Homogeneous Catalysis

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Ligand-Enabled Catalytic C–H Arylation of Aliphatic Amines by a Four-Membered-Ring Cyclopalladation Pathway

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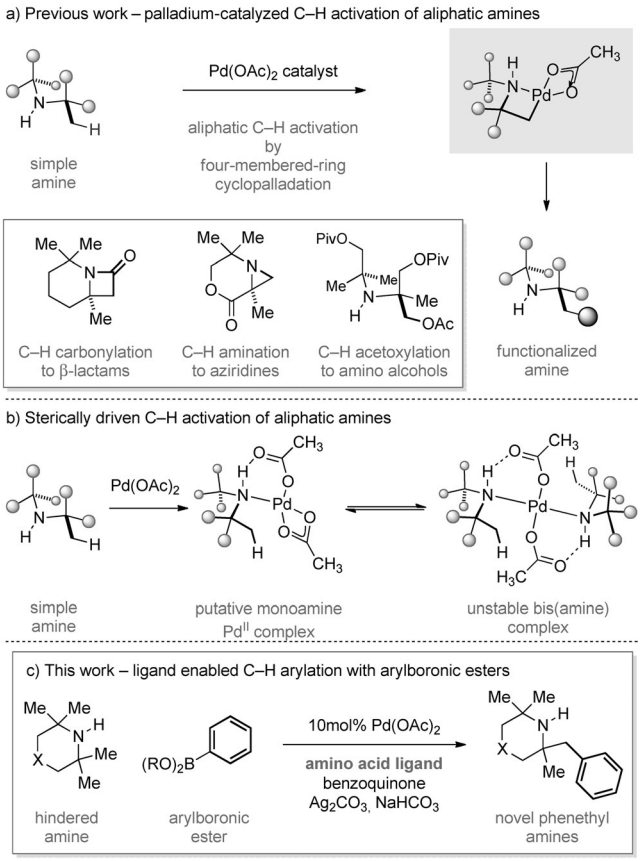
Abstract: *A palladium-catalyzed C–H arylation of aliphatic amines with arylboronic esters is described, proceeding through a four-membered-ring cyclopalladation pathway. Crucial to the successful outcome of this reaction is the action of an amino-acid-derived ligand. A range of hindered secondary amines and arylboronic esters are compatible with this process and the products of the arylation can be advanced to complex polycyclic molecules by sequential C–H activation reactions.*

The development of new catalytic methods which enable the functionalization of aliphatic C–H bonds is an important challenge to the continued advance of chemical synthesis.[1,2] Central to many of the developments in this area is the facilitating role of polar functional groups which steer the C–H bond cleavage by a process called cyclometallation.[3] Among many elegant developments, palladium-catalyzed aliphatic C–H activation directed by synthetically versatile functionalities such as carboxylic acid derivatives,[4] hydroxy motifs,[5] and oximes[6] have been the focus of most attention, and have delivered numerous new transformations through a variety of activation modes. In contrast, the use of the amine functionality as a directing group for cyclopalladation is less common,[3b,7] and is surprising given their importance to the function of biologically relevant molecules, and most successful cases require protecting groups or auxiliaries to modulate the metal-binding properties of the nucleophilic nitrogen motif.[8] As a result, catalytic strategies for the C–H activation of aliphatic amines remain underdeveloped.

Recently, we reported that secondary aliphatic amines can undergo C–H activation through a distinct four-membered-ring cyclopalladation pathway (Scheme 1a).[9] Key to the success of this unusual C–H activation is the steric hindrance around the secondary amine motif. We believe these interactions promote the formation of the putative monoamine/Pd^{II} complex as a result of destabilizing the usually more favorable bis(amine) palladium complex (Scheme 1b). This novel activation process enabled the development of catalytic C–H carbonylation and C–H amination processes to strained nitrogen heterocycles and C–H acetoxylation to amino alcohol derivatives (Scheme 1a). As part of the evolution of this distinct C–H activation mode we questioned whether we could expand the toolbox of direct functionalization reactions to an arylation process.[4a,10] In addition, the novel products would represent highly substituted variants of the biologically relevant phenthylamine scaffold.[11]



Scheme 1. Palladium-catalyzed C–H activation of aliphatic amines.

Herein, we report the development of a palladium-catalyzed C–H arylation of secondary aliphatic amines with arylboronic esters (Scheme 1c). Crucial to the successful outcome of this reaction is an amino-acid ligand for the palladium catalyst,[12] and it also underpins preliminary studies towards enantioselective reaction. Furthermore, the arylated products provide a platform for further catalytic C–H activation reactions to readily generate previously unexplored complex amines, which could be attractive to practitioners of medicinal chemistry.

At the outset of our studies, stoichiometric reactions between a preformed hindered amine cyclopalladation complex (**1**) and various organoboron reagents were investigated using *t*-amyl alcohol as a solvent (Scheme 2). We found that the desired reaction, to give **3a**, was observed with both

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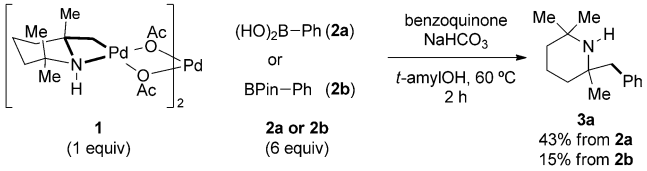
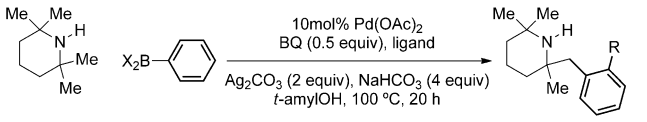


Scheme 2. Initial screening for arylation. PhBPin = phenylboronic acid pinacol ester.

$PhB(OH)_2$ (**2a**) and PhBPin (**2b**) in the presence of benzoquinone and sodium hydrogen carbonate. Even though the yields were low, we were encouraged to find that the arylation process was viable.

Initial catalytic conditions were examined with 10 mol% of $Pd(OAc)_2$ and Ag_2CO_3 as the oxidant and were based on reaction conditions originally reported by Yu et al. (Table 1).[13] Despite initial failure using **2a**, we did find that

Table 1: Selected optimization for C–H arylation.



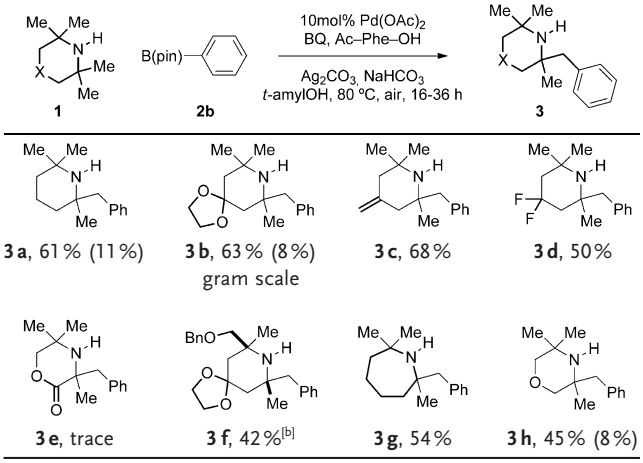
Entry	**1a** (equiv)	**2** (equiv)	**5** (20 mol%)	Yield [%][a] **3a**	**4a**
1	1.0	**2a** (1.5)	none	0	0
2	1.0	**2b** (1.5)	none	3	0
3	1.0	**2b** (1.5)	Ac-Gly-OH (**5a**)	33	19
4	1.0	**2b** (1.5)	Ac-Val-OH (**5b**)	34	21
5	1.0	**2b** (1.5)	Ac-Leu-OH (**5c**)	35	19
6	2.0	**2b** (1.0)	Ac-Gly-OH (**5a**)	50	7
7	2.0	**2b** (1.0)	Ac-Val-OH (**5b**)	56	10
8	2.0	**2b** (1.0)	Ac-Leu-OH (**5c**)	53	10
9[b]	2.0	**2b** (1.0)	Ac-Phe-OH (**5d**)	61	11

[a] Yield determined by GC or ^1H NMR analysis using triphenylmethane as an internal standard. [b] Reaction at 80 °C. BQ = benzoquinone.

the reaction of **2b** in combination with amino-acid derivatives, recently introduced by Yu and co-workers as enabling ligands for C–H activation with palladium complexes,[12] showed a dramatic improvement in conversion into the desired product **3a** (entries 3–5). In addition, we also observed significant quantities of the corresponding diarylation product **4a**, where the second arylation takes place on the *ortho* sp^2-carbon atom of the new phenyl group. However, by changing the stoichiometry of the reaction and an extensive screen of reaction parameters (see the Supporting Information for details), optimal reaction conditions were found to involve the use of *N*-acetyl phenylalanine as a ligand to produce arylated amine **3a** in 61% yield (entries 6–9).

In assessing the scope of the catalytic reaction, we found that a modest range of readily available amine derivatives were suitable substrates for the C–H arylation (Table 2). Besides the standard piperidine derivatives (**3a**,**b**), methylenepiperidine (**3c**), and fluorinated piperidine (**3d**) derivatives could also be readily tolerated to yield 50% to 68%. It is

Table 2: Scope of amine phenylation.[a]



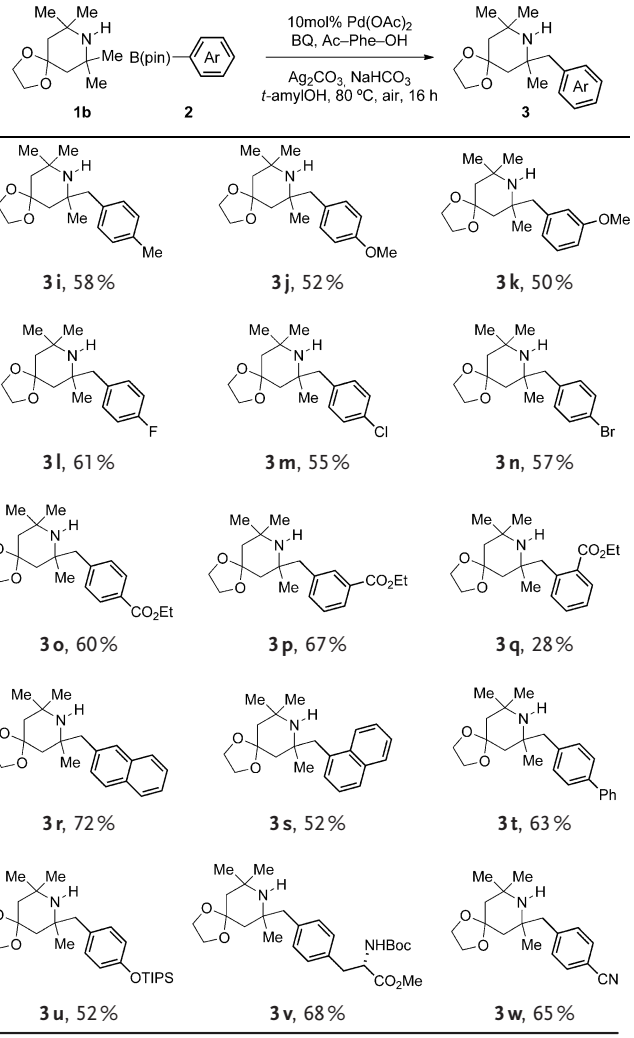
[a] Yields are of isolated products. Yields in brackets are those of the diarylation products. [b] 1.36:1 mixture of regioisomers observed. The other isomer results from arylation on the methyl group closest to the CH_2OBn. See the Supporting Information for details.

noteworthy that the gram-scale reaction starting from 10 mmol **2b** could produce 1.73 grams of the monoarylation product **3b**. Surprisingly, almost no reaction was seen with the morpholinone derivative (to form **3e**), despite our previous success with this type of amine, and acyclic and less-hindered amines were unreactive under these reaction conditions.[14] However, we were pleased to find that a functionalized piperidine derivative (**3f**), a seven-membered-ring azepine (**3g**), and a morpholine scaffold (**3h**), all productively form the corresponding arylated products, and constitute hindered and previously unexplored variants of the pharmaceutically relevant phenethyl amine motif.

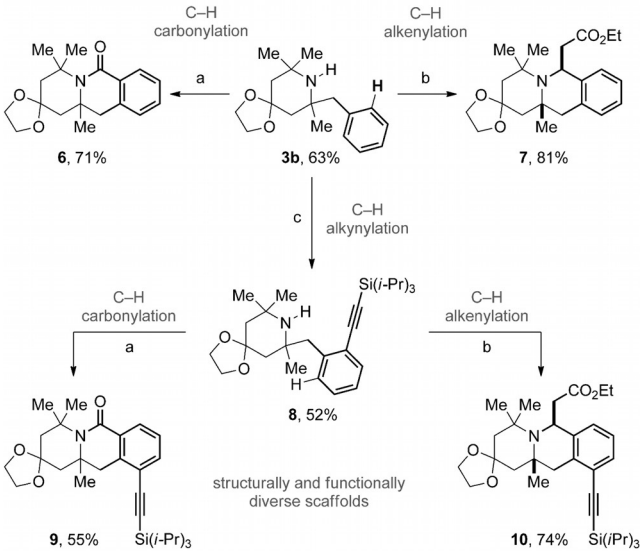
The reaction was readily extended to a variety of arylboronic acid pinacol esters (ArBPins) in good yields (Table 3). ArBPins with substituents at the *meta* (**3k**,**p**) and *para* (**3i**,**j**, **3l–o**, **3t–w**) positions of the aromatic ring afforded the desired products in good yields, while the *ortho* substituents lowered the reactivity (**3q**), presumably because of a deleterious steric effect. Both electron-withdrawing and electron-donating groups on the aromatic ring of ArBPins were well tolerated, and ArBPins displaying halogen substituents could also be introduced to give the desired arylation products (**3l–n**). Extended aromatic groups (**3r–t**) as well as more functionally complex ArBPins could also be transformed into the amine scaffold (**3u**,**v**). Unfortunately, heteroarylboronates that contained pyridine- or thiophene-type motifs were unreactive under these reaction conditions.

To increase the complexity of the arylamine products generated from this reaction we sought to exploit the pathway through which the diarylation side product (**4**) was formed. We questioned whether the previously deleterious second cyclopalladation pathway could be harnessed to enable a subsequent C–H activation event with a different coupling partner. Towards this end, we found that C–H carbonylation,[15] C–H alkenylation,[16] and C–H alkynylation[17] reactions of **3b** successfully led to functionalization on the *ortho*-position of the newly installed phenyl group, thus forming a range of architecturally complex scaffolds

Table 3: Scope of aryl transfer.[a]

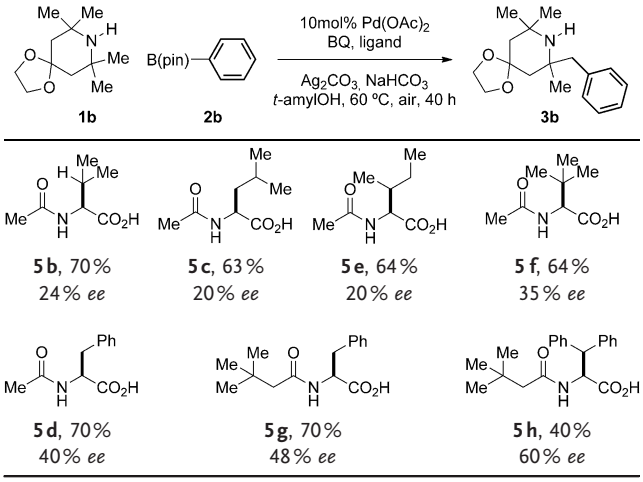


[a] Yields are those of the isolated products. Boc = *tert*-butoxycarbonyl, TIPS = triisopropylsilyl.



Scheme 3. Sequential C–H activation. Reagents and conditions: a) 10 mol% $Pd(OAc)_2$, CO (1 atm), AgOAc, PhMe, 110 °C, 48 h; b) 10 mol% $Pd(OAc)_2$, ethyl acrylate, Ag_2CO_3, PivOH, DCE, 120 °C, air, 48 h; c) 10 mol% $Pd(OAc)_2$, (bromoethynyl)triisopropulsilane, biphenyl-2-carboxylic acid, $KHCO_3$, DCE, 100 °C, N_2, 24 h. DCE = 1,2-dichloroethane.

Table 4: Towards enantioselective C–H arylation.[a]



[a] See the Supporting Information for details. Yield determined by ^1H NMR analysis using triphenylmethane as an internal standard.

(Scheme 3; **6**–**8**). Moreover, we could extend this sequential strategy further by performing either C–H carbonylation or C–H alkenylation on the amine **8** to form the polycyclic amine products **9** and **10**. Taken together, these sequential C–H activation processes provide direct access to a structural and functionally diverse series of complex amine products prepared in only three steps from a readily available amine starting material.[18]

Finally, we investigated the potential for an asymmetric C–H arylation on the basis that Yu et al. have provided numerous examples wherein the amino-acid-derived ligands can provide asymmetric induction.[19] We screened a range of amino-acid ligands under similar reaction conditions (at 60 rather than 80 °C) and a selection of the ligands assessed is shown in Table 4 (see the Supporting Information for more details). We found that the L-phenylalanine-derived ligand **5d** gave the best yield and a maximum enantiomeric excess of 40%. Interestingly, only *N*-acyl substituents displayed any reactivity, and we found that increasing the bulk of the *N*-acyl group resulted in a modest improvement to 48% *ee* (**5g**). Further improvement was gained by changing the amino acid to a β-phenyl-phenylalanine combined with the bulky acyl side chain, and thus a 60% *ee* was obtained (**5h**). At this stage, we need further mechanistic evidence to help us rationally design new ligands for this enantioselective transformation, but the results presented herein represent a rare example of catalytic enantioselective arylation and provide an exciting starting point for further development.[20]

In summary, we have developed a new palladium-catalyzed C–H arylation of aliphatic amines. Central to the success of this reaction is the presence of amino-acid-derived

ligands. The process works for a variety of hindered amines and arylboronic esters to generate novel cyclic arylated amines. We believe that this palladium-catalyzed C–H functionalization proceeds through a four-membered-ring cyclometallation pathway and we have demonstrated the basis of a catalytic enantioselective reaction. Furthermore, linking the C(sp^3)–H arylation and iterative divergent C-(sp^2)–H functionalization reactions provides a facile and straightforward tactic for the rapid construction of complex molecules.

Experimental Section

General procedure for the catalytic C–H arylation: In a 10 mL vial equipped with stir bar, arylboronic acid pinacol ester (0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), Ac-(L)-Phe-OH (8.3 mg, 0.04 mmol), $NaHCO_3$ (67.3 mg, 0.8 mmol), Ag_2CO_3 (110.3 mg, 0.4 mmol), and 1,4-benzoquinone (10.8 mg, 0.1 mmol) were combined, followed by the addition of *t*-amyl-OH (1 mL) and amine substrates (0.4 mmol). Then the vial was sealed under air with a screw cap and a Teflon septum, placed in a preheated oil bath at the described temperature, and stirred for the stated time. The reaction mixture was cooled to room temperature and filtered through celite by eluting with ethyl acetate. The filtrates were further filtered through SCX-2 by eluting with methanol and then an ammonia methanol solution (1M). The ammonia methanol solution filtrate was concentrated in vacuo to recover the amine compounds from the crude reaction mixture. The mixture of amines was then purified by flash column chromatography (Et_3N washed silica gel column) under the stated conditions to provide the pure arylation product.

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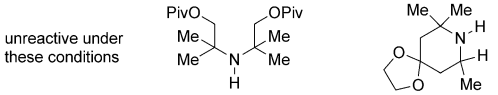
[14] Acyclic and less-hindered amines did not undergo arylation.



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