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Palladium-Catalyzed *N*-Arylation of Cyclopropylamines

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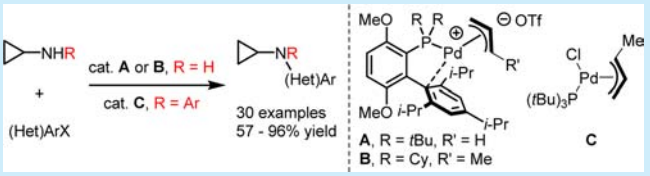
Supporting Information

ABSTRACT: A general method has been developed for the previously challenging arylation of cyclopropylamine and *N*-arylcyclopropylamines. Highly active, air-stable, and commercially available R-allylpalladium precatalysts provide access to a wide range of (hetero)arylated cyclopropylanilines in high yields. Precatalysts [(*t*BuBrettPhos)Pd(allyl)]OTf and [(BrettPhos)Pd(crotyl)]OTf, deliver monoarylated products, while (P*t*Bu$_3$)Pd(crotyl)Cl is suited for preparing unsymmetrical diarylated products. The developed conditions tolerate a range of functional groups and heterocycles, allowing access to an array of arylated cyclopropylamines, a motif present in prominent drug molecules.



Despite the continued advances in new trends in cross-coupling,[1] such as the development of palladium-catalyzed amination reactions involving challenging electro- and nucleophilic substrates (e.g., heterocycles, amides, indoles, ammonia, etc.), significant challenges remain.[2] The success and versatility of these methods are critical for providing high value compounds found in pharmaceutical, agrochemical, and electronics materials.[3] The cyclopropylamine motif,[4] found in prominent fluoroquinolone antibiotics[5] and reverse transcriptase inhibitors (RTI) for controlling HIV (Figure 1),[6]

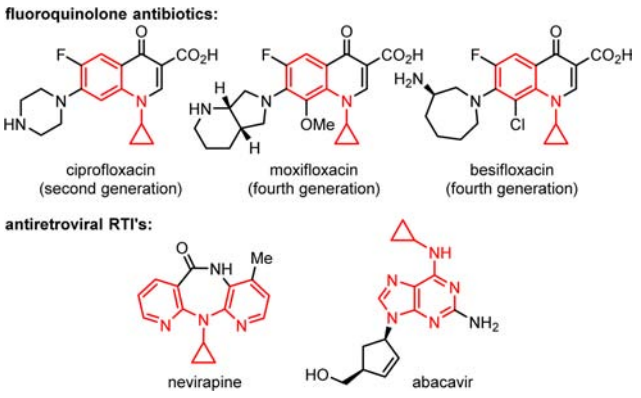
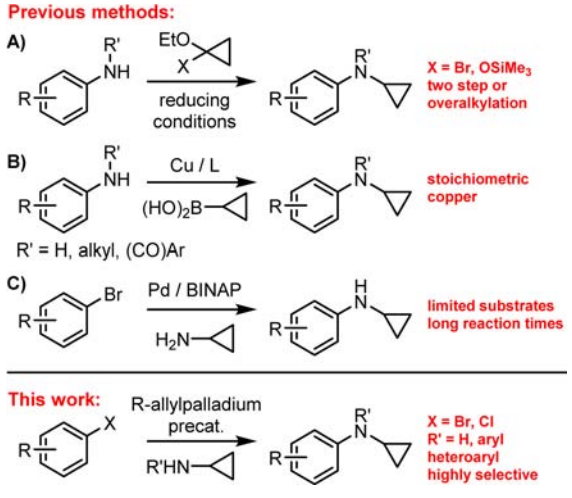


Figure 1. Important active pharmaceutical molecules possessing arylated cyclopropylamine.

constitutes one such valuable example. In addition to possessing important biological attributes, cyclopropylamines are useful probes for organic and biological mechanistic studies to investigate the presence of radical-containing intermediates.[7] Prone to single electron oxidation,[8] cyclopropylamines form N-centered radicals, which readily undergo ring opening to relieve the high strain of the cyclopropyl ring. In spite of their value, the selective and efficient coupling of cyclopropylamines has proven formidable.[9]

While the alkylation of cyclopropylamine proceeds smoothly, arylation is much more challenging. Due to the inherent properties of the cyclopropyl ring, anilines do not readily react with cyclopropyl halides to form the corresponding cyclopropylaniline.[10] Reductive amination strategies and a Smiles rearrangement example have been employed to access arylated cyclopropylamine; however, they are made impractical by two-step protocols using forcing conditions,[11] or require excess silyl ketene acetal reagents under reducing conditions with concomitant overalkylation[12] (Scheme 1A). Several Chan–Lam type couplings exist for accessing cyclopropylanilines[13] and amides,[14,15] but these typically rely on a stoichiometric amount of copper with pyridine-based ligands (Scheme 1B).

Scheme 1. Methods for Accessing Arylated Cyclopropylamines



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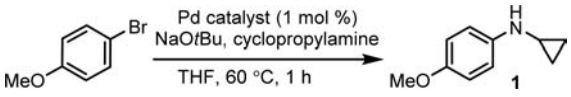
Palladium-catalyzed cross-coupling is an attractive alternative to these existing methods that could allow increased substrate scope and selectivity. However, in 2001 Loeppky and co-workers, using Pd_2dba_3/BINAP as an in situ catalyst system, only succeeded in coupling aryl bromides possessing minimal substitution (Scheme 1C).[16] The moderate yields, limitations in coupling partners (only one heteroaryl halide coupled in 52% yield), and lack of functional group generality have prevented this method from being widely adopted for practical reasons.

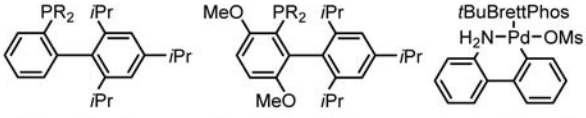
Herein, we report the development of a general method for the arylation of cyclopropylamines using our recently developed, easily activated, air-stable, R-allylpalladium precatalysts[17] (Scheme 1, bottom). Importantly, this method produces a wide range of substituted aryl and heteroaryl cyclopropylamines in good to excellent yields, previously inaccessible through palladium cross-coupling. The highly active, yet selective, allylpalladium precatalysts offer access to both mono- and unsymmetrical diarylated cyclopropylamines.

In our initial screening using 4-bromoanisole as a model substrate, the use of R-allylpalladium precatalysts (1 mol %) based on either BINAP or $P(tBu)_3$ did not lead to the desired arylated amine (**1**), but instead gave minimal conversion to the reduced arene (Table 1, entries 1 and 2). Similar results were

Table 1. Identification of Palladium Precatalyst for Arylation of Cyclopropylamine with 4-Bromoanisole[a]



entry	Pd catalyst	conv (%)[b]	prd ratio[c]
1	[(BINAP)Pd(allyl)]Cl	5	0:1
2	($PtBu_3$)Pd(crotyl)Cl	21	0:1
3	(XPhos)Pd(crotyl)Cl	17	0:1
4	[(*t*BuXPhos)Pd(allyl)]OTf	94	11:1
5	[(BrettPhos)Pd(crotyl)]OTf	83	38:1
6	[(*t*BuBrettPhos)Pd(allyl)]OTf	100	1:0
7[d]	[(*t*BuBrettPhos)Pd(allyl)]OTf	100	1:0
8[d]	$[Pd(allyl)Cl]_2$ / *t*BuBrettPhos	0	n/a
9[d]	*t*BuBrettPhos G3	45	1:0



XPhos, R = Cy
*t*BuXPhos, R = *t*Bu

BrettPhos, R = Cy
*t*BuBrettPhos, R = *t*Bu

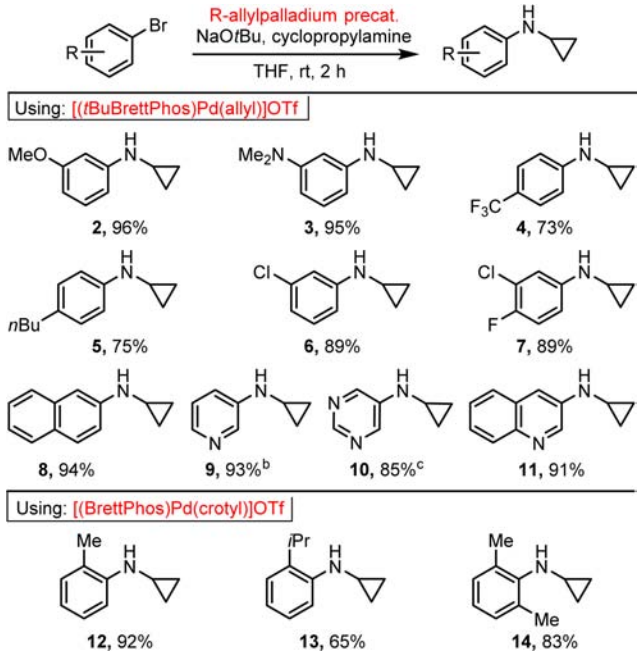
*t*BuBrettPhos G3

[a]General conditions: 1 equiv of 4-bromoanisole, 1 mol % Pd catalyst, 1.2 equiv of NaO*t*Bu, 1.2 equiv of cyclopropylamine, 0.5 M THF. [b]Calibrated GC conversion of 4-bromoanisole using dodecane as an internal standard. [c]Desired product, **1**/anisole. [d]0.3 mol % catalyst loading, rt.

obtained when using an XPhos-based precatalyst (entry 3). However, switching to the more bulky *t*BuXPhos-based precatalyst greatly increased the conversion with promising selectivity for the desired cyclopropylaniline (**1**) (entry 4). An R-allyl palladium precatalyst based on BrettPhos,[18] previously shown to be efficient for coupling primary amines,[17] greatly improved the selectivity while maintaining high conversion (entry 5). Further fine-tuning[19] with bulky [(*t*BuBrettPhos)-Pd(allyl)]OTf gave full conversion to product with complete suppression of the reduction pathway, demonstrating high levels of activity even at low loading (0.3 mol %) at room temperature (entries 6 and 7).[20] The *t*BuBrettPhos based G3 palladacycle[21] gave low conversion under our optimized conditions (entry 9).

With these optimized conditions in hand a range of aryl and heteroaryl bromides were successfully coupled to establish the generality of the reaction (Scheme 2). Aryl bromides can be

Scheme 2. Substrate Scope of Cyclopropylamine Arylation Using (Hetero)aryl Bromides[a]



[a]General conditions, Top: 1 equiv of aryl bromide, 0.3 mol % catalyst loading, 1.2 equiv of NaO*t*Bu, 1.2 equiv of cyclopropylamine, 0.5 M THF; Bottom: 1 mol % [(BrettPhos)Pd(crotyl)]OTf, 0.5 M toluene, 110 °C, 6 h. [b]0.5 M toluene, 60 °C, 2 h. [c]1 mol % catalyst loading, 1.2 equiv of K_2CO_3, 0.5 M 2-methyl-2-butanol, 110 °C, 16 h.

coupled selectively in the presence of a chloro substituent (**6** and **7**), and, additionally, a polyaromatic substrate (**8**) proceeded without incident. Importantly, in contrast to previous methods,[16] heterocyclic substrates including pyridine (**9**), pyrimidine (**10**), and quinoline (**11**) were all coupled in high yields. Sterically hindered substrates containing ortho substituents (**12** and **14**), including a bulky isopropyl group (**13**), necessitated using the less sterically demanding [(BrettPhos)Pd(crotyl)]OTf (Scheme 2, bottom). Additionally a range of functional groups were well tolerated in the arylation of cyclopropylamines, including methoxy (**2**, **20**, **24**, and **27**), dimethylamine (**3** and **28**), trifluoromethyl (**4** and **29**), trifluoromethoxy (**16**), ester (**19**), and nitrile (**28**) groups across Schemes 2−5.

To expand the scope of the electrophiles further, a range of aryl and heteroaryl chlorides were also successfully utilized for arylating cyclopropylamine at 110 °C (Scheme 3). Trifluoromethyl- and trifluoromethoxy-containing aryl chlorides were well tolerated (**15** and **16**), and dichloroarenes were monofunctionalized as the sole observable product (**17** and

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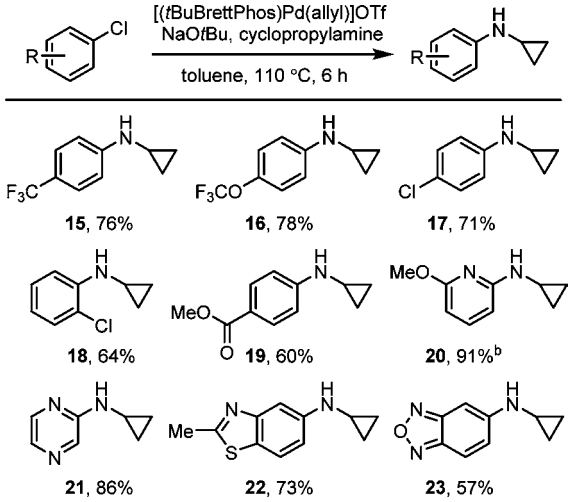
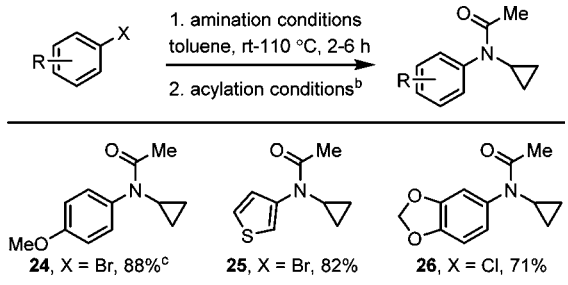
Scheme 3. Substrate Scope of Cyclopropylamine Arylation Using (Hetero)aryl Chlorides[a]



[a]General conditions: 1 equiv of aryl chloride, 1 mol % catalyst loading, 1.2 equiv of NaO*t*Bu, 1.2 equiv of cyclopropylamine, 0.5 M toluene. [b]Reaction time 1 h.

18). Importantly, heteroaryl chloride substrates, including pyridine (**20**), pyrazine (**21**), benzothiazole (**22**), and benzofurazan (**23**), proceeded in good yields. Some arylated cyclopropylamine products, particularly the electron-rich examples, were susceptible to rapid oxidation and decomposition under air, which prevented their isolation by column chromatography.[8] By employing a straightforward, one-pot acylation procedure, we were able to circumvent this issue. As a result, several tertiary cyclopropylamides were isolated in good yields, including sulfur- and oxygen-containing heterocycles (**25** and **26**) (Scheme 4).

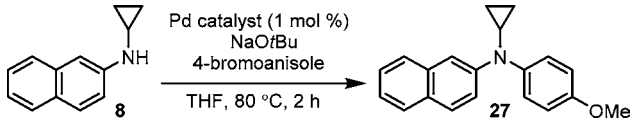
Scheme 4. Demonstration of One-Pot Amination/Acylation of Cyclopropylamines[a]



[a]General conditions: 1 equiv of aryl halide, 1 mol % [(*t*BuBrettPhos)-Pd(allyl)]OTf, 1.2 equiv of NaO*t*Bu, 1.2 equiv of cyclopropylamine, 0.5 M toluene. [b]1.05 equiv of acetic anhydride, 50 °C, 2 h. [c]0.3 mol % catalyst loading; THF used.

In addition to generating these valuable functionalized products, we sought to demonstrate their stability as reagents for a second arylation reaction. Although RuPhos is widely used for amination reactions employing secondary amines,[2b] using (RuPhos)Pd(crotyl)Cl as a precatalyst in the reaction of **8** with 4-bromoanisole under standard reaction conditions,[2b] surprisingly, did not lead to the desired tertiary cyclopropylamine as the major product (Table 2, entry 1); instead anisole was observed in significant quantities. Similarly another bulky biarylphosphine-based (*t*BuXPhos-based) precatalyst gave poor

Table 2. Identification of Palladium Precatalyst for N-Arylation of Aryl Cyclopropylamine 8 with 4-Bromoanisole[a]



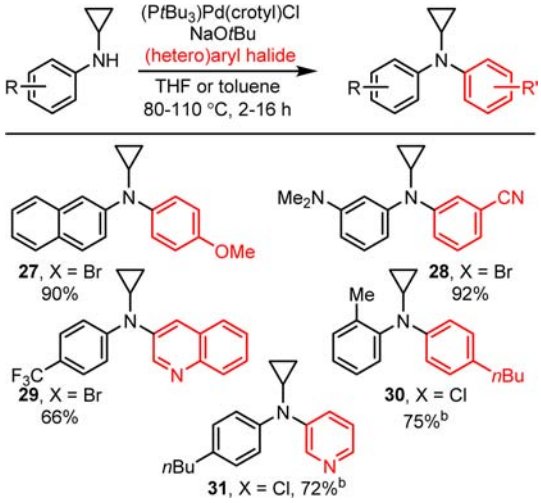
entry	Pd catalyst	prod (%)[b]	anisole (%)
1	(RuPhos)Pd(crotyl)Cl	14	58
2	[(*t*BuXPhos)Pd(allyl)]OTf	16	20
3	(DTBNpP)Pd(crotyl)Cl	99	1
4	(P*t*Bu$_3$)Pd(crotyl)Cl	97	1

[a]General conditions: 1.1 equiv of **8**, 1 mol % catalyst loading, 1.1 equiv of NaO*t*Bu, 1 equiv of 4-bromoanisole, 0.5 M THF. [b]Calibrated GC yields using dodecane as an internal standard.

selectivity (entry 2), while trialkylphosphine-based palladium precatalysts gave uniquely superior reactivity with nearly complete suppression of the dehalogenation pathway, providing the desired diaryl cyclopropylamine in high yields (entries 3 and 4).[22] Although (DTBNpP)Pd(crotyl)Cl (DTBNpP = di(*tert*-butyl)neopentylphosphine) gave slightly better results (entry 3) as compared to P(*t*Bu)$_3$ (entry 4), (P*t*Bu$_3$)Pd-(crotyl)Cl was selected as the precatalyst for expanding the scope of the reaction due to its ready availability.[23]

Scheme 5 highlights the generality and scope of the arylation of cyclopropylanilines. Good to excellent isolated yields (66–

Scheme 5. Synthesis of Diaryl Cyclopropylamines[a]



[a]General conditions: 1 equiv of cyclopropylaniline, 1 mol % catalyst loading, 1 equiv of NaO*t*Bu, 1 equiv of aryl bromide, 0.5 M solvent. [b]Aryl chloride used.

92%) were obtained with examples of electron-rich (**27**), electron-deficient (**28**), and heterocyclic (**29** and **31**) aryl halides. Ortho-substitution on the cyclopropylaniline (**30**) did not hinder the reaction. A somewhat diminished yield was observed for the less electron-rich cyclopropylaniline (**29**).

In summary, we have developed an efficient and general protocol for the stepwise arylation of cyclopropylamine, providing facile access to an array of secondary and tertiary substituted cyclopropylanilines. By employing our highly active R-allylpalladium precatalysts, a broad scope of previously unreactive aryl electrophiles are coupled in good to excellent

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yields. We anticipate that this general strategy will find widespread use in chemical synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00377.

General experimental procedures, product characterization, spectral data (PDF)

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Notes

The authors declare the following competing financial interest(s): A number of the allyl-, and crotyl-palladium precatalysts described in this work are the intellectual property of Johnson Matthey PLC and are commercially available from Johnson Matthey Catalysis and Chiral Technologies (jmcct.com).

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(19) With regards to the optimization of reaction conditions, a weaker base such as K_2CO_3 leads to product formation and, in some cases, is preferable (see compound **10**). In general, however, superior results were obtained with a stronger *tert*-butoxide base.

(20) The precatalyst form is critical for optimal reactivity, as adding $[Pd(allyl)Cl]_2$ together with *t*BuBrettPhos (Table 1, entry 8) resulted in no product formation under the mild optimized conditions.

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