Communication

#-Arylation of Saturated Azacycles and N-Methylamines via Palladium(II)-catalyzed C(sp3)–H Coupling

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α-Arylation of Saturated Azacycles and *N*-Methylamines via Palladium(II)-catalyzed C(sp^3)–H Coupling

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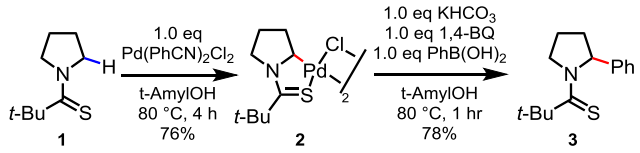
ABSTRACT: Pd(II)-catalyzed α-C(sp^3)–H arylation of pyrrolidines, piperidines, azepanes and *N*-methyl amines with arylboronic acids has been developed for the first time. This transformation is applicable to both a wide array of pyrrolidines and boronic acids, including heteroaromatic boronic acids. A diastereoselective one-pot hetero-diarylation of pyrrolidines is also achieved.

The prevalence of cyclic saturated amines in bioactive natural products and pharmaceutical compounds has led to significant interest in the functionalization of sp^3 C–H bonds adjacent to nitrogen.[1] Important progress has been made in the direct arylation of cyclic amines through α-anion[2], α-radical,[3-5] and α-cation[6] pathways. Extensive efforts at Merck led to the development of an elegant procedure for the enantioselective arylation of *N*-Boc-pyrrolidine via an asymmetric lithiation/Negishi coupling.[2d] In contrast, direct α-arylation through catalytic transition metal-catalyzed C(sp^3)–H bond activation remains under-developed.[7-11] To date, all pioneering studies on metal-catalyzed arylation employ low-valent ruthenium(0) catalysts, although the high reaction temperatures (120-150 °C) required for these transformations often leads to over-arylation and poor stereocontrol. These methods also use a heterocyclic directing group that requires multiple steps to remove.

In 2006, our group disclosed a method for the palladium-catalyzed C(sp^3)–H oxidation of *N*-methylcarbamates.[12] Our early efforts in this field, in conjunction with the high value of α-aryl cyclic amines, prompted us to pursue the development of a method for palladium-catalyzed α-C(sp^3)–H arylation of cyclic amines. Herein we report the discovery of a method for the direct Pd(II)-catalyzed α-C(sp^3)–H cross-coupling of pyrrolidines, piperidines and azepanes with both aryl and heteroaryl boronic acids, a rare of example of the coupling of methylene C–H bonds with organometallic reagents. The excellent monoselectivity of this reaction also enables a one-pot sequential diastereoselective di-arylation.

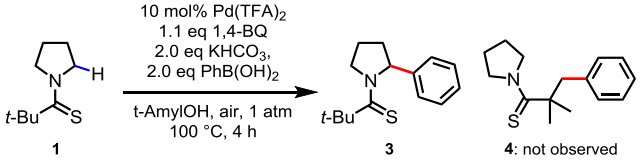
Although our initial efforts to achieve Pd-catalyzed α-C(sp^3)–H arylation with carbamate or heterocyclic directing groups were generally unsuccessful, we were inspired by a 1981 report of the cyclopalladation of N-alkylthioamides[13] to explore the α-C(sp^3)–H arylation of thioamides. As such, we were pleased to find that the palladacycle **2** can be formed as an air-stable yellow solid upon heating of thioamide **1** with stoichiometric $Pd(PhCN)_2Cl_2$ (Scheme 1). We further discovered that palladacycle **2** readily undergoes efficient cross-coupling with phenyl boronic acids at 80°C in *tert*-amyl alcohol in the presence of a mild base and stoichiometric 1,4-benzoquinone (1,4-BQ) to provide 2-phenyl pyrrolidine **3** in 78% yield. This reaction can be conducted without exclusion of oxygen with no decrease in yield. Consistent with our early discovery of Pd(II)-catalyzed cross-coupling of C-H bonds with organotin reagents,[14] 1,4-BQ is essential as a promoter for reductive elimination; no product formation is observed in the absence of 1,4-BQ.

Scheme 1. Stoichiometric α-Arylation of Pyrrolidine



Upon further reaction development, we found that the formation of palladacycle **2** and subsequent cross-coupling with phenylboronic acid can be rendered catalytic by treatment of pyrrolidine **1** with 10 mol% $Pd(TFA)_2$ catalyst and 1,4-BQ (Table 1). We were pleased to find that arylation of the pyrrolidine is highly mono- selective (>20:1 mono:diarylation). It is interesting to note that no functionalization is observed at the terminal methyl groups of the thioamide (**4**), despite significant precedent for the preferential activation of primary C–H bonds over secondary C–H bonds.[15] It is also surprising that our workhorse catalyst, $Pd(OAc)_2$, gives negligible amount of product (Table 1, entries 1-6). 1,4-BQ is also uniquely successful as the oxidant in this transformation due to facile oxidation of the thioamide with the other oxidants that we examined, including Ag(I) salts and peroxides; the resultant amide is an unreactive byproduct in this directed α-arylation.

Table 1. Optimization of the α-arylation of amines[a,b]



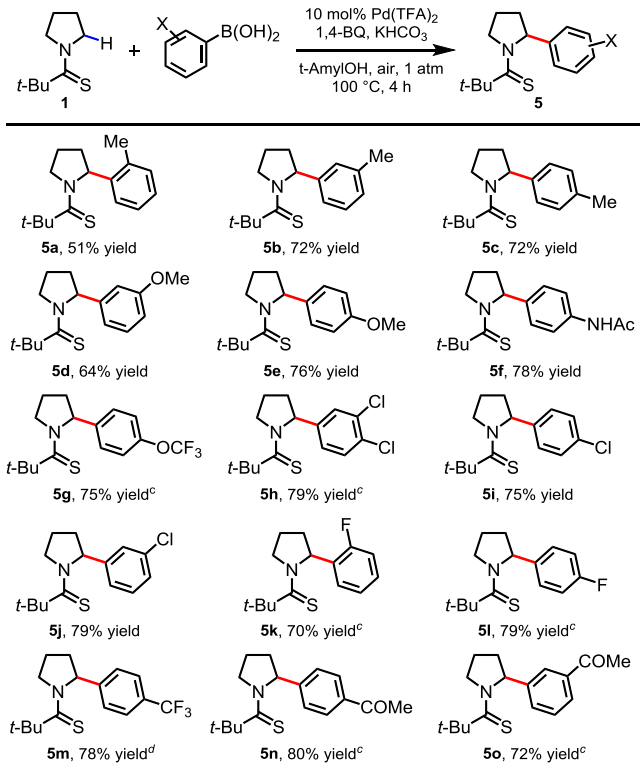
entry	deviation from standard conditions	yield(%)
1	none	82
2	10 mol% $PdCl_2(PhCN)_2$	63
3	10 mol% $PdCl_2$	57
4	10 mol% $Pd(OAc)_2$	7
5	10 mol% $Pd(OTf)_2$•MeCN	22
6	10 mol% allylPdCl$_2$	37
7	no BQ	0
8	0.5 eq BQ	34
9	1.5 eq BQ	61
10	with 2.0 eq PhBPin	8
11	with 2.0 eq $PhBF_3K$	0

[a]Reaction conditions: thioamide **1** (0.2 mmol, 1.0 eq), arylboronic acid (0.4 mmol, 2.0 eq), $Pd(TFA)_2$ (0.02 mmol, 0.1 eq), 1,4-BQ (0.22 mmol, 1.1 eq), $KHCO_3$ (0.4 mmol, 2.0 eq), *t*-AmylOH (4.0 mL), 100 °C, 4 h; [b]The yield was determined by ^{1}H NMR analysis of the crude product using mesitylene as the internal standard.

With these optimized reaction conditions in hand, we next evaluated the scope of the arylboronic acids that can participate in this transformation. As shown in Table 2, this C–H arylation

protocol is tolerant of a broad range of coupling partners, including both electron-rich (Table 2, entries **5a-f**, 51-78% yield) and electron- poor (Table 2, entries **5g-o**, 70-80% yield) boronic acids. However, the use of electron-rich boronic acids does lead to slight increase in the formation of the corresponding diarylated product (4-8%). We were pleased to find that *para*-, *meta*-, and even sterically hindered *ortho*-substituted boronic acids (**5a, 5k**, 51-70% yield) can all be effectively coupled in this transformation. This reaction is tolerant of a range of functional groups, including ketones (**5n**, **5o**, 72-80% yield), amides (**5f**, 78% yield), ethers (**5e**, **5g**, 75-76% yield), and aryl halides (**5h-l**, 70-79% yield).

Table 2. α-Arylation of Pyrrolidine: Boronic Acid Scope[a,b]

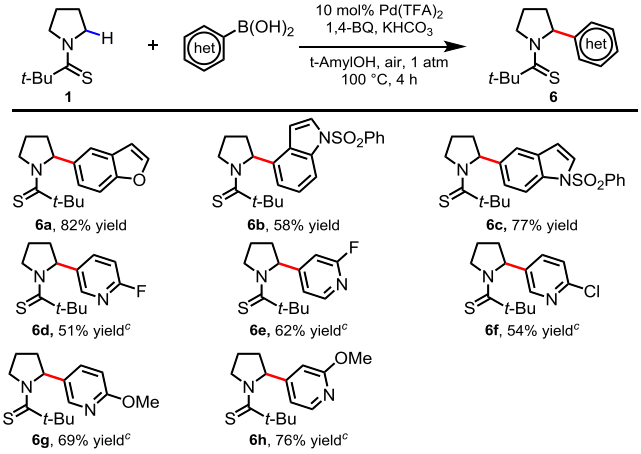


[a]Reaction conditions: thioamide **1** (0.2 mmol, 1.0 eq), arylboronic acid (0.4 mmol, 2.0 eq), $Pd(TFA)_2$ (0.02 mmol, 0.1 eq), 1,4-BQ (0.22 mmol, 1.1 eq), $KHCO_3$ (0.4 mmol, 2.0 eq), *t*-AmylOH (4.0 mL), 100 °C, 4 h. [b]Yield after isolation by chromatography. [c]1.2 eq 1,4-BQ. [d]1.4 eq 1,4-BQ.

The relatively efficient coordination of the thioamide directing group with Pd(II) catalysts led us to speculate that this coupling reaction would be compatible with heteroarylboronic acids, which are generally challenging coupling partners in palladium-catalyzed C(sp^3)–H functionalization reactions due to their propensity to coordinate to the palladium catalyst. As such, we were pleased to find that a broad range of heteroarylboronic acids react in this transformation to provide α-heteroaryl pyrrolidines (Table 3). Electron-rich benzofuran- and indole-containing boronic acids are particularly good coupling partners and provide the corresponding pyrroldine products in excellent yields (**6a-c**, 58-82% yield). A variety of substituted pyridinylboronic acids can be effectively coupled in good yield with complete mono-selectivity (**6d-h**, 51-76% yield). However, the coupling of unsubstituted pyridinylboronic acids was not successful under current conditions. Presumably, the pyridyl outcompetes the thioamide for coordinating with Pd catalyst. Similar phenonmenon have been observed in asymmetric hydrogenation of 2-pyridyl cyclic imines.[16]

We next turned our attention to the scope of pyrrolidines that can be used in this transformation. As shown in Table 4, 3-substituted (**8a-8e**, 51-99% yield) and 2-substituted (**8g-l**, 54-86% yield) pyrrolidines couple efficiently in this transformation with moderate to high levels of diastereoselectivity. In all cases arylation occurs selectively at the less hindered α-methylene with preferential formation of the *trans*-diastereoisomer.[17] An array of heteroatom-substituted pyrrolidines are tolerated in this

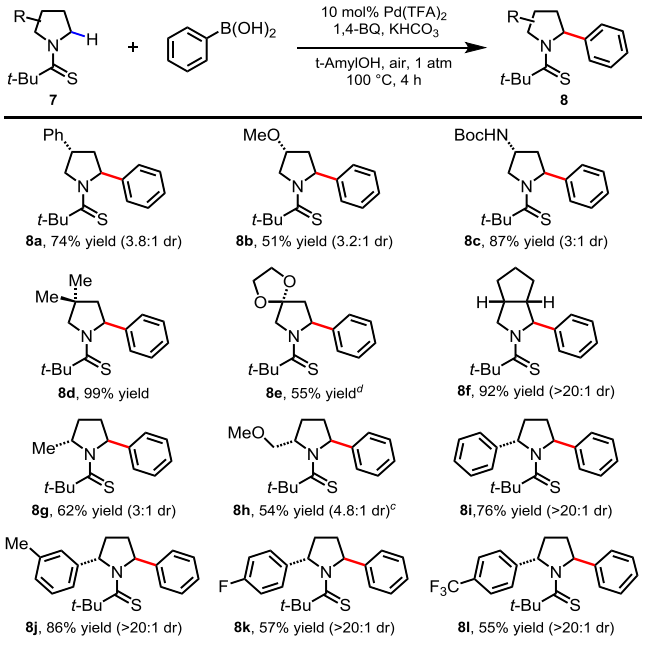
Table 3. Heteroaryl Boronic Acid Scope[a,b]



[a]Reaction conditions: thioamide **1** (0.2 mmol, 1.0 eq), arylboronic acid (0.4 mmol, 2.0 eq), $Pd(TFA)_2$ (0.02 mmol, 0.1 eq), 1,4-BQ (0.22 mmol, 1.1 eq), $KHCO_3$ (0.4 mmol, 2.0 eq), *t*-AmylOH (4.0 mL), 100 °C, 4 h. [b]Yield after isolation by chromatography. [c]3 eq 1,4-BQ.

transformation (**8b**,**c**,**e**,**h**, 51-87% yield). A (3,3,0)-bicyclic pyrrolidine is also an effective substrate in this transformation, providing the desired product in 92% yield (**8f**). An array of 2,5-diaryl pyrrolidines can be synthesized using this protocol with extremely high levels of diastereoselectivity (**8i-l**, 55-86% yield, >20:1 dr). In accordance with our previous observation that electron-rich boronic acids lead to higher levels of diarylation, aryl pyrrolidines **8i**,**j** (76-86% yield) showed higher reactivity than aryl pyrrolidines **8k**,**l** (55-57% yield).

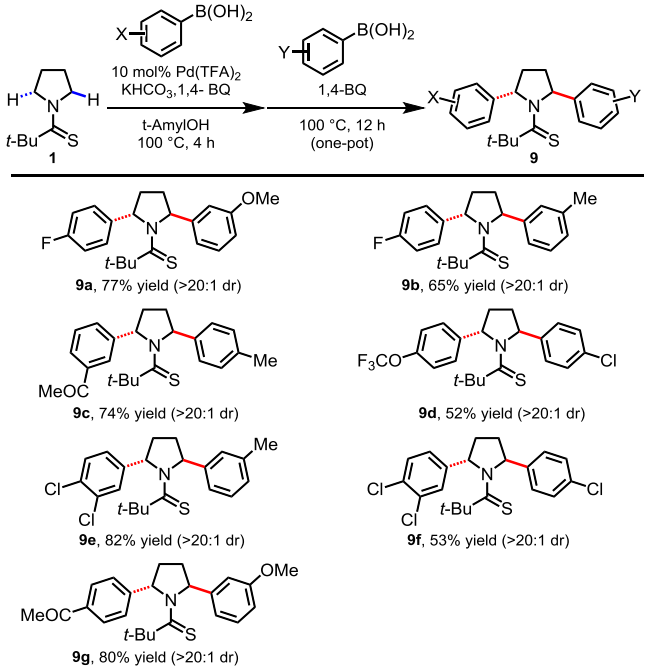
Table 4. Pyrrolidine Substrate Scope[a,b]



[a]Reaction conditions: thioamide **7** (0.2 mmol, 1.0 eq), arylboronic acid (0.4 mmol, 2.0 eq), $Pd(TFA)_2$ (0.02 mmol, 0.1 eq), 1,4-BQ (0.4 mmol, 2.0 eq), $KHCO_3$ (0.4 mmol, 2.0 eq), *t*-AmylOH (4.0 mL), 100 °C, 4 h. [b]Yields after isolation by chromatography. [c]0.15 eq $Pd(TFA)_2$ (0.03 mmol). [d]1.4 eq 1,4-BQ (0.28 mmol), 0.15 eq $Pd(TFA)_2$ (0.03 mmol).

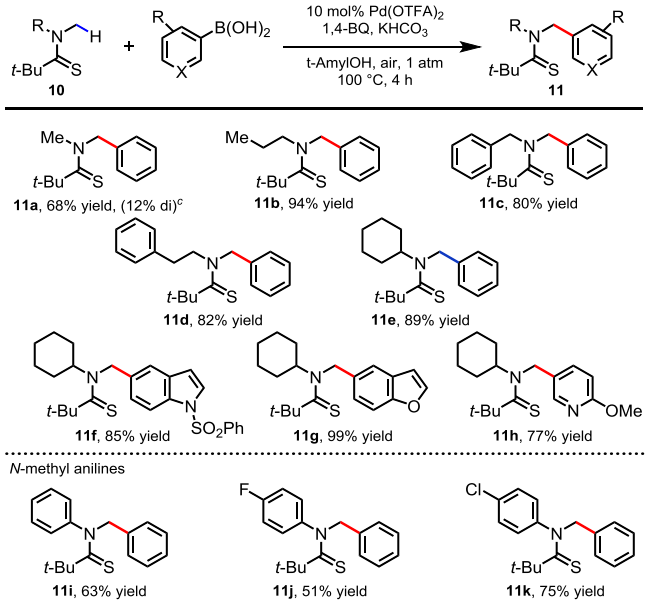
We subsequently found that this arylation can be extrapolated into a consecutive one-pot hetero-diarylation of pyrrolidines to provide 2,5-diarylated pyrrolidine products (Table 5). All of these reactions proceed with complete diastereoselectivity (>20:1 dr). Notably, this one-pot procedure does not require the addition of a second batch of palladium catalyst. We observed that the use of a more mono-selective electron-deficient boronic acid in the first arylation step provides higher yields of the hetero-diarylated product with negligable formation of the undesired homo-diarylated byproducts.

Table 5. One-pot Hetero-diarylation of Pyrrolidines[a,b]



[a]Reaction conditions: thioamide **1** (0.2 mmol, 1.0 eq), arylboronic acid-1 (0.4 mmol, 2.0 eq), $Pd(TFA)_2$ (0.02 mmol, 0.1 eq), 1,4-BQ (0.28 mmol, 1.4 eq), $KHCO_3$ (0.4 mmol, 2.0 eq), *t*-AmylOH (4.0 mL), 100 °C, 4 h then arylboronic acid-2 (0.4 mmol, 2.0 eq), 1,4-BQ (0.4 mmol, 2.0 eq), 12 h. [b]Yield after isolation by chromatography, dr determined by ^{1}H NMR.

Table 6. Arylation of *N*-Methylamines[a,b]

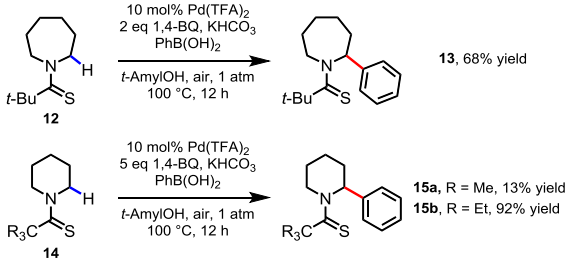


[a]Reaction conditions: thioamide **10** (0.2 mmol, 1.0 eq), arylboronic acid (0.4 mmol, 2.0 eq), $Pd(TFA)_2$ (0.02 mmol, 0.1 eq), 1,4-BQ (0.4 mmol, 2.0 eq), $KHCO_3$ (0.4 mmol, 2.0 eq), *t*-AmylOH (4.0 mL), 100 °C, 4 h. [b]Yield after isolation by chromatography. [c]1.0 eq 1,4-BQ (0.2 mmol).

In examining the reactivity of other *N*,*N*-dialkylthioamides in our α-C(sp^3)–H arylation reaction, we discovered that *N*-methyl thioamides are also competent substrates in this transformation. As shown in Table 6, a variety of *N*-methyl thioamides can be arylated to provide the corresponding benzyl thioamides in good yield (**11a-e**, 68-94% yield). The reaction of *N*-methyl thioamides with both electron-rich and electron-deficient heteroarylboronic acids can also be achieved (**11f-h**, 77-99% yield). In all cases the reaction is completely regioselective; no methylene C(sp^3)–H arylation is observed. Surprisingly, *N*-methyl anilines also undergo regioselective α-C(sp^3)–H arylation (**11i-k**, 51-75% yield) without reacting at the *ortho*-positions of the aryl group.

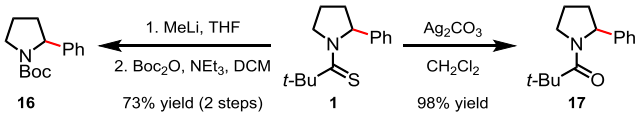
We also explored the application of our methodology to the arylation of larger azacycles. As shown in Scheme 2, azepane **12** undergoes arylation in good yield under standard reaction conditions (**13**, 68% yield). In contrast, the arylation of piperidine **14a** proceeds in poor yield, even with addition of a large excess of 1,4-BQ (**15a**, 13% yield). Further studies demonstrated that, while palladacycle formation from **14a** is facile, the rate reductive elimination is significantly slower than reductive elimination from complex **2**. As such, we hoped to optimize this transformation via the use of a more bulky thioamide directing group in order to promote reductive elimination.[18] We were pleased to find that the use of a the bulky 2,2-diethylbutanoic acid directing group (**14b**) provides the corresponding product in excellent yield without formation of any diarylated byproduct (**15b**, 92% yield).

Scheme 2. Arylation of Larger Azacycles



Lastly, these arylated products can be readily deprotected by cleavage of the thioamide to the corresponding amine with methyl lithium at 0 °C in good yield after protection as the Boc-carbamate **16** (73% yield, Scheme 3).[19] Alternatively, the thioamide **1** can be converted to amide **17** by oxidation with silver(II)-salts in nearly quantitative yield.

Scheme 3. Deprotection of Thioamide



In conclusion, we have demonstrated the α-arylation of saturated azacycles and *N*-methyl amines via Pd(II)-catalyzed C(sp^3)–H coupling with boronic acids. This method allows for highly monoselective arylation as well as sequential diastereoselective di-arylation of pyrrolidines. The successful C–H coupling of pyrrolidines with aryl boronic acids also demonstrates the first example of Pd-catalyzed cross-coupling of methylene C–H bonds with organometallic reagents.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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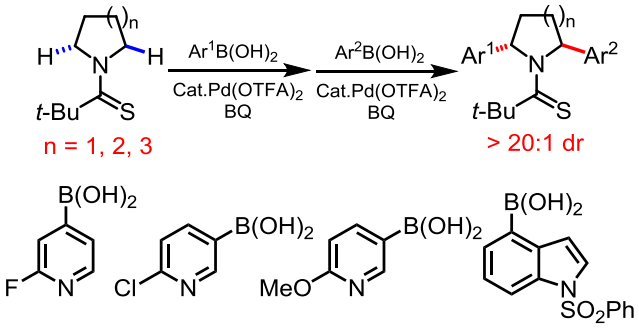
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N
H
t-Bu
S
n
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BQ
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Cat.Pd(OTFA)2
BQ
Ar1
Ar2
N
t-Bu
S
n
> 20:1 dr
B(OH)2
F
N
B(OH)2
Cl
N
B(OH)2
MeO
N
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N
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