; found 421.2596.

*tert-Butyl 4-(2-cyclopropyl-5-phenylpyrazolo[1,5-a]pyrimidin-7-yl)piperidine-1-carboxylate (**8aia**).* The reaction was performed according to the general procedure employing 37.0 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6i**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a** with slight modification in reaction concentration (0.200 M, 1.50 mL of dioxane). Purification by silica gel column chromatography (2%−10% EtOAc/CH_2Cl_2) afforded **8aia** (70.4 mg, 56%) as a white solid. mp: 108−110 °C. FTIR (neat): 1964, 1611, 1557, 1419, 1366, 1272, 1226, 1159, 1120, 981, 769, 685, 661 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.07−7.95 (m, 2H), 7.54−7.37 (m, 3H), 6.95 (s, 1H), 6.30 (s, 1H), 4.46−4.16 (m, 2H), 3.74 (tt, J = 12.1, 3.2 Hz, 1H), 2.96 (m, 2H), 2.27−2.08 (m, 3H), 1.77−1.64 (m, 2H), 1.48 (s, 9H), 1.11−1.01 (m, 2H), 0.95−0.85 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.5, 155.8, 154.7, 151.3, 149.6, 137.9, 130.0, 128.8, 127.1, 100.5, 92.4, 79.7, 43.8, 36.4, 29.3, 28.5, 10.2, 9.4. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{31}N_4O_2^+$, 419.2442; found 419.2445.

*tert-Butyl 4-(2,5-diphenylpyrazolo[1,5-a]pyrimidin-7-yl)-piperidine-1-carboxylate (**8aja**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6j**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a** with slight modification in reaction concentration (0.200 M, 1.50 mL of dioxane). Purification by silica gel column chromatography (2%−10% EtOAc/CH_2Cl_2) afforded **8aja** (70.6 mg, 52%) as an off-white solid. mp: 171−173 °C. FTIR (neat): 1662, 1612, 1464, 1420, 1236, 1165, 1134, 764, 744, 691 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 8.07 (d, J = 6.7 Hz, 2H), 8.03 (d, J = 6.9 Hz, 2H), 7.55−7.44 (m, 5H), 7.40 (t, J = 7.4 Hz, 1H), 7.06 (s, 1H), 7.01 (s, 1H), 4.51−4.23 (m, 2H), 3.86 (tt, J = 12.1, 3.4 Hz, 1H), 3.09−2.90 (m, 2H), 2.33−2.24 (m, 2H), 1.86−1.71 (m, 2H), 1.50 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 156.1, 155.9, 154.7, 151.8, 150.1, 137.7, 133.1, 130.2, 128.9, 128.7, 127.2, 126.6, 101.5, 93.8, 79.8, 44.3, 43.4, 36.7, 29.3, 28.5. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{28}H_{31}N_4O_2^+$, 455.2442; found 455.2434.

*tert-Butyl 4-(5-phenyl-2-(trifluoromethyl)pyrazolo[1,5-a]-pyrimidin-7-yl)piperidine-1-carboxylate (**8aka**).* The reaction was performed according to the general procedure employing 45.6 mg (0.300 mmol) of aminopyrazole **6k**, 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, and 137 mg (0.450 mmol, 1.50 equiv) of ylide **7a**. Purification by silica gel column chromatography (100% CH_2Cl_2, then 10−25% EtOAc/hexanes) afforded **8aka** (102 mg, 76%) as an off-white solid. mp: 164−167 °C. FTIR (neat): 1684, 1612, 1423, 1232, 1161, 1128, 1103, 955, 774, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.10−8.05 (m, 2H), 7.56−7.50 (m, 3H), 7.23 (s, 1H), 6.98 (s, 1H), 4.52−4.19 (m, 2H), 3.80 (tt, J = 12.1, 3.4 Hz, 1H), 3.10−2.91 (m, 2H), 2.28−2.19 (m, 2H), 1.83−1.68 (m, 2H), 1.50 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.8, 154.8, 152.9, 149.2, 146.8 (q, J = 38.2 Hz), 137.1, 131.0, 129.2, 127.5, 121.4 (q, J = 269.7 Hz), 103.8, 95.9, 80.0, 43.8, 36.6, 29.4, 28.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.4. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{26}F_3N_4O_2^+$, 447.2002; found 447.1996.

General Procedure for Two-Step, One-Pot Annulations with Aminopyrazoles, Aldehydes, and Formyl Sulfoxonium Ylide 7i (0.3 mmol scale). Aminopyrazole (0.300 mmol, 1.00 equiv), aldehyde (0.600 mmol, 2.00 equiv), PivOH (1.20 mmol, 4.00 equiv, 123 mg), 3 Å molecular sieves (~300 mg), and dioxane (0.200 M, 1.50 mL) were added to a flame-dried 2−5 mL Biotage microwave vial (No. 351521) charged with a stir bar on the benchtop. The vial was capped with a Teflon-lined cap, flushed with nitrogen for ~2 min, and then heated with a Biotage Initiator+ (No. 356007), which employs an external IR sensor and a closed reaction vessel. The resultant mixture was stirred in the microwave reactor for 30 min at

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150 °C using the following settings (absorption level, low; vial type, 2−5 mL; prestirring, 0; initial power, 0; dynamic deflector optimization, ON; pressure: OFF; power, OFF; fixed hold time, ON; stir rate, 600). After cooling to rt, the cap was opened, and $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (10 mol %, 0.030 mmol, 25 mg), KOAc (0.30 mmol, 1.0 equiv, 29 mg) and formyl sulfoxonium ylide **7i** (0.330 mmol, 1.10 equiv, 39.7 mg) were added. The vial was capped with a Teflon-lined cap, flushed with nitrogen for ∼2 min and then heated in the microwave reactor for 1 h at 150 °C using the above settings. After cooling to rt, the crude mixture was transferred to a separatory funnel with CH_2Cl_2 (50 mL). PivOH was removed by extracting with saturated $NaHCO_3$ (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with saturated $NaHSO_3$ (10 wt %, 100 mL) to remove remaining aldehyde.[16] The organic layer was dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. The product was purified by silica gel column chromatography.

*3,5-Diphenylpyrazolo[1,5-a]pyrimidine (**8aai**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a** and 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**. Purification by silica gel column chromatography (2%−5% EtOAc/CH_2Cl_2) afforded **8aai** (63.5 mg, 78%) as a yellow solid. mp: 135−137 °C. FTIR (neat): 1612, 1559, 1521, 1493, 1413, 1267, 1192, 972, 815, 758, 682, 635, 549 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, *J* = 7.4 Hz, 1H), 8.44 (s, 1H), 8.22−8.12 (m, 4H), 7.57−7.42 (m, 5H), 7.32−7.25 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.9, 144.7, 143.2, 137.0, 135.3, 132.2, 130.6, 128.9, 128.7, 127.3, 126.2, 126.2, 110.7, 105.3. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{14}N_3^+$, 272.1182; found 272.1183.

*3-Phenyl-5-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidine (**8bai**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a** and 82.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5b**. Purification by silica gel column chromatography (2%−5% EtOAc/CH_2Cl_2) afforded **8bai** (77.9 mg, 77%) as a yellow solid. mp: 130−132 °C. FTIR (neat): 1619, 1414, 1329,1318, 1122, 1104, 1071, 1015, 810, 766, 752, 691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, *J* = 7.3 Hz, 1H), 8.46 (s, 1H), 8.24 (d, *J* = 8.2 Hz, 2H), 8.16−8.08 (m, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.32−7.23 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.1, 144.5, 143.5, 140.2, 135.6, 132.1 (q, *J* = 32.7 Hz), 131.8, 128.8, 127.6, 126.5, 126.3, 125.9 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.3 Hz), 111.3, 105.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.8. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{13}F_3N_3^+$, 340.1056; found 340.1053.

*5-(4-Methoxyphenyl)-3-phenylpyrazolo[1,5-a]pyrimidine (**8cai**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a** and 73.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5c**. Purification by silica gel column chromatography (2%−5% EtOAc/CH_2Cl_2) afforded **8cai** (66.4 mg, 73%) as a yellow solid. mp: 136−138 °C. FTIR (neat): 1604, 1563, 1412, 1251, 1180, 1023, 845, 789, 767, 694, 547 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 7.4 Hz, 1H), 8.41 (s, 1H), 8.21−8.06 (m, 4H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.31−7.17 (m, 2H), 7.02 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.7, 155.5, 144.7, 143.0, 135.1, 132.3, 129.5, 128.9, 128.7, 126.1, 126.0, 114.3, 110.2, 104.8, 55.4. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{16}N_3O^+$, 302.1288; found 302.1300.

*5-(3-Bromophenyl)-3-phenylpyrazolo[1,5-a]pyrimidine (**8dai**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a** and 70.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5d**. Purification by silica gel column chromatography (2%−5% EtOAc/CH_2Cl_2) afforded **8dai** (91.4 mg, 87%) as a yellow solid. mp: 115−117 °C. FTIR (neat): 1610, 1558, 1492, 1406, 1260, 1194, 780, 762, 686, 548, 535 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, *J* = 7.4 Hz, 1H), 8.45 (s, 1H), 8.28 (t, *J* = 1.8 Hz, 1H), 8.17−8.10 (m, 2H), 8.08 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.61 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.32−7.21 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.2, 144.5, 143.4, 139.0, 135.5, 133.4, 131.9, 130.4, 130.3, 128.8, 126.4, 126.3, 125.9, 123.2, 111.1, 105.1. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{13}BrN_3^+$, 350.0287; found 350.0294.

*5-(6-Chloropyridin-3-yl)-3-phenylpyrazolo[1,5-a]pyrimidine (**8kai**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a** and 84.9 mg (0.600 mmol, 2.00 equiv) of aldehyde **5k**. Purification by silica gel column chromatography (2%−10% EtOAc/CH_2Cl_2) afforded **8kai** (73.9 mg, 80%) as a yellow solid. mp: >240 °C. FTIR (neat): 1612, 1560, 1413, 1314, 1129, 1104, 1022, 971, 817, 768, 500, 472 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.10 (d, *J* = 2.5 Hz, 1H), 8.71 (d, *J* = 7.4 Hz, 1H), 8.46 (s, 1H), 8.43 (dd, *J* = 8.4, 2.6 Hz, 1H), 8.16−8.02 (m, 2H), 7.52−7.40 (m, 3H), 7.31−7.25 (m, 1H), 7.23 (d, *J* = 7.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.3, 152.0, 148.4, 144.4, 143.6, 137.2, 135.9, 131.62, 131.58, 128.8, 126.6, 126.2, 124.6, 111.3, 104.5. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{12}ClN_4^+$, 307.0745; found 307.0748.

*5-(1-Methyl-1H-pyrazol-4-yl)-3-phenylpyrazolo[1,5-a]pyrimidine (**8nai**).* The reaction was performed according to the general procedure employing 47.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6a** and 66.1 mg (0.600 mmol, 2.00 equiv) of aldehyde **5n**. Purification by silica gel column chromatography (10%−35% EtOAc/CH_2Cl_2) afforded **8nai** (54.3 mg, 66%) as a yellow solid. mp: 172−174 °C. FTIR (neat): 1616, 1583, 1551, 1514, 1236, 1187, 992, 887, 863, 808, 768, 690, 555, 516 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 7.3 Hz, 1H), 8.37 (s, 1H), 8.12−8.06 (m, 2H), 8.04 (d, *J* = 1.9 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.30−7.20 (m, 1H), 6.93 (d, *J* = 7.3 Hz, 1H), 3.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.0, 144.7, 143.0, 138.5, 135.1, 132.3, 130.1, 128.7, 126.1, 126.0, 122.2, 109.6, 105.4, 39.4. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{14}N_5^+$, 276.1244; found 276.1247.

*2-Methyl-3,5-diphenylpyrazolo[1,5-a]pyrimidine (**8aci**).* The reaction was performed according to the general procedure employing 52.0 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6c** and 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**. Purification by silica gel column chromatography (5%−25% EtOAc/hexanes) afforded **8aci** (70.2 mg, 82%) as a yellow solid. mp: 138−140 °C. FTIR (neat): 1609, 1559, 1493, 1422, 816, 767, 700, 689, 594 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, *J* = 7.3 Hz, 1H), 8.16−8.06 (m, 2H), 7.88−7.81 (m, 2H), 7.54−7.41 (m, 5H), 7.35−7.28 (m, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 2.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.7, 153.0, 145.9, 137.1, 134.4, 132.5, 130.3, 128.8, 128.7, 128.4, 127.2, 126.1, 109.3, 104.7, 14.5. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{16}N_3^+$, 286.1339; found 286.1343.

*2-Ethyl-3-methyl-5-phenylpyrazolo[1,5-a]pyrimidine (**8adi**).* The reaction was performed according to the general procedure employing 37.6 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6d** and 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**. Purification by silica gel column chromatography (5%−20% EtOAc/hexanes) afforded **8adi** (51.1 mg, 72%) as a yellow solid. mp: 77−79 °C. FTIR (neat): 1611, 1515, 1494, 1260, 1086, 1020, 795, 764, 742, 682, 645, 534 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, *J* = 7.3 Hz, 1H), 8.14−8.03 (m, 2H), 7.54−7.40 (m, 3H), 7.09 (d, *J* = 7.3 Hz, 1H), 2.84 (q, *J* = 7.6 Hz, 2H), 2.34 (s, 3H), 1.34 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.2, 154.3, 146.6, 137.6, 134.3, 130.0, 128.8, 127.0, 103.8, 103.0, 20.8, 13.3, 6.8. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{16}N_3^+$, 238.1339; found 238.1338.

*5-Phenylpyrazolo[1,5-a]pyrimidine (**8aei**).* The reaction was performed according to the general procedure employing 25.0 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6e** and 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, with slight modification in reaction concentration (0.100 M, 3.00 mL of dioxane). Purification by silica gel column chromatography (5%−20% EtOAc/hexanes) afforded **8aei** (17.5 mg, 30%) as a yellow solid. ^1H and ^{13}C NMR spectra matched with previously reported literature.[17] ^1H NMR (600 MHz, $CDCl_3$): δ 8.69 (d, *J* = 7.3 Hz, 1H), 8.12 (d, *J* = 2.3 Hz, 1H), 8.09−8.05 (m, 2H), 7.55−7.45 (m, 3H), 7.26 (d, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 156.2, 148.5, 145.6, 137.1, 135.1, 130.5, 129.0, 127.2, 105.5, 97.0.

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*2-(tert-Butyl)-5-phenylpyrazolo[1,5-a]pyrimidine (**8afi**).* The reaction was performed according to the general procedure employing 41.8 mg (0.300 mmol, 1.00 equiv) of aminopyrazole **6f** and 61.0 μL (0.600 mmol, 2.00 equiv) of aldehyde **5a**, with slight modification in reaction concentration (0.100 M, 3.00 mL of dioxane). Purification by silica gel column chromatography (10%−30% Et_2O/hexanes) afforded **8afi** (45.7 mg, 61%) as a tan solid. mp: 88−90 °C. FTIR (neat): 1609, 1544, 1415, 1358, 1242, 793, 765, 739, 689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 7.3 Hz, 1H), 8.09−7.97 (m, 2H), 7.54−7.42 (m, 3H), 7.15 (d, *J* = 7.3 Hz, 1H), 6.54 (s, 1H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8, 155.7, 148.9, 137.4, 134.7, 130.2, 128.9, 127.1, 104.5, 93.2, 32.8, 30.4. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{18}N_3^+$, 252.1495; found 252.1485.

General Procedure for Two-Step, One-Pot Annulations Using Ethyl Glyoxylate 5p as the Aldehyde (0.3 mmol scale). Aminopyrazole **6a** (0.300 mmol, 1.00 equiv, 47.8 mg), PivOH (1.20 mmol, 4.00 equiv, 123 mg), and 3 Å molecular sieves (∼300 mg) were added to a flame-dried 2−5 mL Biotage microwave vial (No. 351521) that was charged with a stir bar on the benchtop. The vial was capped with a Teflon-lined cap and flushed with nitrogen for ∼2 min. Under positive nitrogen pressure, the solution of ethyl glyoxylate **5p** (65.4 μL of a 50% (v/v) in toluene, 0.330 mmol, 1.10 equiv) in dioxane (0.100 M, 3.00 mL) was quickly added. The reaction mixture was then heated with a Biotage Initiator+ (No. 356007), which employs an external IR sensor and a closed reaction vessel. The resultant mixture was stirred in the microwave reactor for 30 min at 150 °C using the following settings (absorption level, low; vial type, 2−5 mL; prestirring, 0; initial power, 0; dynamic deflector optimization, ON; pressure: OFF; power, OFF; fixed hold time, ON; stir rate, 600). After cooling to rt, the cap was opened, and $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (10 mol %, 0.030 mmol, 25 mg), KOAc (0.30 mmol, 1.0 equiv, 29 mg) and sulfoxonium ylide **7a** (0.450 mmol, 1.50 equiv, 137 mg) or formyl sulfoxonium ylide **7i** (0.330 mmol, 1.10 equiv, 39.7 mg) were added. The vial was capped with a Teflon-lined cap, flushed with nitrogen for ∼2 min and then heated in the microwave reactor for 1 h at 150 °C using the above settings. After cooling to rt, the crude mixture was transferred to a separatory funnel with CH_2Cl_2 (50 mL). PivOH was removed by extracting with saturated $NaHCO_3$ (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. The product was purified by silica gel column chromatography.

*Ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)-3-phenylpyrazolo[1,5-a]pyrimidine-5-carboxylate (**8paa**).* The reaction was performed according to the general procedure employing 137 mg (0.450 mmol, 1.50 equiv) of sulfoxonium ylide **7a**. Purification by silica gel column chromatography (10%−30% EtOAc/hexanes) afforded **8paa** (111 mg, 82%) as a yellow solid. mp: 140−142 °C. FTIR (neat): 1717, 1691, 1668, 1427, 1239, 1171, 866, 765, 728, 693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 8.12−8.06 (m, 2H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.39 (s, 1H), 7.31−7.25 (m, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 4.43−4.21 (m, 2H), 3.76 (tt, *J* = 12.1, 3.4 Hz, 1H), 3.06−2.88 (m, 2H), 2.23−2.15 (m, 2H), 1.80−1.66 (m, 2H), 1.48 (s, 9H), 1.46 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.2, 154.6, 152.8, 146.5, 144.2, 142.9, 131.4, 128.8, 126.8, 126.6, 113.2, 103.7, 79.8, 62.4, 43.9, 36.7, 29.0, 28.4, 14.2. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{31}N_4O_4^+$, 451.2340; found 451.2339.

*Ethyl 3-phenylpyrazolo[1,5-a]pyrimidine-5-carboxylate (**8pai**).* The reaction was performed according to the general procedure employing 39.7 mg (0.330 mmol, 1.10 equiv) of formyl sulfoxonium ylide **7i**. Purification by silica gel column chromatography (10%−30% EtOAc/hexanes) afforded **8pai** (64.6 mg, 81%) as a yellow solid. mp: 120−122 °C. FTIR (neat): 1724, 1297, 1138, 1015, 761, 685, 602, 556 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, *J* = 7.3 Hz, 1H), 8.52 (s, 1H), 8.13−8.01 (m, 2H), 7.53 (d, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.33−7.25 (m, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.7, 146.5, 143.8, 143.7, 135.5, 131.1, 128.9, 126.9, 126.5, 113.3, 107.5, 62.5, 14.2. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{14}N_3O_2^+$, 268.1081; found 268.1078.

General Procedure for Two-Step, One-Pot Annulations Using Trimethyl Orthoformate 5q as the Aldehyde (0.3 mmol scale). Aminopyrazole **6a** (0.300 mmol, 1.00 equiv, 47.8 mg) and PivOH (1.20 mmol, 4.00 equiv, 123 mg) were added to a flame-dried 2−5 mL Biotage microwave vial (No. 351521) charged with a stir bar on the benchtop. The vial was capped with a Teflon-lined cap and flushed with nitrogen for ∼2 min. Under positive nitrogen pressure, the solution of trimethyl orthoformate **5q** (0.33 mL, 3.0 mmol, 10 equiv) in dioxane (0.100 M, 3.00 mL) was quickly added. The reaction mixture was then heated with a Biotage Initiator+ (No. 356007), which employs an external IR sensor and a closed reaction vessel. The resultant mixture was stirred in the microwave reactor for 30 min at 150 °C, using the following settings (absorption level, low; vial type, 2−5 mL; prestirring, 0; initial power, 0; dynamic deflector optimization, ON; pressure: OFF; power, OFF; fixed hold time, ON; stir rate, 600). After cooling to rt, the cap was opened, and $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (10 mol %, 0.030 mmol, 25 mg), KOAc (0.30 mmol, 1.0 equiv, 29 mg) and sulfoxonium ylide **7a** (0.450 mmol, 1.50 equiv, 137 mg) or formyl sulfoxonium ylide **7i** (0.330 mmol, 1.10 equiv, 39.7 mg) were added. The vial was capped with a Teflon-lined cap, flushed with nitrogen for ∼2 min, and then heated in the microwave reactor for 1 h at 150 °C using the above settings. After cooling to rt, the crude mixture was transferred to a separatory funnel with CH_2Cl_2 (50 mL). PivOH was removed by extracting with saturated $NaHCO_3$ (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. The product was purified by silica gel column chromatography.

*tert-Butyl 4-(5-methoxy-3-phenylpyrazolo[1,5-a]pyrimidin-7-yl)-piperidine-1-carboxylate (**8qaa**).* The reaction was performed according to the general procedure employing 137 mg (0.450 mmol, 1.50 equiv) of sulfoxonium ylide **7a**. Purification by silica gel column chromatography (10%−20% EtOAc/hexanes) afforded **8qaa** (95.4 mg, 78%) as a white solid. mp: 135−137 °C. FTIR (neat): 1684, 1629, 1545, 1426, 1392, 1229, 1167, 1120, 945, 865, 762, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 8.06−7.97 (m, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.24−7.16 (m, 1H), 6.17 (s, 1H), 4.41−4.17 (m, 2H), 4.06 (s, 3H), 3.62 (tt, *J* = 12.1, 3.4 Hz, 1H), 3.05−2.83 (m, 2H), 2.19−2.08 (m, 2H), 1.69−1.54 (m, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.2, 154.7, 153.9, 143.7, 141.8, 132.5, 128.6, 125.6, 108.4, 95.9, 79.7, 53.9, 43.7, 36.4, 29.4, 28.4. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{29}N_4O_3^+$, 409.2234; found 409.2236.

*5-Methoxy-3-phenylpyrazolo[1,5-a]pyrimidine (**8qai**).* The reaction was performed according to the general procedure employing 39.7 mg (0.330 mmol, 1.10 equiv) of formyl sulfoxonium ylide **7i**. Purification by silica gel column chromatography (10%−20% EtOAc/hexanes) afforded **8qai** (24.3 mg, 36%) as a yellow solid. mp: 84−86 °C. FTIR (neat): 1633, 1535, 1434, 1405, 1285, 1184, 1019, 946, 793, 757, 686, 512 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 8.40 (d, *J* = 7.4 Hz, 1H), 8.30 (s, 1H), 8.06−7.97 (m, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.26−7.18 (m, 1H), 6.35 (d, *J* = 7.4 Hz, 1H), 4.08 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 161.8, 143.3, 142.8, 137.0, 132.3, 128.6, 125.7, 125.6, 108.3, 100.2, 54.1. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{12}N_3O^+$, 226.0975; found 226.0973.

Procedure for Three-Component Reaction of Aminopyrazole 6a, Aldehyde 5n, and β-Keto Sulfoxonium Ylide 7a (1 mmol scale). Aminopyrazole **6a** (1.00 mmol, 1.00 equiv, 159 mg), aldehyde **5n** (2.00 mmol, 2.00 equiv, 220 mg), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol %, 0.0500 mmol, 41.7 mg), PivOH (4.00 mmol, 4.00 equiv, 409 mg), KOAc (1.00 mmol, 1.00 equiv, 98.1 mg), 3 Å molecular sieves (∼1 g), sulfoxonium ylide **7a** (1.50 mmol, 1.50 equiv, 455 mg), and dioxane (0.400 M, 2.50 mL) were added to a flame-dried 2−5 mL Biotage microwave vial (No. 351521) charged with a stir bar on the benchtop. The vial was capped with a Teflon-lined cap, flushed with nitrogen for ∼5 min, and then heated with a Biotage Initiator+ (No. 356007), which employs an external IR sensor

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and a closed reaction vessel. The resultant mixture was stirred in the microwave reactor for 1 h at 150 °C using the following settings (absorption level, low; vial type, 2−5 mL; prestirring, 0; initial power, 0; dynamic deflector optimization, ON; pressure: OFF; power, OFF; fixed hold time, ON; stir rate, 600). After cooling to rt, the crude mixture was transferred to a separatory funnel with CH_2Cl_2 (150 mL). PivOH was removed by extraction with saturated $NaHCO_3$ (300 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic extracts were washed with saturated $NaHSO_3$ (10 wt %, 300 mL) to remove the remaining aldehyde.[16] The organic layer was dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. Purification by silica gel column chromatography (5%−30% EtOAc/CH_2Cl_2) afforded **8naa** (351 mg, 77%) as a light yellow solid. ^1H and ^{13}C NMR spectra matched with **8naa** obtained from small scale (0.3 mmol).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02606.

NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(2) For representative approved drugs and clinical candidates within this heterocycle framework outside of the pyrazolopyrimidine subclass, see: zolpidem, alpidem, olprinone, zolimidine, miroprofen, necopidem, saripidem, minodronic acid, GSK812397, soraprazan, divaplon, and fasiplon. The compound structure, bioactivity, list of literature, and access to ongoing clinical trials, applications, and usage can be obtained by searching the compound name in PubChem.

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