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Expedient Synthesis of α-Heteroaryl Piperidines Using a Pd-Catalyzed Suzuki Cross-Coupling–Reduction Sequence

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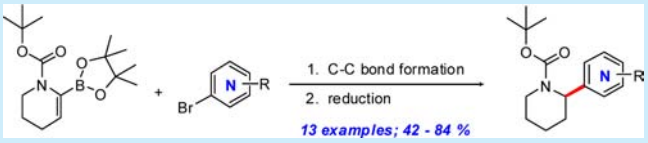
Supporting Information

ABSTRACT: A method for the modular synthesis of α-heteroaryl piperidines is reported. The two-step procedure consists of an initial Pd-catalyzed Suzuki cross-coupling of the heteroaryl bromide with a boronate ester derived from *N*-Boc piperidone, followed by subsequent tetrahydropyridine reduction. Using this method, α-heteroaryl piperidine products featuring a broad range of pharmaceutically relevant azine and diazine substitutions have been prepared.



Piperidines featuring α-aryl substitution are frequently sought after pharmacophores that are well-represented in both successfully marketed drugs and in chemical series being pursued in drug discovery (Figure 1).[1] As a result of the importance of this structural motif in pharmaceutical research,[2] the development of robust synthetic methods that allow access to a diverse scope of α-heteroaryl piperidines is a thriving area of investigation. Typically, 2-aryl piperidines are prepared through reduction of the corresponding 2-aryl pyridines under catalytic hydrogenation conditions.[1c] However, this approach is inherently limited, as the synthesis of piperidines featuring α-pyridyl substitution is not feasible due to undesired over-reduction of both pyridines. Initially the known procedures for accessing this privileged scaffold suffered from long synthetic sequences, low yields, and poor selectivity; however, there have since been several recent reports that have addressed some of these limitations.[3]

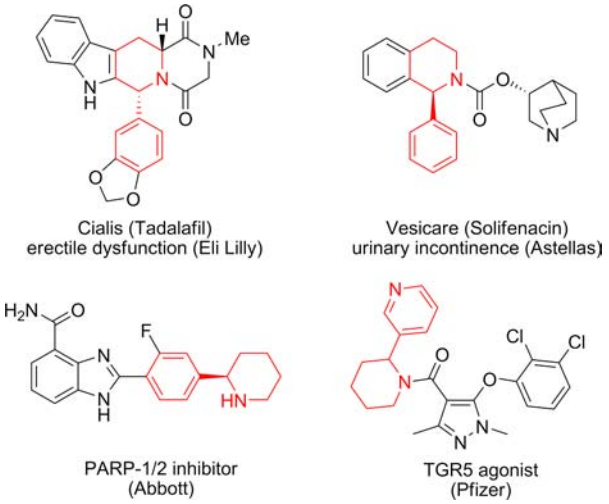
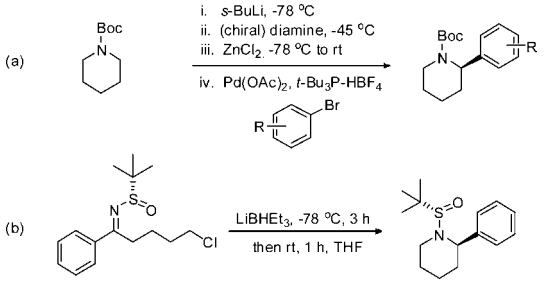


Figure 1. Selected examples of α-aryl piperidines found in biologically active compounds.

Building from the precedent set by Campos and others for the enantioselective α-arylation of *N*-Boc pyrrolidines,[4] the α-arylation of *N*-Boc piperidines with aryl bromides has been achieved by Gawley[3g] and Coldham[3i] via an α-deprotonation, transmetalation to $ZnCl_2$, and Pd-catalyzed Negishi coupling sequence (Scheme 1a). Due to the hydrolytic instability of the intermediate organolithium species, an inherent limitation of this method is the requirement for rigorously dried solvents and reagents. This necessity invariably limits the usage and success of this method in the context of rapid analogue generation for driving structure–activity relationships (SARs) in drug discovery. As an alternative approach, the diastereoselective synthesis of α-aryl pyrrolidines and piperidines by reductive cyclization of substituted *N*-sulfinyl ketimines with pendant alkyl chlorides was described by Reddy and co-workers (Scheme 1b).[3h] Despite showing excellent control of diastereoselectivity, this method incorporates the diversified aromatic moiety early in the synthetic sequence, thus introducing additional manipulations per analogue. Whereas both approaches provide powerful asymmetric syntheses of α-aryl piperidines, the ability to rapidly screen an array of heteroaromatics neither is facile nor has been described in the

Scheme 1. Alternative Syntheses of 2-Aryl Piperidines



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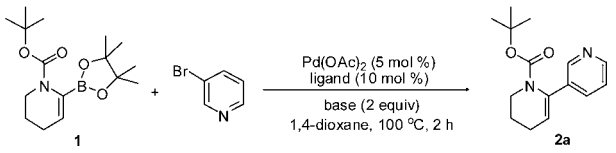
literature. Furthermore, the broad compatibility of such methods with heteroaromatic halides has yet to be demonstrated for piperidine substrates.[5] In this context, the identification of a robust method for the coupling of a versatile, bench-stable synthetic intermediate with a large feedstock of heteroaromatic halides would be ideal for rapidly exploring the chemical space associated with this privileged pharmacophore.

In surveying the literature for suitable conditions to address this limitation, we identified the δ-valerolactam derived boronate ester **1** as a promising intermediate that was poised for rapid coupling with a diverse set of heteroaromatics. The Suzuki coupling of **1** with simple substituted aryl bromides and triflates was initially developed by Occhiato and co-workers for the preparation of 2-aryl tetrahydropyridines;[6] however, attempts to extend this methodology to include heteroaromatic bromides were met with poor yields and incomplete conversions, specifically when employing 2-pyridyl bromides (<50% yield). Given this limitation and the importance of substituted azines in drug discovery, where control of lipophilicity is critical for the optimization of drug-like properties, we initiated a focused study on the development of a robust synthetic route to efficiently access these motifs. Herein, we report the optimization of a catalyst system capable of coupling a breadth of azine heteroaryl bromides to **1**, as well as conditions for the subsequent tetrahydropyridine reduction to access the desired α-heteroaryl piperidines.

Building on conditions[6b] previously reported by Occhiato and co-workers (Table 1, entry 1), we initiated our studies by

Table 1. Optimization of α-Heteroaryl Tetrahydropyridine Synthesis[a]



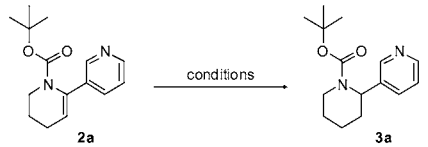
1 2a

entry	ligand	base	yield[b]
1	PPh_3	$K_3PO_4 \cdot H_2O$	61
2	PCy_3	$K_3PO_4 \cdot H_2O$	7
3	SPhos	$K_3PO_4 \cdot H_2O$	18
4	BINAP	$K_3PO_4 \cdot H_2O$	45
5	DPPF	$K_3PO_4 \cdot H_2O$	37
6	P(*o*-tolyl)$_3$	$K_3PO_4 \cdot H_2O$	22
7	P(*p*-C_6H_4OMe)$_3$	$K_3PO_4 \cdot H_2O$	63
8	P(*p*-$C_6H_4CF_3$)$_3$	$K_3PO_4 \cdot H_2O$	60
9	P(*p*-C_6H_4F)$_3$	$K_3PO_4 \cdot H_2O$	72
10	P(C_6F_5)$_3$	$K_3PO_4 \cdot H_2O$	<5
11	P(*p*-C_6H_4F)$_3$	Na_2CO_3 (2 M, aq)	24
12	P(*p*-C_6H_4F)$_3$	$CsOH \cdot H_2O$	83
13[c]	**P(*p*-C_6H_4F)$_3$**	**$CsOH \cdot H_2O$**	**>95 (91)**[d]

[a]Conditions: **1**/ArBr/base = 1:1.5:2 (0.11 mmol scale), 5 mol % [Pd], Pd/L = 1:2, [**1**] = 0.2 M in 1,4-dioxane at 100 °C for 2 h. [b]Yield determined by ^{1}H NMR relative to 2,6-dimethoxytoluene as an internal standard. [c]Toluene used in place of 1,4-dioxane as solvent. [d]Isolated yield of **2a** using a 0.3 mmol scale of **1**.

evaluating a series of related triarylphosphine ligands with subtle steric and electronic differences for the Pd-catalyzed Suzuki coupling of vinyl boronate **1** with 3-bromopyridine, employing 5 mol % $Pd(OAc)_2$ and 10 mol % ligand with $K_3PO_4 \cdot H_2O$ (2 equiv) at 100 °C in 1,4-dioxane for 2 h (Table 1). Initial attempts to improve the yield of **2a** by using ligands with established success in challenging Suzuki cross-coupling reactions,[7] such as electron-rich phosphines (PCy_3 and SPhos) or bidentate phosphines (BINAP and DPPF), provided inferior yields of product (entries 2−5; 7−45%). The use of P(*o*-tolyl)$_3$, a ligand with a larger steric profile, showed a significant drop in yield when compared with PPh_3 (Table 1, entry 1 vs 6). Eventually, it was observed that improvements in yield showed a more subtle reliance on the electronic features of the triarylphosphine ligands employed. Whereas the use of *p*-OMe- and *p*-CF_3-substituted triarylphosphines showed similar yields of **2a** to that observed for PPh_3 (entries 7 and 8), a modest increase in yield to 72% was achieved when employing P(*p*-C_6H_4F)$_3$ (entry 9). In contrast, moving to the perfluorinated ligand, P(C_6F_5)$_3$, showed a dramatic decrease in yield (entry 10). After further investigation into base and solvent effects (entries 11−13),[8] we identified that the combination of $Pd(OAc)_2$ and P(*p*-C_6H_4F)$_3$ in toluene solvent with $CsOH \cdot H_2O$ as the base provided near-quantitative conversion of **1** to tetrahydropyridine **2a**.[9,10] Finally, the successful reduction of **2a** to the desired α-pyridyl piperidine **3a** was realized using either catalytic hydrogenation under H_2 or transfer hydrogenation conditions (Scheme 2).

Scheme 2. Tetrahydropyridine Reduction Conditions[a]



2a 3a

a. 10 wt % Pd/C, H_2 (50 psi), EtOH, rt, 6 h; 74%
b. 10 wt % Pd/C, $HSiEt_3$ (20 equiv), MeOH, rt, 6 h; 88%
c. 10 wt % Pd/C, NH_4CO_2H (20 equiv), EtOH, 65 °C, 6 h; 94%

[a]Yield determined by ^{1}H NMR relative to 2,6-dimethoxytoluene as an internal standard.

Having defined a highly effective two-step sequence for the preparation of **3a**, a selection of other azine heteroaryl bromides was pursued to highlight the scope of α-heteroaryl piperidine synthesis using this method (Scheme 3). Other 3-pyridyl bromide substrates featuring pyrrolidinyl (**3b**) and methyl ester (**3c**) substitutions were successful in generating the desired piperidines (60 and 44% yield respectively). In addition, the use of 2- and 4-pyridyl substrates with electron-donating methoxy (**3d**) or electron-withdrawing fluoro (**3f**) and trifluoromethyl (**3e**, **3g**) groups was also tolerated using the optimized conditions. Using the two-step protocol, the α-diazine piperidines derived from 2-bromo-5-methylpyrazine (**3h**), 4-bromopyridazine (**3i**), and 5-bromopyrimidine (**3j**) were isolated in good yields following reduction (48−76% yield). In addition to substituted pyridines, the two-step procedure also translated well to related fused heteroaromatic substrates, such as quinoline (**3k**), isoquinoline (**3l**), and azaindole (**3m**) providing the desired piperidines in good yields (66−78% yield). Importantly, this method provides a robust strategy for accessing α-azine piperidines, which would otherwise be incompatible with standard 2-aryl pyridine reduction approaches.[1c]

In summary, we have developed a facile method for the synthesis of α-heteroaryl piperidines by enabling a robust two-step procedure involving initial Suzuki cross-coupling of lactam-derived boronate **1** with a variety of azine heteroaryl bromides and subsequent tetrahydropyridine reduction. Importantly, a

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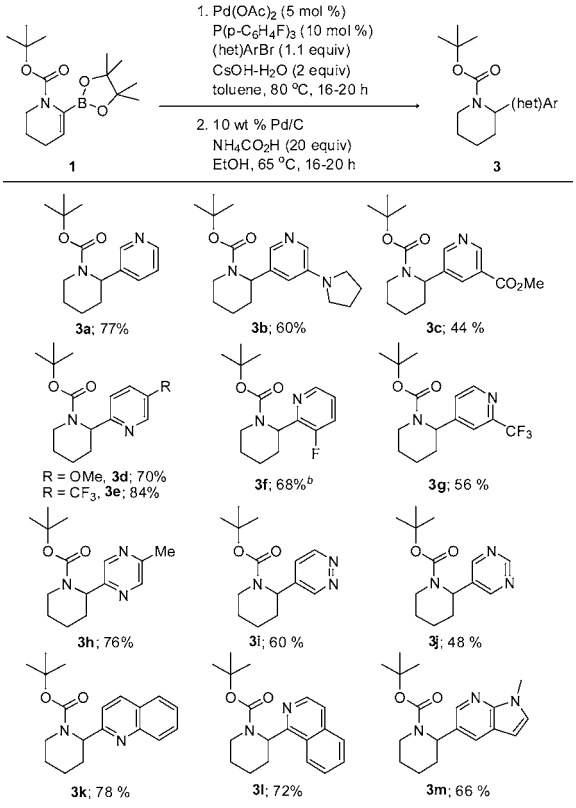
Scheme 3. Scope of α-Heteroaryl Piperidine Synthesis[a]



[a]Isolated yields. [b] Reduction conditions: 10 wt % Pd/C, H_2 (50 psi), EtOH, rt, 16 h.

broad range of pharmaceutically relevant azine and diazine substrates were shown to be compatible with this method. In view of the stability of the boronate ester and the ease of reaction setup, this protocol is a useful and practical synthetic sequence that should help fuel rapid SAR studies around this important pharmacophore in drug discovery programs.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) Notably, the use PPh_3 with the optimized base ($CsOH·H_2O$) and solvent (toluene) also provided improved results, affording **2a** in quantitative yield (^{1}H NMR).