Copper-Catalyzed Chan–Lam Cyclopropylation of Phenols and Azaheterocycles

Joseph Derosa‡†, Miriam L. O'Duill‡†, Matthew Holcomb†, Mark N. Boulous†, Ryan L. Patman§, Fen Wang§, Michelle Tran-Dubé§, Indrawan McAlpine§, Keary M. Engle†**

†Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

§ Pfizer Oncology Medicinal Chemistry, 10770 Science Center Drive, San Diego, California 92121, United States

* indrawan.mcalpine@pfizer.com; keary@scripps.edu

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Abstract. Small molecules containing cyclopropane–heteroatom linkages are commonly needed in medicinal chemistry campaigns, yet are problematic to prepare using existing methods. To address this issue, a scalable Chan–Lam cyclopropylation reaction using potassium cyclopropyl trifluoroborate has been developed. With phenol nucleophiles, the reaction effects *O*-cyclopropylation, whereas with 2-pyridones, 2-hydroxybenzimidazoles, and 2-aminopyridines the reaction brings about *N*-cyclopropylation. The transformation is catalyzed by $Cu(OAc)_2$ and 1,10-phenanthroline and employs 1 atm O_2 as the terminal oxidant. This method is operationally convenient to perform and provides a simple, strategic disconnection toward the synthesis of cyclopropyl aryl ethers and cyclopropyl amine

derivatives bearing an array of functional groups.

Introduction. Cyclopropyl groups are prevalent in drug molecules and bioactive compounds,[1] with 8 of the top 200 best-selling therapeutics from last year containing a cyclopropyl moiety.[2] As such, methods for introducing these substituents are of significant interest in both academia and the pharmaceutical industry. The goal of the present study was to expand the synthetic toolkit for appending cyclopropyl groups to phenols and aza-heterocycles.

Medicinal Chemistry Considerations. The rationale for incorporating cyclopropyl substituents in the context of medicinal chemistry merits a brief introduction. Sound decision-making in drug discovery campaigns is often guided by disciplined optimization of lipophilic efficiency (LipE), a metric that is used to capture the efficiency of a compound's potency as a function of its lipophilicity.[3] Increasing the lipophilicity of a compound or series in the absence of other changes can often result in higher metabolic clearance and thus higher dosing requirements to achieve sufficient efficacy. Therefore, from a practical standpoint, judicious use of lipophilic groups is advised and the metabolic consequences of their incorporation should be considered in parallel to any observed potency gain.

To interrogate the metabolic stability of the cyclopropyl functionality within the context of drug-like molecules, we performed a pairwise analysis of matched molecular pairs (MMPs) for a series of cyclopropyl-to-alkyl group transforms using the Pfizer database and tools developed by our computational ADME group.[5] For this analysis, we focused on mining MMPs for transforms of interest that contained clearance endpoints from Pfizer's high-throughput human liver microsome (HLM) assay. Figure 1 summarizes the transforms that were examined and the corresponding statistics; for each transformation, the percentages of cases that fall into each of three categories (decrease, no change, or increase) are represented by the color-coded pie chart, and the numerical values represent the corresponding mean change with the associated confidence interval. The data show that, on average,

cyclopropyl ring-opening transforms (*i*-Pr, **2a** and *n*-Pr, **2b**) along with ring expansion transforms (cyclobutyl, **2c** and cyclopentyl, **2d**) result in an increase in HLM clearance.[5] It is important to point out the intrinsic variability in the HLM assay, as illustrated by the relatively wide confidence intervals observed. Nevertheless, general trends are useful to analyze, and these increases in microsomal clearance can be rationalized as a result of increasing lipophilicity across the aforementioned transformations.[6] To demonstrate this point, we evaluated the transform of cyclopropyl **1** (clogP ~1.6) to ethyl **2e** (clogP ~1.7), having approximately equal lipophilic contributions, and found no meaningful change in clearance for 82% of the 1752 MMPs with HLM data. Therefore, it is not surprising that methyl-bearing MMPs **2f** (clogP Me~1.1) show a 30% increase in microsomal stability, and thus represent the only transform examined with a clear metabolic advantage to cyclopropyl substitution. Improving metabolic stability in a series is a common medicinal chemistry objective in order to improve pharmacokinetic properties.[7] In light of this analysis, new methodologies to introduce the cyclopropyl motif are warranted and believed to be of broad interest due to the privileged nature of this functionality.

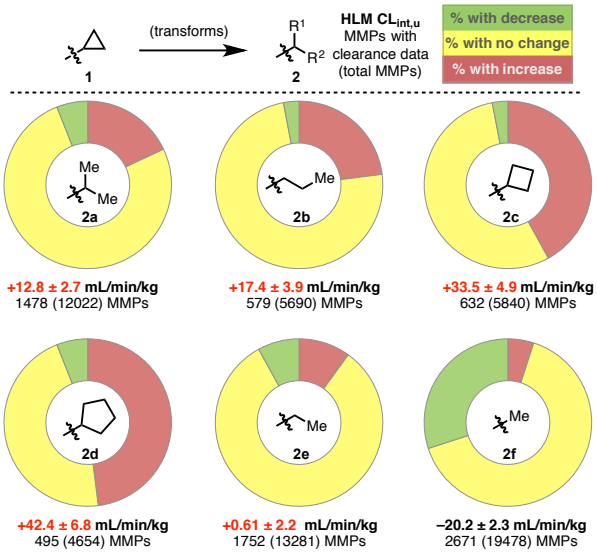


Figure 1. Transformations examined to probe trends in microsomal stability. For each transform, the number of total matched molecular pairs (MMPs) with human liver microsome (HLM) unbound intrinsic clearance ($CL_{int,u}$) is provided below the individual pie chart, along with the total number of MMPs in the Pfizer data base in parentheses. The percentages of MMPs with HLM $Cl_{int,u}$ data that fall

into each of three categories (decrease, no change, or increase) are represented by the color-coded pie chart, where increase and decrease are defined by a ±20% change. The numerical value immediately beneath each pie chart represents the mean change in HLM Cl_{int} corresponding with that transform.

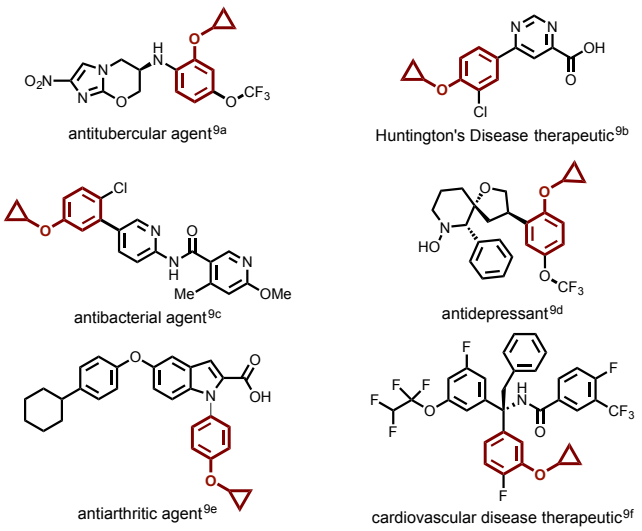
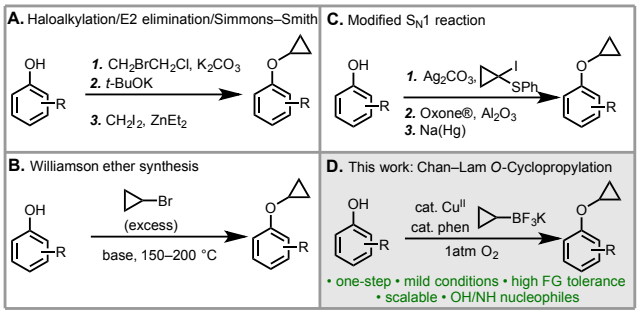


Figure 2. Representative bioactive compounds bearing cyclopropylaryl ethers.[9]

While methodology to access cyclopropyl amines has been vigorously pursued in recent years,[8] cyclopropyl ethers have received less attention. Nevertheless, small molecules containing cyclopropyl aryl ethers have a range of biological activities across several different medical indications (Figure 2).[9] Despite their utility, current methods for their synthesis remain limited and sometimes incompatible with structurally complex, heteroatom-rich substrates. This gap in synthetic methodology motivated the present study.

Results and Discussion. In terms of synthetic strategy, the most prudent retrosynthetic disconnection of a cyclopropyl aryl ether is of the O–*c*-Pr bond to give the corresponding phenol and a cyclopropyl source. The alternative disconnection of the Ar–O bond is complicated by the fact that cyclopropanol readily rearranges to form propanal.[10] Indeed, this retrosynthetic logic underlies all existing methods (Scheme 1).[11–13] In one approach, a multi-step sequence consisting of *O*-alkylation with a 1,2-dihaloethane electrophile, base-mediated E2 elimination, and Simmons–Smith

cyclopropanation[11] is used. While this route provides access to the desired compounds, it requires at least three steps, uses reagents with poor functional group compatibility, and can be low-yielding (Scheme 1a).[11b] A second approach is the reaction between a cyclopropyl halide electrophile and a phenoxide nucleophile in a Williamson ether synthesis (Scheme 1b).[12] Unfortunately, cyclopropyl halides are poor electrophiles in S_N2 reactions and can undergo competitive E2 elimination. Thus, high temperatures (typically ≥150 °C) are required to enable addition of the aryloxide into the corresponding *in situ* formed cyclopropene. Under these forcing conditions, functional group compatibility can be limited and formation of undesired allyl-containing byproducts is sometimes observed. A third strategy was reported in 1999 by Hollingworth and coworkers. This method exploits a sulfur-stabilized carbocation in a modified S_N1 reaction to form the key O–C(cyclopropyl) bond. Subsequent oxidation/reduction then excises the sulfide (Scheme 1c).[13] While inventive, this route nonetheless suffers from limited phenol substrate scope due to the difficulty of the S_N1 step with electron-poor phenols and requires subsequent oxidation/reduction steps that are incompatible with many functional groups.



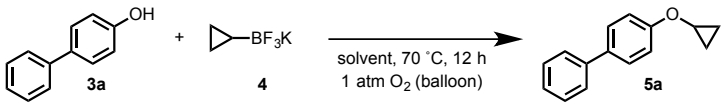
Scheme 1. Comparisons of different methods for *O*-cyclopropylation of phenols.[11–13]

The limitations of these existing methods prompted us to consider an alternative, whereby a phenol could react with a nucleophilic cyclopropyl source in an oxidative coupling reaction. We envisioned that a reaction of this type would avoid the aforementioned complications with cyclopropyl

halide electrophiles and would not require any additional concession steps. Herein, we describe the realization of this idea and report a new method for generating cyclopropyl aryl ethers using Chan–Lam-type coupling.[14] While the initial focus was on phenols, it was later found that this protocol is also efficient for *N*-cyclopropylation with select aza-heterocycles (*vide infra*).

Reaction Optimization. At the outset, we took inspiration from recent reports on Chan–Lam *N*-cyclopropylation for the preparation of cyclopropylamine derivatives.[8] Of particular importance for our investigation, Mudryk and coworkers reported that *N*-cyclopropyl 4-nitrobenzenesulfonamide (pK_a(DMSO) 13.9 for $NsNH_2$)[15] underwent Chan–Lam coupling with cyclopropyl boronic acid,[8d] lending credence to the notion that phenols (pK_a(DMSO) = 10–19) would be of an appropriate acidity and would be sufficiently nucleophilic to be competent reaction partners. This approach was further motivated by other recent reports on Chan–Lam *O*- and *N*-alkylation using alkyl boronates/boronic acids.[16–18] To the best of our knowledge, there is only one example in which a phenol has been reported to react with a cyclopropylboronic acid in the presence of a copper promoter. In a 2010 patent, Cacatian and coworkers report a single reaction proceeding in 13% yield using 1 equivalent of $Cu(OAc)_2$ and 2 equivalents of bipyridine.[19]

Table 1. Optimization of reaction conditions for *O*-cyclopropylation of phenols.[a]



Entry	$Cu^{I/II}$ (10 mol%)	Ligand	Base (2 equiv)	Solvent	Yield (%)[b]
1	$Cu(OAc)_2$	20% pyridine	---	DCE/H_2O (2:1)	24
2	$Cu(OAc)_2$	20% pyridine	---	toluene/H_2O (2:1)	35
3	$Cu(OAc)_2$	20% pyridine	---	MeCN/H_2O (2:1)	21
4	---	20% pyridine	---	toluene/H_2O (2:1)	0
5	$Cu(OAc)_2$	20% pyridine	KOAc	toluene/H_2O (2:1)	41
6	$Cu(OAc)_2$	20% pyridine	K_2CO_3	toluene/H_2O (2:1)	47
7	$Cu(OAc)_2$	---	K_2CO_3	toluene/H_2O (2:1)	0
8	$Cu(OAc)_2$	20% pyridine	K_2CO_3	toluene/H_2O (1:1)	43
9	$Cu(OAc)_2$	20% pyridine	K_2CO_3	toluene/H_2O (3:1)	36
10	$Cu(OAc)_2$	10% bipy	K_2CO_3	toluene/H_2O (2:1)	71
11[c]	$Cu(OAc)_2$	10% bipy	K_2CO_3	toluene/H_2O (2:1)	49
12	$Cu(OAc)_2$	10% phen	K_2CO_3	toluene/H_2O (2:1)	84
13	$Cu(HCO_2)_2$	10% phen	K_2CO_3	toluene/H_2O (2:1)	82
14	$Cu(OTf)_2$	10% phen	K_2CO_3	toluene/H_2O (2:1)	63
15	CuI	10% phen	K_2CO_3	toluene/H_2O (2:1)	56
16	CuBr	10% phen	K_2CO_3	toluene/H_2O (2:1)	56

phen = 1,10-phenanthroline, bipy = 2,2'-bipyridine. [a] Reaction conditions (unless otherwise specified): **3a** (0.3 mmol), **4** (0.9 mmol), solvent, 1 atm O_2 (balloon), 12 h, 70 °C. [b] ^1H NMR yield using dibromomethane as internal standard. [c] Reaction run under air instead of an O_2 balloon.

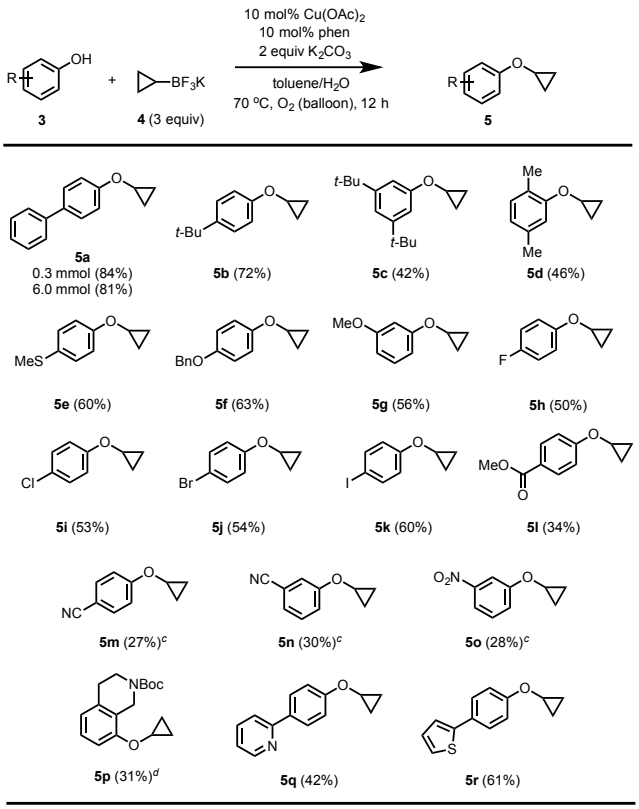
Based on these earlier precedents, we began our reaction optimization efforts using cyclopropyl boronic acid as the coupling partner in the presence of catalytic quantities of copper(II) salts. While we did observe product formation under these conditions, we soon turned to the more stable potassium trifluoroborate salt due to inconsistent results with cyclopropyl boronic acid, which we believe stems from its decomposition during reaction setup (evidenced by a visible yellowing of the typically white solid).[20] To our delight, the use of potassium cyclopropyl trifluoroborate nearly doubled the yield and improved reproducibility. Using 1 atm O_2 as the terminal oxidant, we were pleased to find that the reaction led to consistent product formation with only 10% $Cu(OAc)_2$ (Table 1). Interestingly, the use of bidentate ligands dramatically improved the efficiency of the reaction, with 1,10-phenanthroline ultimately providing the highest yield (entries 10 and 12). The optimal solvent mixture was found to be 3:1 toluene:H_2O. We believe that water is necessary for solubilizing the reaction components and promoting transmetalation by facilitating formation of the mixed boronate species *via* hydrolysis.[21] Various bases were screened (entries 5–6), and K_2CO_3 proved to be optimal. It was found that the

reaction vessel must be purged with an O_2 balloon and left under an atmosphere of O_2 for the duration of the reaction to achieve optimal yields.[22] With 95% N_2/ 5% O_2 gas mixtures, the reaction only delivered trace product (<5%) after 3 hours. Other oxidants, such as ditertbutylperoxide, did not give the desired product in appreciable yield (<5%). Simply running the reaction open to air or purging the reaction vessel with O_2 and sealing it resulted in reduced yields (entry 11). The reaction proceeded with good to high yields over a large variety of copper(II) species. Notably, copper(II) formate ($Cu(HCO_2)_2$), a copper(II) species that is seldom used in Chan–Lam coupling was found to be nearly as effective as the optimal catalyst, $Cu(OAc)_2$. Copper(I) salts also provided the desired product in moderate yield (entries 15 and 16). Ultimately, $Cu(OAc)_2$ was used for subsequent studies because of its efficiency in the reaction and its widespread availability.[23]

Substrate Scope. Having optimized the reaction conditions, we next examined the scope of phenol nucleophiles (Table 2). Phenols with diverse functional groups, differing electronic properties, and varied substitution patterns were tested. In most cases, the desired product was obtained in moderate to high yield (**5a–r**). Phenols containing one or more electron-donating substituents at the *ortho-*, *meta-*, or *para-* position on the aromatic ring were generally high-yielding, with the reaction tolerating ethers, thioethers, and alkyl groups (**5a–5g**). Substitution at the *ortho*-position led to diminished yields, likely due to steric hindrance (**5d**). Furthermore, the reaction proceeds smoothly in the presence of halide substituents (**5h–k**), which presents the opportunity to diversify the products *via* subsequent cross-coupling. The introduction of strong electron-withdrawing groups at either the *meta-* or *para*-positions led to lower yields, requiring higher catalyst loading (**5l–o**). Moreover, in these cases, competitive formation of the undesired *O*-allylated byproduct was observed. We postulate that this is due to the attenuated nucleophilicity of the corresponding electron-poor phenoxides, which could potentially reduce the affinity of the substrate for the Cu(II) center and/or raise the activation energy for the C–O reductive elimination step. Although the yields are generally lower for electron-poor phenols, it is important to note that the reaction is nevertheless compatible with a wide variety of functional groups

that one might encounter in medicinal chemistry, such as esters, nitriles, halogens, and nitro groups, providing preparatively useful quantities of the product in all of these cases. Notably, methyl ester does not hydrolyze under the reaction conditions and gives the desired cyclopropylated product (**5l**). We were pleased to observe that the reaction proceeded to a modest extent in the presence of various heterocycles (**5p–r**), including those that could potentially bind to copper.

Table 2. Substrate scope of phenol *O*-cyclopropylation.[a]



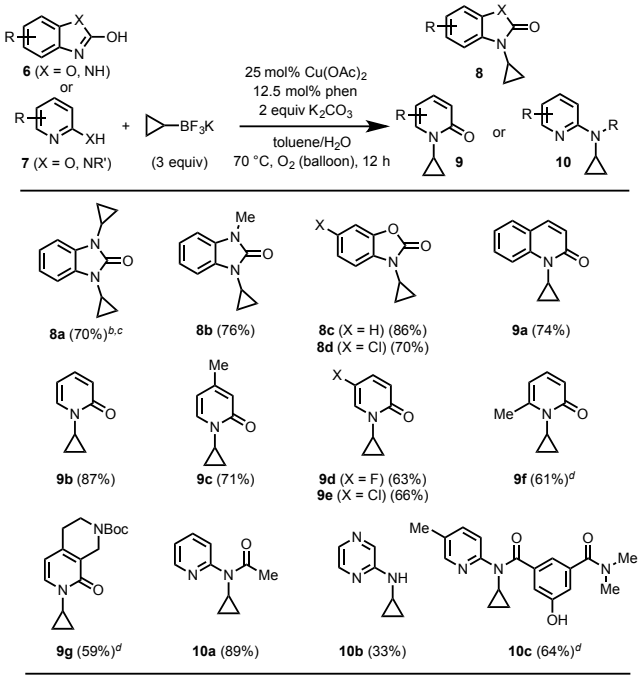
[a] All reactions were run on 0.3 mmol scale unless noted otherwise. [b] Percentages correspond to isolated yields. [c] 25 mol% $Cu(OAc)_2$, 12.5 mol% phen. [d] 25 mol% $Cu(OAc)_2$, 25 mol% phen.

We also established that the reaction could be performed on larger scale. In particular, 6 mmol of our standard substrate, *p*-phenyl phenol (**3a**), yielded 81% (>1 gram) of the desired cyclopropylated product **5a**.

These reaction conditions are not *generally* effective in promoting *N*-cyclopropylation of nitrogen nucleophiles; for example, unprotected, *N*-Boc, and *N*-Ac anilines were unreactive under these

conditions. Nevertheless, extensive screening of potential reaction partners revealed three classes of aza-heterocycles, 2-pyridones,[24] 2-aminopyridines,[25] and 2-hydroxybenzimidazoles, are reactive substrates using this method (Table 3). Interestingly, subjecting simple 2-hydroxybenzimidazole to the reaction conditions resulted in bis-*N*,*N*'-cyclopropylation in high yield (**8a**). Although 2-hydroxpyridine itself reacted smoothly to form product **9b**, other derivatives were cyclopropylated in lower yields (**9a–g**). 2-Aminopyridine derivatives were also reactive; in this case, the exo-cyclic nitrogen proved to be the more reactive position (**10a–c**). In compound **10c** the amide is preferentially functionalized over the free phenol, likely due to the two electron-withdrawing carbonyl substituents, which are expected to attenuate reactivity.

Table 3. Substrate scope of azaheterocycle *N*-cyclopropylation.[a]



[a] All reactions were run on a 0.3–0.6 mmol scale. Percentages correspond to isolated yields. [b] 13% of the mono-cyclopropylated product (**8a'**) was also isolated. [c] With 10% $Cu(OAc)_2$ and 10% phen under otherwise identical conditions: 49% **8a** (bis), 15% **8a'** (mono). The connectivity of **8a'** was confirmed by single-crystal X-ray diffraction (see SI). [d] 25 mol% $Cu(OAc)_2$, 25 mol% phen.

Conclusion. In summary, we have developed a Chan–Lam protocol for *O*-cyclopropylation of phenols and *N*-cyclopropylation of select azaheterocycles. The reaction uses a simple copper(II)

precatalyst with 1 atm O_2 as the terminal oxidant and allows for a range of structurally and functionally diverse nucleophiles to be smoothly coupled with potassium cyclopropyl trifluoroborates in good to high yields. A broad range of functional groups, including halides, ethers, esters, heterocycles, and nitro groups were tolerated. Compared to existing synthetic methods, this approach has several advantages. It is operationally convenient to perform, uses commercially available reagents, employs an inexpensive copper(II) catalyst, has high levels of functional group tolerance, and gives minimal byproduct formation in most cases. We envision that this reaction will find immediate use in medicinal chemistry laboratories as a tool for late-stage installation of cyclopropyl groups. Additionally, in the long term, it could potentially be adapted for use on larger scale in early- or late-stage development.

Experimental Section.

General Information. Unless otherwise noted, all materials were used as received from commercial sources without further purification. Consistently high yields were obtained with potassium cyclopropyltrifluoroborate purchased from Boron Molecular. Batches from other suppliers sometimes afforded lower yields; we therefore recommend calibrating the reaction using the 4-phenylphenol substrate and purifying the trifluoroborate salt *via* soxhlet extraction if yields are lower than expected. ^{1}H and ^{13}C spectra were recorded on Bruker DRX-500 and AV-600. Spectra were internally referenced to $SiMe_4$ or solvent signals. The following abbreviations (or combinations thereof) were used to explain multiplicities: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. High-resolution mass spectra (HRMS) were recorded on an Agilent ESI-TOF (LC/MSD TOF); compounds that could not be ionized under these conditions were measured on an Agilent 5973 Inert GC-MS mass spectrometer. Compounds with no mass spec data reported in this manuscript could not be ionized on either of these machines. Of the compounds that could not be ionized, five representative examples were further analyzed by elemental analysis. Melting points were measured on a MEL-TEMP II (Laboratory Devices, USA) apparatus and are uncorrected

General Procedure for *O*- and *N*-Cyclopropylation of Phenols and Azaheterocycles: To a 5-mL

scintillation vial equipped with a Teflon-coated magnetic stir bar were added the phenol substrate (0.3 mmol), cyclopropyl potassium trifluoroborate (133.2 mg, 0.9 mmol), $Cu(OAc)_2$, 1,10-phenanthroline, and K_2CO_3 (83.0 mg, 0.6 mmol). The vial was charged with toluene (0.5 mL) and water (0.15 mL) and sealed with a septum cap. *Caution! Because the reaction involves heating an organic solvent under O_2, a blast shield should be used at all times, particularly in large-scale experiments. After the indicated reaction time, the reaction vessel should be allowed to cool to room temperature behind the blast shield prior to workup.* The septum was pierced with a 21G needle connected to an O_2 balloon. The septum cap was partially unscrewed to purge the vial for 5 seconds and then resealed by tightening the cap. The reaction was stirred under O_2 (balloon) at 70 °C for 12 h, after which it was quenched with sat. NH_4Cl (aq.) and extracted with EtOAc. The combined organics were dried over $MgSO_4$, filtered and concentrated in vacuo. ^1H NMR yields were determined by integration of the cyclopropyl product peak relative to 1.0 equiv dibromomethane as internal standard. Crude products were then purified by silica flash column chromatography. The optimal catalyst/ligand loading was found to vary depending on the substrate employed:

- General Procedure A (typical phenol substrates):

  $Cu(OAc)_2$ (5.4 mg, 10 mol %), 1,10-phenanthroline (5.4 mg, 10 mol %)

- General Procedure B (electron-poor phenols and azaheterocycles):

  $Cu(OAc)_2$ (13.6 mg, 25 mol%), 1,10-phenanthroline (6.8 mg, 12.5 mol%)

- General Procedure C (Pfizer examples, more valuable substrates)

  $Cu(OAc)_2$ (13.6 mg, 25 mol%), 1,10-phenanthroline (13.5 mg, 25 mol%)

Characterization of New Compounds:

Data for *O*-cyclopropyl aryl ether products ***5*a–5r** and *N*-cyclopropylated azaheretocycle products **8a–8d**, **9a–9g**, **10a–10c** as well as starting material **S4** are included below. Original NMR spectra can be found in the supporting information. Analytical data for compounds **S1–S3** have been reported

elsewhere.

4-Cyclopropoxy-1,1'-biphenyl (5a): The title compound was prepared from 4-phenylphenol (54 mg, 0.3 mmol) according to General Procedure A. Purification by silica gel chromatography with 10:1 hexanes:EtOAc as the eluent gave the product as a white solid (52.9 mg, 84% yield). **mp** = 109–110 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65–7.49 (m, 4H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.33–7.28 (m, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 3.81–3.75 (m, 1H), 0.81 (d, *J* = 4.5 Hz, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 128.9, 128.2, 126.9, 115.4, 51.0, 6.4. **EA** calc'd for $C_{15}H_{14}O$: C, 85.68%; H, 6.71%, found: C, 85.31%; H, 6.81%.

1-(*tert*-Butyl)-4-cyclopropoxybenzene (5b): The title compound was prepared from 4-(*tert*-butyl)phenol (45 mg, 0.3 mmol) according to general procedure A. Purification by silica gel chromatography with 10:1 hexanes:EtOAc as the eluent gave the product as a yellow oil (41.0 mg, 72% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.71 (dq, *J* = 5.9, 4.4 Hz, 1H), 1.30 (s, 9H), 0.76 (d, *J* = 4.1 Hz, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.0, 144.0, 126.5, 114.8, 100.0, 51.1, 34.5, 32.0, 6.6; **GC/MS** (EI) *m/z* calcd for $C_{13}H_{18}O$ $[M]^+$ 190.1358, found 190.

1,3-Di-*tert*-butyl-5-cyclopropoxybenzene (5c): The title compound was prepared from 3,5-di-*tert*-butylphenol (61.8 mg, 0.3 mmol) according to General Procedure A. Purification by silica gel chromatography with 10:1 hexanes:EtOAc as the eluent gave the product as a colorless oil (30.9 mg, 42% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.04 (t, *J* = 1.7 Hz, 1H), 6.92 (d, *J* = 1.6 Hz, 2H), 3.79–3.60 (m, 1H), 1.32 (s, 18H), 0.77 (d, *J* = 6.4, 3.6, 1.6 Hz, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 158.6, 152.2, 115.3, 109.4, 50.6, 35.1, 31.6, 6.3; **GC/MS** (EI) *m/z* calcd for $C_{17}H_{26}O$ $[M]^+$ 246.1984, found 246.

2-Cyclopropoxy-1,4-dimethylbenzene (5d): The title compound was prepared from 2,5-

dimethylphenol (36.6 mg, 0.3 mmol) according to General Procedure A. Purification by silica gel chromatography with 10:1 hexanes:EtOAc as the eluent gave the product as a yellow oil (22.3 mg, 46% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.03–6.93 (m, 2H), 6.69 (dt, *J* = 7.4, 1.2 Hz, 1H), 3.79–3.64 (m, 1H), 2.35 (s, 3H), 2.13 (s, 3H), 0.88–0.64 (m, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.3, 136.8, 130.7, 123.7, 121.4, 113.4, 50.9, 21.9, 16.1, 6.7.

(**4-Cyclopropoxyphenyl)(methyl)sulfane (5e):** The title compound was prepared from 4-(methylthio)phenol (42 mg, 0.3 mmol) according to General Procedure A. Purification by silica gel chromatography with 10:1 hexanes:EtOAc as the eluent gave the product as a yellow solid (32.4 mg, 60% yield). **mp** = 52–55 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.75–3.67 (m, 1H), 2.44 (s, 3H), 0.76 (d, *J* = 3.0 Hz, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.9, 130.4, 129.5, 116.1, 51.3, 18.4, 6.6. **EA** calc'd for $C_{10}H_{12}OS$: C, 66.63%; H, 6.71%, found: C, 66.98%; H, 7.11%.

1-(Benzyloxy)-4-cyclopropoxybenzene (5f): The title compound was prepared from 4-(benzyloxy)phenol (60 mg, 0.3 mmol) according to General Procedure A. Purification by silica gel chromatography with 10:1 hexanes:EtOAc as the eluent gave the product as an off-white solid (45.0 mg, 63% yield). **mp** = 77–79 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 9.2 Hz, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 5.00 (s, 2H), 3.66 (dt, *J* = 5.5, 2.4 Hz, 1H), 0.73 (d, *J* = 3.2 Hz, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 153.6, 153.6, 137.7, 129.0, 128.3, 127.9, 116.1, 116.1, 116.1, 100.0, 71.1, 51.5, 6.6. **EA** calc'd for $C_{16}H_{16}O_2$: C, 79.97%; H, 6.71%, found: C, 79.76%; H, 6.34%.

1-Cyclopropoxy-3-methoxybenzene (5g): The title compound was prepared from 3-methoxyphenol (37.2 mg, 0.3 mmol) according to General Procedure A. Purification by silica gel chromatography with 10:1 hexanes:EtOAc as the eluent gave the product as a colorless oil (27.5 mg, 56% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.18 (t, *J* = 8.2 Hz, 1H), 6.67 (ddd, *J* = 8.1, 2.3, 0.8 Hz, 1H), 6.62 (t, *J* = 2.4 Hz, 1H), 6.53 (ddd, *J* = 8.2, 2.4, 0.8 Hz, 1H), 3.79 (d, *J* = 0.5 Hz, 3H), 3.75–3.69 (m, 1H), 0.77 (d, *J* = 4.5 Hz, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 130.2, 107.8, 106.8, 101.8, 55.7, 51.2, 6.6; **GC/MS** (EI) *m/z* calcd for $C_{10}H_{12}O_2$ $[M]^+$ 164.0837, found 164.

1-Cyclopropoxy-4-fluorobenzene (5h): The title compound was prepared from 4-fluorophenol (33.6 mg, 0.3 mmol) according to General Procedure A. Purification by silica gel chromatography with 10:1 hexanes:EtOAc as the eluent gave the product as a yellow oil (22.6 mg, 50% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.08–6.87 (m, 4H), 3.80–3.56 (m, 1H), 0.84–0.67 (m, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 116.2, 116.1, 116.0, 51.6, 30.1, 6.6.

1-Chloro-4-cyclopropoxybenzene (5i): The title compound was prepared from 4-chlorophenol (38.4 mg, 0.3 mmol) according to General Procedure A. Purification by silica gel chromatography with 10:1 hexanes:EtOAc as the eluent gave the product as an orange oil (26.7 mg, 53% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 10.7, 5.9 Hz, 2H), 7.06 (t, *J* = 8.3 Hz, 2H), 3.79 (tt, *J* = 5.9, 2.9 Hz, 1H), 0.85 (d, *J* = 5.3 Hz, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 129.6, 127.3, 126.2, 116.6, 51.5, 6.6.

1-Bromo-4-cyclopropoxybenzene (5j): The title compound was prepared from 4-bromophenol (51.9 mg, 0.3 mmol) according to General Procedure A. Purification by silica gel chromatography with 10:1 hexanes:EtOAc as the eluent gave the product as a yellow oil (34.5 mg, 54% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.1 Hz, 2H), 6.92 (d, *J* = 7.1 Hz, 2H), 3.70 (dd, *J* = 6.0, 3.4 Hz, 1H), 0.77 (ddt, *J* = 5.4, 3.4, 1.9 Hz, 4H), **^{13}C NMR** (150 MHz, $CDCl_3$) δ 132.6, 117.2, 113.6, 51.4, 30.1, 6.6;

GC/MS (EI) *m/z* calcd for C_9H_9OBr $[M]^+$ 211.9837, found 212.

1-Iodo-4-cyclopropoxybenzene (5k): The title compound was prepared from 4-iodophenol (66.0 mg, 0.3 mmol) according to General Procedure A. Purification by silica gel chromatography with 10:1 hexanes:EtOAc as the eluent gave the product as an orange solid (46.6 mg, 60% yield). **mp** = 49–50 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69–7.56 (d, 2H), 6.99–6.81 (d, 2H), 3.78 (m, *J* = 6.1, 2.8 Hz, 1H), 0.85 (m, *J* = 7.5, 2.8 Hz, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.0, 138.3, 117.6, 83.2, 51.1, 6.3; **GC/MS** (EI) *m/z* calcd for C_9H_9OI $[M]^+$ 259.9698, found 260. **EA** calc'd for C_9H_9OI: C, 41.56%; H, 3.49%, found: C, 41.37%; H, 3.14%.

Methyl 4-cyclopropoxybenzoate (5l): The title compound was prepared from methyl 4-hydroxybenzoate (45.6 mg, 0.3 mmol) according to General Procedure A. Purification by silica gel chromatography with 10:1 hexanes:EtOAc as the eluent gave the product as a yellow oil (19.6 mg, 34% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.9 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 2H), 3.78 (m, *J* = 6.1, 3.2 Hz, 1H), 0.97–0.65 (d, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 167.3, 163.2, 131.9, 123.3, 115.1, 52.3, 51.6, 6.7.

4-(Cyclopropyloxy)benzonitrile (5m): The title compound was prepared from 4-cyanophenol (35.6 mg, 0.3 mmol) according to General Procedure B. The standard reaction conditions afforded an inseparable mixture of the desired *O*-cyclopropylated product, as well as *O*-allylated product **S1**. After aqueous workup, the mixture was redissolved in H_2O (0.8 mL) and acetone (6.2 mL), and treated with OsO_4 (2.5 wt% in *i*-PrOH, 0.15 mL, 0.015 mmol, 5 mol%) and NMO (53 mg, 0.45 mmol, 1.5 equiv). The reaction was stirred at rt, after which it was quenched with aqueous sodium bisulfite, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica flash column

chromatography (eluent: 2% EtOAc/Hex to 5% EtOAc/Hex) afforded the title compound as a colorless oil (13.0 mg, 27% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60–7.56 (m, 2H), 7.12–7.07 (m, 2H), 3.78 (tt, *J* = 6.0, 3.0 Hz, 1H), 0.85–0.81 (m, 2H), 0.82–0.78 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 162.6, 134.0, 119.4, 116.0, 104.4, 51.5, 6.4.

4-(Allyloxy)benzonitrile (S1):[26] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63–7.55 (m, 2H), 6.99–6.94 (m, 2H), 6.03 (ddd, *J* = 22.5, 10.6, 5.3 Hz, 1H), 5.48–5.38 (m, 1H), 5.36–5.28 (m, 1H), 4.59 (dt, *J* = 5.3, 1.6 Hz, 2H).

3-(Cyclopropyloxy)benzonitrile (5n): The title compound was prepared from 3-cyanophenol (35.6 mg, 0.3 mmol) according to General Procedure B. The standard reaction conditions afforded an inseparable mixture of the desired *O*-cyclopropylated product, as well as *O*-allylated product **S2**. After aqueous workup, the mixture was redissolved in H_2O (0.8 mL) and acetone (6.2 mL), and treated with OsO_4 (2.5 wt% in *i*-PrOH, 0.15 mL, 0.015 mmol, 5 mol%) and NMO (53 mg, 0.45 mmol, 1.5 equiv). The reaction was stirred at rt, after which it was quenched with aqueous sodium bisulfite, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica flash column chromatography (eluent: 2% EtOAc/Hex to 5% EtOAc/Hex) afforded the title compound as a colorless oil (14.1 mg, 30% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (t, *J* = 8.0 Hz, 1H), 7.34–7.32 (m, 1H), 7.27–7.23 (m, 2H), 3.75 (tt, *J* = 6.0, 3.0 Hz, 1H), 0.85–0.81 (m, 2H), 0.81–0.78 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.3, 130.4, 124.9, 120.5, 118.9, 118.1, 113.2, 51.4, 6.4.

2-(Allyloxy)benzonitrile (S2):[27] **^{1}H NMR** (500 MHz, $CDCl_3$) 7.19–7.14 (m, 3H), 6.88 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 2H), 5.99–6.06 (m, 1H), 5.42 (d, *J* = 17.7, 1H), 5.33 (d, *J* = 10.7 Hz, 1H), 4.56 (d, *J* = 5.3 Hz, 2H).

1-(Cyclopropyloxy)-3-nitrobenzene (5o): The title compound was prepared from 3-nitrophenol (41.7 mg, 0.3 mmol) according to General Procedure B. The standard reaction conditions afforded an inseparable mixture of the desired *O*-cyclopropylated product, as well as *O*-allylated product **S3**. After aqueous workup, the mixture was redissolved in H_2O (0.8 mL) and acetone (6.2 mL), and treated with OsO_4 (2.5 wt% in *i*-PrOH, 0.15 mL, 0.015 mmol, 5 mol%) and NMO (53 mg, 0.45 mmol, 1.5 equiv). The reaction was stirred at rt, after which it was quenched with aqueous sodium bisulfite, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica flash column chromatography (eluent: 2% EtOAc/Hex to 10% EtOAc/Hex) afforded the title compound as a yellow oil (14.8 mg, 28% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (t, *J* = 2.3 Hz, 1H), 7.86–7.81 (m, 1H), 7.42 (t, *J* = 8.2 Hz, 1H), 7.34–7.30 (m, 1H), 3.82 (tt, *J* = 6.2, 2.9 Hz, 1H), 0.89–0.84 (m, 2H), 0.84–0.79 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 160.0, 149.5, 130.2, 122.3, 116.4, 109.9, 51.9, 6.7.

1-(Allyloxy)-3-nitrobenzene (S3):[28] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25–7.80 (m, 4H), 6.11–5.99 (m, 1H), 5.45 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.37–5.32 (m, 1H), 4.63 (dt, *J* = 5.3, 1.5 Hz, 2H).

***tert*-butyl-8-cyclopropoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (5p):** The title compound was prepared from *tert*-butyl-8-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (74.8 mg, 0.300 mmol) according to General Procedure C. Purification was performed using flash column chromatography (12g SiO_2, Isco, 100% Hept. to 10% EtOAc) to afford the title compound as a colorless oil (27.0 mg, 31% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.19–7.12 (m, 1 H) 7.08 (d, *J* = 8.07 Hz, 1 H) 6.77 (br d, *J* = 7.34 Hz, 1 H) 4.45 (br s, 2 H) 3.80–3.72 (m, 1H) 3.64 (br t, *J* = 5.69 Hz, 2 H) 2.82 (br t, *J* = 5.50 Hz, 2 H) 1.52 (s, 9 H) 0.78 (br d, *J* = 3.48 Hz, 4 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 155.48 (br s, 1C), 154.99 (br s, 1C), 135.85 (br s, 1C), 126.57, 122.49 (br s, 1C), 121.08 (br s, 1C), 109.62, 79.55, 50.76, 41.53 (br s, 1C), 40.97–40.39 (m, 1C), 29.00 (br s, 1C), 28.49 (s, 3C), 6.20 (br s, 2C); **HRMS** (ESI-TOF) *m/z* calcd for $C_{17}H_{23}NO_3^+$ $[M+Na]^+$ = 312.1570, found 312.1551.

2-(4-cyclopropoxyphenyl)pyridine (5q): The title compound was prepared from 4-(pyridin-2-yl)phenol (51.3 mg, 0.3 mmol) according to General Procedure A. Purification by silica gel chromatography with 10:1 hexanes:EtOAc as the eluent gave the product as an off-white solid (26.6 mg, 42% yield). **mp** = 82–84 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.8 Hz, 1H), 7.97–7.93 (m, 2H), 7.71 (dd, *J* = 23.5, 7.8 Hz, 2H), 7.22–7.11 (m, 3H), 3.80 (t, *J* = 4.6 Hz, 1H), 0.87–0.74 (m, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 160.1, 157.1, 149.3, 137.1, 132.1, 128.3, 121.6, 120.1, 115.4, 51.1, 6.4; **HRMS** (ESI-TOF) *m/z* calcd for $C_{14}H_{14}NO$ $[M+H]^+$ 212.1070, found 212.1064.

2-(4-Cyclopropoxyphenyl)thiophene (5r): The title compound was prepared from 4-(thiophen-2-yl)phenol (52 mg, 0.3 mmol) according to General Procedure A. Purification by silica gel chromatography with 10:1 hexanes:EtOAc as the eluent gave the product as an off-white solid (39.5 mg, 61% yield). **mp** = 88–89 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71–7.53 (m, 2H), 7.32–7.24 (m, 2H), 7.27–7.03 (m, 3H), 3.94–3.76 (m, 1H), 0.88 (d, *J* = 5.1 Hz, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.0, 144.8, 128.3, 128.0, 127.5, 124.3, 122.5, 115.8, 51.3, 6.7; **GC/MS** (EI) *m/z* calcd for $C_{13}H_{12}OS$ $[M]^+$ 216.0609, found 216. **EA** calc'd for $C_{13}H_{12}OS$: C, 72.19%; H, 5.59%, found: C, 72.31%; H, 6.00%.

1,3-Dicyclopropyl-1,3-dihydro-2*H*-benzimidazol-2-one (8a): The title compound was prepared from 2-hydroxybenzimidazole (40.2 mg, 0.3 mmol) according to General Procedure B. Purification by silica flash column chromatography (eluent: 5% EtOAc/Hexane to 20% EtOAc/Hexane) afforded the title compound as a white solid (31.8 mg, 49% yield), along with separable mono-cyclopropylated product **8a'**. **mp** = 92–94 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21–7.13 (m, 2H), 7.12–7.04 (m, 2H), 2.83 (tt, *J* = 7.0, 3.7 Hz, 2H), 1.11–1.05 (m, 4H), 0.99 (ddd, *J* = 8.0, 5.4, 3.8 Hz, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 155.0, 130.1, 121.2, 108.4, 22.5, 6.0; **HRMS** (ESI-TOF) *m/z* calcd for $C_{13}H_{15}N_2O$ $[M+H]^+$ 215.1184,

found 215.1180.

1-Cyclopropyl-1*H*-benzimidazol-2-ol (8a'): The title compound was prepared according to the procedure described above for **8a** and was isolated as a white solid (7.7 mg, 15% yield). **mp** = 184–188 °C; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 10.03 (brs, 1H, O*H*), 7.23–7.19 (m, 1H), 7.14–7.04 (m, 3H), 2.91 (tt, *J* = 7.0, 3.6 Hz, 1H), 1.18–1.09 (m, 2H), 1.08–1.02 (m, 2H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 156.1, 131.5, 127.6, 121.7, 121.4, 109.5, 108.9, 22.4, 6.2; **HRMS** (ESI-TOF) *m/z* calcd for $C_{10}H_{11}N_2O$ $[M+H]^+$ 175.0871, found 175.0876; **X-ray** (single-crystal): Colorless block crystals of X-ray diffraction quality were obtained by slow evaporation of a solution of **8a'** in $CDCl_3$ (CCDC 1584673).[29]

1-Cyclopropyl-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (8b): The title compound was prepared from 1-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (44.5 mg, 0.3 mmol) according to General Procedure B. Purification by silica flash column chromatography (eluent: 10% EtOAc/Hex) afforded the title compound as a white solid (43.0 mg, 76% yield). **mp** = 84–86 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20–7.15 (m, 1H), 7.10–7.05 (m, 2H), 6.95–6.90 (m, 1H), 3.36 (s, 3H), 2.86 (tt, *J* = 7.1, 3.7 Hz, 1H), 1.11–1.06 (m, 2H), 1.02–0.97 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 154.8, 130.3, 129.8, 121.3, 121.1, 108.5, 107.2, 27.0, 22.6, 6.1; **HRMS** (ESI-TOF) *m/z* calcd for $C_{11}H_{13}N_2O$ $[M+H]^+$ 189.1028, found 189.1022.

3-Cyclopropylbenzo[*d*]oxazol-2(3*H*)-one (8c): The title compound was prepared from 2-hydroxybenzoxazolinone (40.5 mg, 0.3 mmol) according to General Procedure B. Purification by silica flash column chromatography (eluent: 5 % EtOAc/Hex to 10% EtOAc/Hex) afforded the title compound as a white solid (45.3 mg, 86% yield). **mp** = 62–63 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21–7.13 (m, 3H), 7.12–7.08 (m, 1H), 2.92 (tt, *J* = 7.0, 3.6 Hz, 1H), 1.15–1.08 (m, 2H), 1.08–1.02 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 154.4, 142.3, 132.0, 123.8, 122.5, 109.9, 109.2, 23.3, 6.0; **HRMS** (ESI-

TOF) *m/z* calcd for $C_9H_9N_2O_2$ $[M+H]^+$ 177.0659, found 177.0659.

6-Chloro-3-cyclopropyl-1,3-benzoxazol-2(3*H*)-one (8d): The title compound was prepared from 6-chlorobenzoxazol-2(3*H*)-one (50.9 mg, 0.3 mmol) according to General Procedure B. Purification by silica flash column chromatography (eluent: 10% EtOAc/Hex to 20% EtOAc/Hex) afforded the title compound as an orange solid (44.3 mg, 70% yield). **mp** 110–112 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.18–7.12 (m, 2H), 7.08–7.03 (m, 1H), 2.90 (tt, *J* = 7.0, 3.6 Hz, 1H), 1.15–1.07 (m, 2H), 1.05–0.98 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.0, 142.6, 130.8, 128.1, 123.9, 110.8, 109.7, 23.4, 6.0; **GC/MS** (EI) *m/z* calcd for $C_{10}H_8ClNO_2$ $[M]^+$ 209.0244, found 209.

1-Cyclopropylquinolin-2(1*H*)-one (9a): The title compound was prepared from 2-hydroxyquinoline (43.5 mg, 0.3 mmol) according to General Procedure B. Purification by silica flash column chromatography (eluent: 30% EtOAc/Hex to 50% EtOAc/Hex) afforded the title compound as a yellow oil (41.0 mg, 74% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 9.5 Hz, 1H), 7.55–7.45 (m, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 6.59 (d, *J* = 9.4 Hz, 1H), 2.93 (tt, *J* = 7.7, 4.1 Hz, 1H), 1.39–1.30 (m, 2H), 0.93–0.85 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.8, 141.1, 139.1, 130.0, 128.6, 122.5, 122.2, 121.0, 115.6, 26.2, 10.5; **HRMS** (ESI-TOF) *m/z* calcd for $C_{12}H_{12}NO$ $[M+H]^+$ 186.0913, found 186.0914.

1-Cyclopropylpyridin-2-one (9b): The title compound was prepared from 2-hydroxypyridine (47.6 mg, 0.5 mmol) according to General Procedure B. Purification by silica flash column chromatography (eluent: 2% MeOH/DCM to 5% MeOH/DCM), followed by preparative TLC (eluent: 5% MeOH/DCM) afforded the title compound as a yellow oil (24.8 mg, 37% yield). The connectivity (*i.e.*, *N*- versus *O*-cyclopropylation) was confirmed by NOESY analysis and by the diagnostic carbonyl signal at 164.3 ppm in the ^{13}C NMR spectrum. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.63–8.57 (m, 2H), 7.87–7.83 (m, 1H),

7.44 (tt, J = 6.8, 1.2 Hz, 1H), 4.64 (tt, J = 7.7, 3.6 Hz, 1H), 2.47–2.42 (m, 2H), 2.19–2.15 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.3, 139.0, 136.9, 120.9, 105.7, 32.3, 6.8; **HRMS** (ESI-TOF) *m/z* calcd for $C_8H_{10}NO$ $[M+H]^+$ 136.0757, found 136.0757.

1-Cyclopropyl-4-methylpyridin-2-one (9c): The title compound was prepared from 2-hydroxy-4-methylpyridine (32.7 mg, 0.3 mmol) according to General Procedure B. Purification by silica flash column chromatography (eluent: DCM to 2% MeOH/DCM) afforded the title compound as a pale-yellow oil (31.9 mg, 71% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.11 (d, J = 7.1 Hz, 1H), 6.29 (s, 1H), 5.92 (dd, J = 7.1, 1.9 Hz, 1H), 3.24 (tt, J = 7.6, 4.2 Hz, 1H), 2.10 (s, 3H), 1.09–1.01 (m, 2H), 0.82–0.75 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.2, 150.6, 135.8, 119.2, 108.2, 31.8, 21.2, 6.7; **HRMS** (ESI-TOF) *m/z* calcd for $C_9H_{12}NO$ $[M+H]^+$ 150.0913, found 150.0912.

1-Cyclopropyl-5-fluoropyridin-2-one (9d): The title compound was prepared from 2-hydroxy-5-fluoropyridine (33.9 mg, 0.3 mmol) according to General Procedure B. Purification by silica flash column chromatography (eluent: DCM to 2% MeOH/DCM) afforded the title compound as a pale-yellow oil (29.0 mg, 63% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25–7.19 (m, 1H), 7.17 (t, J = 3.9 Hz, 1H), 6.48 (dd, J = 10.0, 5.4 Hz, 1H), 3.30 (tt, J = 7.7, 4.3 Hz, 1H), 1.14–1.09 (m, 2H), 0.86–0.81 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 162.3, 147.1 (d, J = 231 Hz), 131.0 (d, J = 24 Hz), 122.3 (d, J = 37 Hz), 121.5 (d, J = 7 Hz), 32.7, 7.1; **^{19}F NMR** ($CDCl_3$, 376 MHz, $CDCl_3$) δ –149.35; **HRMS** (ESI-TOF) *m/z* calcd for C_8H_9FNO $[M+H]^+$ 154.0663, found 154.0663.

1-Cyclopropyl-5-chloropyridin-2-one (9e): The title compound was prepared from 2-hydroxy-5-chloropyridine (38.9 mg, 0.3 mmol) according to General Procedure B. Purification by silica flash column chromatography (eluent: DCM to 2% MeOH/DCM), followed by preparative TLC (eluent: 2% MeOH/DCM) afforded the title compound as a yellow oil (33.8 mg, 66% yield). **^{1}H NMR** (500 MHz,

$CDCl_3$) δ 7.30 (d, *J* = 2.8 Hz, 1H), 7.21 (dd, *J* = 9.7, 2.9 Hz, 1H), 6.48 (d, *J* = 9.7 Hz, 1H), 3.28 (tt, *J* = 7.6, 4.2 Hz, 1H), 1.15–1.09 (m, 2H), 0.86–0.82 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.7, 140.1, 134.7, 121.8, 112.0, 32.9, 31.1, 7.1; **HRMS** (ESI-TOF) *m/z* calcd for C_8H_9ClNO $[M+H]^+$ 170.0367, found 170.0367.

1-Cyclopropyl-6-methylpyridin-2(1*H*)-one (9f): The title compound was prepared from 6-methylpyridin-2(1*H*)-one (32.7 mg, 0.300 mmol) according to General Procedure C. Purification was performed using flash column chromatography (12 g SiO_2, Isco, 100% Hept. to 10% MeOH/EtOAc) to afford the title compound as a pale-yellow gum (27.5 mg, 61% yield). **^{1}H NMR** (400MHz, $CDCl_3$) δ 7.15 (dd, *J* = 9.2, 6.7 Hz, 1H), 6.39 (d, *J* = 9.2 Hz, 1H), 5.97 (d, *J* = 6.7 Hz, 1H), 2.83 (tt, *J* = 7.1, 4.2 Hz, 1H), 2.46 (s, 3H), 1.31–1.23 (m, 2H), 0.92–0.85 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.24, 148.59, 138.60, 118.44, 106.83, 28.08, 20.53, 10.33 (s, 2C); **HRMS** (ESI-TOF) *m/z* calcd for $C_9H_{11}NO^+$ $[M+H]^+$ 150.0913, found 150.0915.

***tert*-Butyl-7-cyclopropyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2(1*H*)-carboxylate (9g):** The title compound was prepared from *tert*-butyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2(1*H*)-carboxylate (75.1 mg, 0.300 mmol) according to General Procedure C. Purification was performed using flash column chromatography (12g SiO_2, Isco, 100% Hept. to 10% MeOH/EtOAc) to afford the title compound as a pale-yellow gum (55.4 mg, 63% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.12 (br d, *J*=6.97 Hz, 1 H) 5.95 (br d, *J* = 6.97 Hz, 1 H) 4.39 (s, 2 H) 3.61 (br t, *J* = 5.59 Hz, 2 H) 3.34 (dt, *J* = 7.24, 3.53 Hz, 1 H) 2.64–2.56 (m, 2 H) 1.50 (d, *J* = 1.10 Hz, 9 H) 1.12 (br d, *J* = 7.15 Hz, 2 H) 0.83–0.88 (m, 2 H); **^{13}C NMR** (150MHz, $CDCl_3$) δ = 162.04, 154.95 (br s, 1C), 144.63 (br s, 1C), 133.18, 123.98 (br s, 1C), 106.95 (br s, 1C), 79.95 (br s, 1C), 42.28 (br s, 1C), 39.47 (br s, 1C), 31.77, 28.52, 28.47 (s, 3C), 6.56 (s, 2C); **HRMS** (ESI-TOF) *m/z* calcd for $C_{16}H_{22}N_2O_3^+$ $[M+H]^+$ = 291.1703, found 291.1707.

***N*-Cyclopropyl-*N*-(pyridin-2-yl)acetamide (10a):** The title compound was prepared from 2-acetamidopyridine (40.8 mg, 0.3 mmol) according to General Procedure B. Purification by silica flash column chromatography (eluent: 1% MeOH/DCM) afforded the title compound as a brown oil (47.0 mg, 89% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.7 Hz, 1H), 7.68 (td, *J* = 7.7, 2.0 Hz, 1H), 7.21–7.10 (m, 2H), 3.11 (tt, *J* = 7.2, 3.8 Hz, 1H), 2.16 (s, 3H), 0.95–0.84 (m, 2H), 0.60–0.46 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 172.8, 155.3, 148.8, 137.8, 122.2, 121.8, 30.5, 23.6, 9.2; **HRMS** (ESI-TOF) *m/z* calcd for $C_{10}H_{13}N_2O$ $[M+H]^+$ 177.1022, found 177.1021.

***N*-Cyclopropylpyrazin-2-amine (10b):** The title compound was prepared from 2-aminopyrimidine (28.5 mg, 0.3 mmol) according to General Procedure B. Purification by silica flash column chromatography (eluent: 1–2% MeOH/DCM) afforded the title compound as a pale-yellow solid (13.2 mg, 33% yield). **mp =** 82–85 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.34 (s, 2H), 6.58 (t, *J* = 4.8 Hz, 1H), 5.67 (brs, 1H, –N*H*), 2.77 (dddd, *J* = 9.2, 7.1, 3.6, 2.1 Hz, 1H), 0.89–0.80 (m, 2H), 0.59–0.52 (m, 2H); **^{13}C NMR**(150 MHz, $CDCl_3$) δ 163.4, 158.2, 111.2, 111.2, 23.9, 7.5, 7.5; **HRMS** (ESI-TOF) *m/z* calcd for $C_7H_{10}N_3$ $[M+H]^+$ 136.0869, found 136.0871.

5-Hydroxy-*N*^{1},*N*^{1}-dimethyl-*N*^{3}-(5-methylpyridin-2-yl)isophthalamide (S4): The title compounds was prepared in a similar method as a previously published Pfizer patent (white solid).[30] **mp =** 202–205 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 9.97 (s, 1H), 8.21 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.65 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.47 (s, 1H), 7.43–7.36 (m, 1H), 6.93 (dd, *J* = 1.3, 2.1 Hz, 1H), 2.98 (br s, 3H), 2.93 (br s, 3H), 2.28 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 169.9, 165.6, 157.8, 150.4, 148.2, 138.9, 138.4, 136.1, 129.3, 117.5, 117.2, 116.2, 114.9, 35.2, 17.8 (carbon signal suspected under solvent peak); **HRMS** (ESI-TOF) *m/z* calcd for $C_{16}H_{17}N_3O_3^+$ $[M+H]^+$ 300.1343, found 300.1345.

***N*¹-Cyclopropyl-5-hydroxy-*N*³,*N*³-dimethyl-*N*¹-(5-methylpyridin-2-yl)isophthalamide (10c):** The title compound was prepared from 5-hydroxy-*N*¹,*N*¹-dimethyl-*N*³-(5-methylpyridin-2-yl)isophthalamide (**S4**) (180 mg, 0.6 mmol) according to General Procedure C. Purification by ISCO (0–100% EtOAc/Heptanes, then 10% MeOH/EtOAc) afforded the title compound as a light tan foam (130 mg, 64%). Structure elucidated by HMBC. **¹H NMR** (400 MHz, DMSO-d_6) δ 9.80 (s, 1 H), 8.26–8.08 (m, 1 H), 7.57 (ddd, *J* = 8.07, 2.45, 0.61 Hz, 1 H), 7.16 (d, *J* = 8.07 Hz, 1 H), 6.81 (dd, *J* = 2.32, 1.47 Hz, 1 H), 6.65 (dd, *J* = 2.38, 1.41 Hz, 1 H), 6.60 (t, *J* = 1.41 Hz, 1 H), 3.10 (tt, *J* = 7.21, 3.73 Hz, 1 H), 2.90 (br s, 3 H), 2.62 (br s, 3 H), 2.23 (s, 3 H), 0.81–0.69 (m, 2 H), 0.63–0.52 (m, 2 H); **¹³C NMR** (100 MHz, DMSO-d_6) δ 171.1, 169.6, 157.3, 153.5, 149.1, 139.0, 138.9, 137.7, 132.0, 122.5, 116.9, 115.9, 115.30, 39.0, 35.0, 31.4, 17.7, 8.3; **HRMS** (ESI-TOF) *m*/*z* calcd for $C_{19}H_{21}N_3O_3^+$ $[M+H]^+$ 340.1656, found 340.1663

Author contributions. ‡These authors contributed equally.

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Supporting Information Available. Photographic depiction of reaction setup, matched molecular pair (MMP) data, X-ray crystallographic data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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