Ni-Catalyzed Reductive Cross-Coupling of Cyclopropylamines and Other Strained Ring NHP Esters with (Hetero)Aryl Halides

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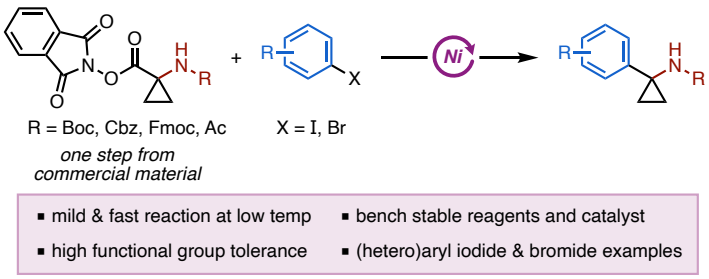
nickel, cyclopropylamine, arylation, NHP ester, cross-coupling, cross-electrophile



ABSTRACT: A nickel-catalyzed reductive cross-coupling of cyclopropylamine NHP esters with (hetero)aryl halides is reported. This efficient protocol provides direct access to 1-arylcyclopropylamines, a bioisosteric motif commonly used in small molecule drug discovery. The reaction proceeds rapidly (<2 h) with excellent functional group tolerance and without requiring heat or air-sensitive reagents. The method can also be extended to the arylation of four-membered strained rings. The NHP esters are easily obtained from the corresponding commercially available carboxylic acids in one step with high yields and no column chromatography.

In contemporary medicinal chemistry, discovery teams must consider expansive biochemical, cellular, metabolic, and protein structure datasets to strike a balance of physiochemical properties, potency, and safety.[1] Among the various binding interactions that can occur between a small molecule drug and the targeted protein, the 3-D network of hydrogen bonding interactions is a key driver of potency.[2]

A frequently encountered hydrogen bonding motif is the N–H bond present in benzylamines.[2a] However, the methylene group present in benzylamines and heteroaryl methylamines readily undergoes cytochrome oxidation, rendering it a "metabolic soft spot" (Figure 1a).[3] Bioisosteric replacement of benzylamines can easily be accomplished with a *gem*-dimethyl group to block this metabolism.[4] However, this strategy inevitably introduces additional lipophilicity (increasing cLogP),[5] which may negatively affect water-solubility and protein-binding selectivity.[6] To circumvent this, fusing the carbon atoms together as rigid ring can afford compounds with lower lipophilicity and higher solubility.[7] Cyclopropanes also possess greater sp^2-character which renders their C–H bonds less susceptible to undesired metabolism.[8] Cyclopropylamines are also significantly less basic than benzylamines and *gem*-dimethylamines, leading to decreased binding promiscuity to off-target proteins.[9] Proactive de-risking of CYP enzyme inhibition and glutathione trapping during development has enabled the progression of numerous compounds containing cyclopropylamines into the clinic and on to commercialization (Figure 1b). [10, 11]

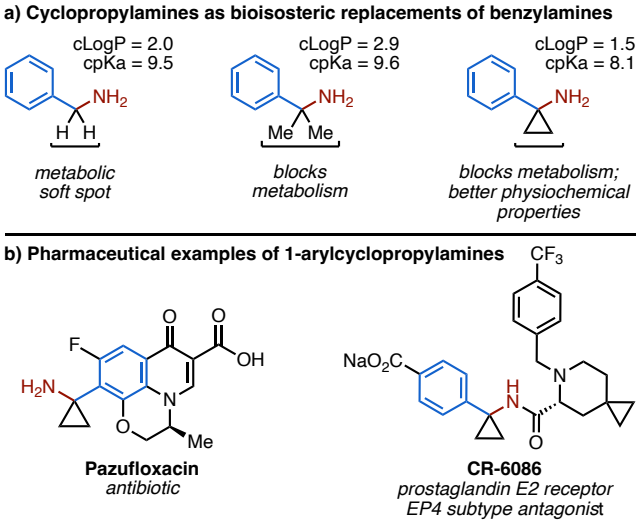
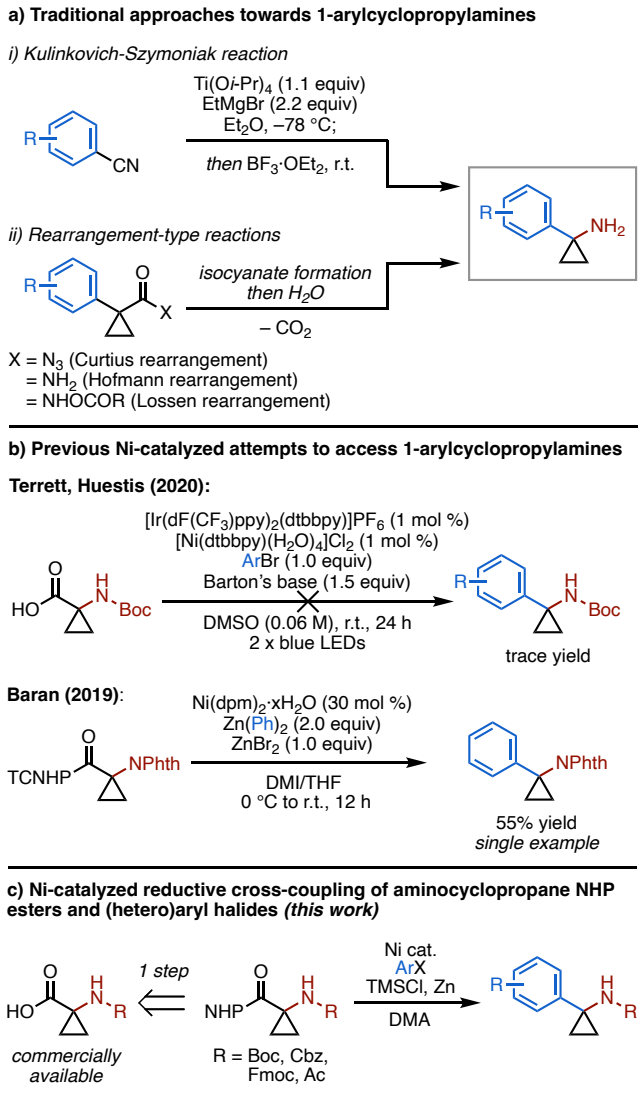


Figure 1. Examples and Properties of Biologically Relevant 1-Arylcyclopropylamines

In recent years, medicinal chemistry synthetic route designs have shifted from using stoichiometric amounts of moisture- and air-sensitive reagents to catalytic approaches based on modular assemblies of air-stable and commercially available building blocks.[12] To this end, we realized that no such modular

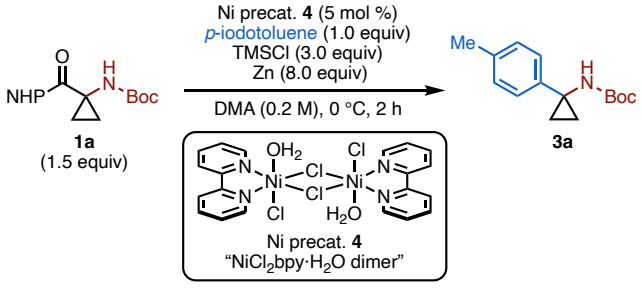
Scheme 1. Strategies to Access 1-Arylcyclopropylamines



approach was available for the synthesis of 1-arylcyclopropylamines. Only a handful of synthetic methods are available, with almost all 1-arylcyclopropylamines reported in the literature being constructed *via* the Kulinkovich-Szymoniak reaction[13] or the Curtius rearrangement[14] (Scheme 1a). However, these strategies require stoichiometric organometallic or azide reagents. A recent multi-kilogram clinical delivery by AstraZeneca illustrates the scarcity of approaches to this class of molecules, with the Kulinkovich-Szymoniak reaction achieving only 37% yield of the 1-arylcyclopropylamine product.[15] The high prevalence of (hetero)aryl halides in medicinal and process chemistry, combined with the aforementioned paucity of direct and reliable approaches to 1-arylcyclopropylamines, has inspired us to address this problem.

To realize a building block approach, we envisioned engaging a protected cyclopropylamine precursor with a (hetero)aryl halide *via* a cross-coupling strategy. To this end, commercially available 1-aminocyclopropanecarboxylic acid offered an attractive entry point to α-aminocyclopropyl radicals via decarboxylation. In 2020, Terrett and Huestis reported the synthesis of 1-arylaminooxetanes from aryl halides and 3-((*tert*-butoxycarbonyl)amino)oxetane-3-carboxylic acid via dual photoredox/Ni catalysis (Scheme 1b, top).[16] In this report, structurally related 1-(Boc-amino)cyclopropanecarboxylic acids were unreactive under these conditions, further demonstrating the challenge in accessing these products *via* a catalytic system. Recent reports from Baran[17] and Weix[18] have sparked a renaissance in the decarboxylative chemistry of *N*-hydroxyphthalimide (NHP) esters.[19] In 2019, Baran and coworkers reported the synthesis of a single *N*-phthalimide-protected 1-arylcyclopropylamine in 55% yield *via* the coupling of a tetrachloro-*N*-hydroxyphthalimide (TCNHP) ester with an aryl organozinc (Scheme 1b, bottom).[20] Weix and coworkers have also developed Ni-catalyzed cross-electrophile reductive couplings of aryl halides with aliphatic NHP esters as the coupling partner.[18b] In light of these works, as well as our previous experience with Ni-catalyzed reductive cross-couplings of NHP esters,[21] we set out to uncover a modular synthesis of hindered 1-arylcyclopropylamines from readily available starting materials.

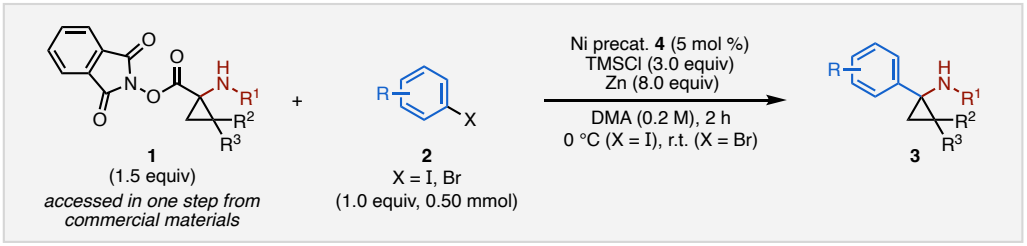
Table 1. Optimization[a]



entry	deviation from standard conditions	ArI conversion (%)[b]	**3a** yield (%)[b]
1	none	100	85 (83%[c])
2	r.t. instead of 0 °C	100	77
3[d]	no TMSCl	0	0
4	TMSCl (1.0 equiv)	79	53
5	Zn (4.0 equiv)	100	82
6	Zn (2.0 equiv)	94	49
7	no Ni	0	0

[a]Reactions were performed on 0.10 mmol scale. See the SI for full details. [b]Calibrated GC-MS yields using dodecane as an internal standard. [c]Isolated yield on 0.5 mmol scale. [d]Reaction left for 24 h.

Reaction optimization began using NHP ester **1a** and *p*-iodotoluene (Table 1). During optimization, we discovered that the commonly used Ni precatalyst "$NiCl_2$bpy" exists as the bimetallic species $[(bipy)_2Ni_2(\mu\text{-}Cl)_2Cl_2(H_2O)_2]$ **4**. Powder X-ray diffraction (PXRD) of both commercially sold and synthesized "$NiCl_2$bpy" was found to be identical to the bimetallic nickel species that was previously characterized by single crystal X-ray crystallography (see SI for details).[22,23] The desired 1-arylcyclopropylamine product **3a** could be obtained in 85% yield after 2 h using **1a** (1.5 equiv), *p*-iodotoluene (1.0 equiv), Ni precatalyst **4** (5 mol %), TMSCl (3.0 equiv), and non-activated zinc flakes[24] (8.0 equiv) in DMA (0.2 M) at 0 °C (entry 1). While the exact role of the chlorosilane is not yet well understood within the context of reductive couplings using NHP esters, our group[21] and others[25] have observed this additive to be crucial to achieve conversion and product formation. We hypothesize



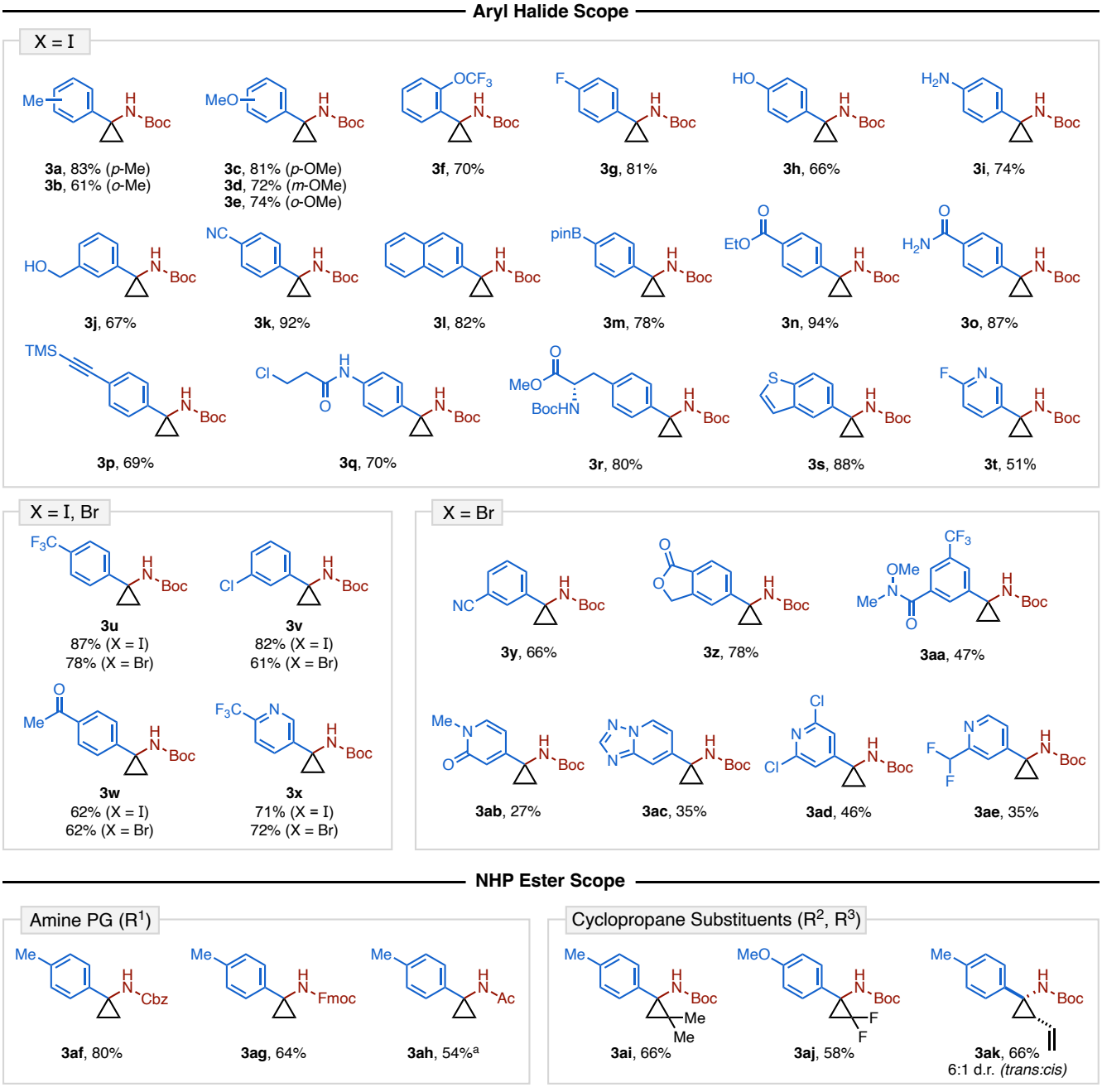


Figure 2. Scope of the Ni-catalyzed reductive coupling of NHP ester **1** and aryl halides **2**. Reactions performed on 0.5 mmol scale, isolated yields are reported. Conditions: To a solution of **1** (1.5 equiv), **2** (0.5 mmol), Ni precat. **4** (5 mol %), and non-activated Zn flakes (8.0 equiv) in DMA (0.2 M) was added TMSCl (3.0 equiv) and the reaction mixture was stirred for 2 h (X = I, 0 °C; X = Br, r.t.). [a]Reaction performed on 0.25 mmol scale.

that chlorosilanes can help to facilitate reduction of the NHP ester to generate an alkyl radical which is captured by nickel and subsequently arylated.[26]

The stoichiometry of both the chlorosilane and the metal reductant could be decreased to give **3a** in moderate yields, albeit with reduced conversion of aryl iodide (entries 4–6). However, we observed that the more challenging aryl halide

coupling partners benefited from the higher chlorosilane and reductant loadings.

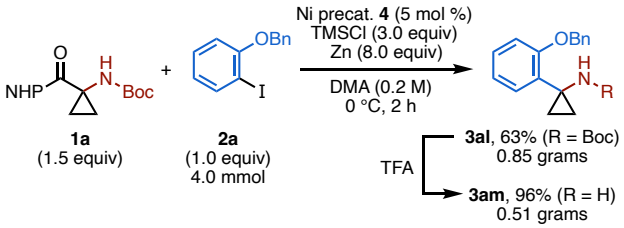
With optimized conditions in hand, the scope of the reaction was explored. The reaction was found to work well with a wide range of aryl iodides (Figure 2). A variety of electron-neutral (**3a**, **3b**, **3j**), electron-rich (**3c**, **3e**, **3h**, **3i**), and electron-deficient (**3d**, **3f**, **3g**, **3n**, **3o**, **3q**, **3u**, **3w**) substrates were obtained in good to excellent yields. *ortho*-Substituted iodoarenes gave the corresponding products in good yields (**3b**, **3e**, **3f**), highlighting the ability to introduce steric bulk next to the newly formed quaternary center. Aryl iodides containing other cross-coupling handles remained untouched, such as chloride, boronic ester, and TMS-protected alkyne, (products **3v**, **3m**, and **3p**, respectively) illustrating potential orthogonality for further product diversification. Base-sensitive functional groups, which could be problematic when using previously reported methods with organometallic reagents to access these products, were found to be well tolerated, as exemplified through products containing an unprotected phenol (**3h**), aniline (**3i**), benzyl alcohol (**3j**), ketone (**3w**), and amide (**3o**, **3q**). Furthermore, phenylalanine-derived substrate **3r** was obtained in good yield. The functional group tolerance observed here further emphasizes the mild conditions and excellent chemoselectivity of the reaction. Finally, heteroaryl iodides such as pyridines and benzothiophene were efficiently cross-coupled, as seen in products **3t**, **3x**, and **3s**, respectively.

Due to the greater commercial availability and stability of aryl bromides, we next explored their use as coupling partners. We found that electron-deficient aryl bromides were viable substrates under these conditions by simply raising the reaction temperature to room temperature. Electron-deficient aryl bromides such as CF_3-containing substrates afforded the corresponding products (**3u**, **3aa**) in moderate to good yields. Products containing handles which could be used for further functional group manipulation, such as chloride (**3v**, **3ad**), nitrile (**3y**), ketone (**3w**), benzolactone (**3z**), and a Weinreb amide (**3aa**), were obtained in moderate to good yields. Electron-deficient heteroaryl bromides, such as 5-bromo-2-(trifluoromethyl)pyridine and 4-bromo-2,6-dichloropyridine, led to the 1-pyridyl cyclopropylamines (**3x** and **3ad**) in moderate to good yields. More challenging, less electron-deficient heterocycles, such as *N*-methyl-2-pyridone and [1,2,4]triazolo[1,5-*a*]pyridine , were also found to be tolerated, affording products **3ab** and **3ac** in acceptable yields.

The scope of NHP esters was also investigated. The NHP esters were prepared in a simple one-step protocol from the corresponding commercially available carboxylic acid precursors and with no column chromatography required (see SI). In addition to the Boc-protected products, other protecting groups such as Cbz (**3af**), Fmoc (**3ag**), and acetyl (**3ah**) were found to be compatible under the reaction conditions and gave products in moderate to good yields. Introducing substituents on the cyclopropane ring did not decrease the efficiency of the cross-coupling, as commercially available precursors afforded products containing a *gem*-dimethyl (**3ai**), a *gem*-difluoro (**3aj**), and a 2-vinyl (**3ak**) group in good yields. Product **3ak** was isolated as a mixture of diastereomers (66%, combined yield) in 6:1 d.r. *(trans:cis)*.

To demonstrate the applicability of this method, a gram scale reaction was performed with NHP ester **1a** and 2-iodophenol **2a** affording 0.85 grams of product **3al** in 63% isolated yield (Scheme 2). Removal of the Boc group in the presence of TFA afforded the corresponding primary 1-arylcyclopropylamine **3am** in 96% yield (60% over 2 steps). The synthesis of **3am** by AstraZeneca via a Kulinkovich-Szymoniak reaction was previously reported in only 37%,[15] probably due to the known limitation for the necessary use of electron-deficient benzonitriles to obtain the products in high yield.[27]

Scheme 2. Gram-Scale Synthesis of Compound 3al



Other α-amino strained rings are also compatible in this chemistry (Figure 3). Small rings containing heteroatoms such as an oxetane, a Boc-protected azetidine, and a 2-azabicyclo[2.1.1]hexane were arylated to afford **3ap**, **3aq**, and **3ar** respectively, in moderate to good yields. Both a cyclobutane (**3an**) and a *gem*-difluoro cyclobutane (**3ao**) product could also be obtained under these conditions. Each of these strained ring motifs are highly desirable sp^3-rich functional groups that can be leveraged as bioisosteres or used to alter metabolism of biologically active molecules.[28] Notably, this NHP ester strategy provides orthogonal access to the 1-aryl aminooxetanes reported by Terrett and Huestis while simultaneously promoting arylation of strained cycloalkanes, which were incompatible under the dual photoredox/nickel-catalyzed arylation approach.[16]

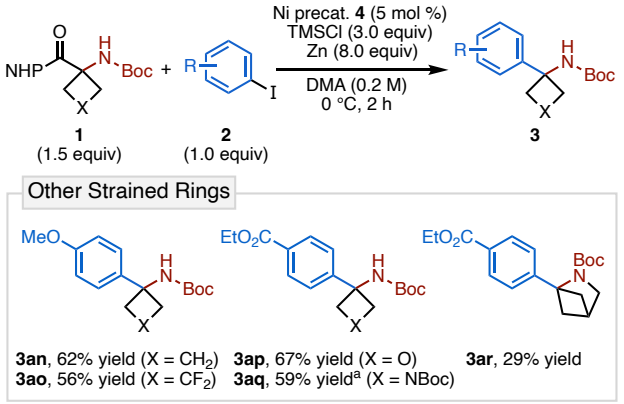


Figure 3. Evaluation of Additional Small Ring Substrates. See Figure 2 for the abbreviated reaction procedure. [a]Reaction run with $NiCl_2$(dtbbpy) (20 mol %).

In conclusion, we have developed a Ni-catalyzed reductive cross-coupling approach to access a wide variety of 1-arylcyclopropylamine products. This method makes use of bench-stable NHP esters (prepared in one step from commercial materials) and (hetero)aryl iodides and bromides, as well as a simple nickel precatalyst. We have demonstrated that this reaction operates under mild conditions (0 °C or r.t., 2 h) with high functional group compatibility and orthogonality, thereby overcoming challenges that previously reported synthetic methods typically encounter. The reaction can also be extended to the arylation of other strained ring substrates. 1-Arylcyclopropylamines are sought-after bioisosteric building blocks for small molecule drug design, and we anticipate that

this work will help provide a simple and direct approach to these motifs.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Reaction optimization tables, synthetic procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank NSERC (Discovery Grants and Canada Research Chair programs), the Canada Foundation for Innovation (project no. 35261), the Ontario Research Fund, the Alfred P. Sloan Foundation, and the University of Toronto for generous financial support of this work. We also acknowledge the Canada Foundation for Innovation (project no. 19119) and the Ontario Research Fund for funding the Centre for Spectroscopic Investigation of Complex Organic Molecules and Polymers. M.S.W. and A.L.G. thank NSERC for graduate scholarships (PGS D). Jack Sheng is thanked for assistance with NMR. M.P.H. thanks Antonio G. DiPasquale for assistance with PXRD, Crystal Ye and Patrick Huang for assistance with HPLC, and Yuhui Zhou for assistance with NMR and HRMS.

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