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Remote Functionalization: Palladium-Catalyzed C5(sp3)-H Arylation of 1-Boc-3-aminopiperidine through the Use of a Bidentate Directing Group — Source link

Ben F. Van Steijvoort, Nadya Kaval, Artem A. Kulago, Bert U. W. Maes

Institutions: University of Antwerp

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Ben F. Van Steijvoort, Nadya Kaval, Artem A. Kulago and Bert U. W. Maes*

In honor of Miha Tišler's 90th birthday

Organic Synthesis, Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, B-2020, Antwerp, Belgium

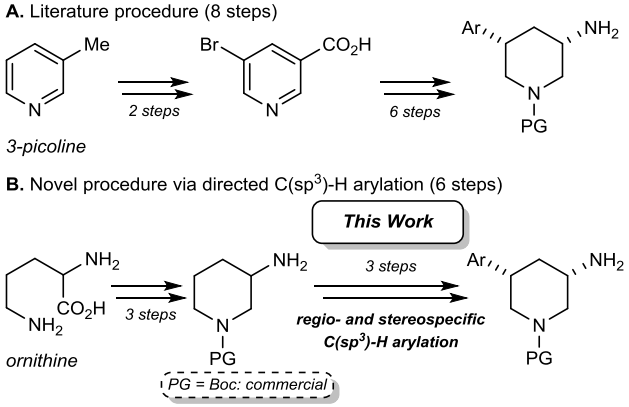
ABSTRACT: A protocol for the Pd-catalyzed C5(sp^3)-H arylation of readily available 1-Boc-3-(picolinoylamino)piperidine with iodo(hetero)arenes is reported. The substrate can be obtained from a biorenewable feedstock, namely *L*-arginine. The use of the right N1 protective group is decisive to get arylation. The addition of a catalytic amount of 2,6-dimethylbenzoic acid and performing the reaction at high concentration are important to achieve a high conversion and yield. The procedure gives arylated 1-Boc-3-(picolinoylamino)piperidines in a regiospecific (C5) and stereospecific (cis) manner. Orthogonal cleavage of the amide over the carbamate group allows one to further selectively derivatize the amino moieties of the piperidine scaffold.

KEYWORDS: C(sp^3)-H activation, regiospecific, stereospecific, cyclic amine, palladium catalysis, biorenewable

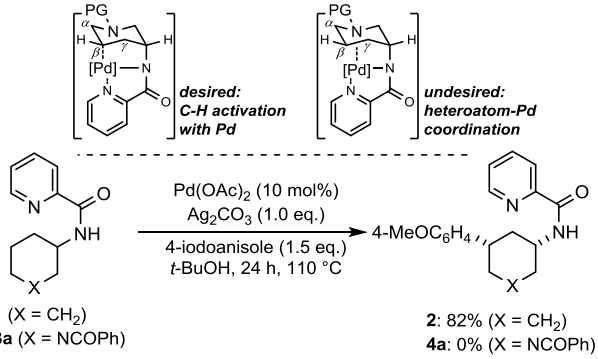
Substituted saturated cyclic amines constitute an important and valuable core structural motif in a wide range of biologically active molecules of natural and synthetic origin.[1] Within this substrate class, C-substituted piperidines form a particularly interesting group based on their prevalence in top-selling APIs, such as methylphenidate, fentanyl and paliperidone (7 examples in top 100 in 2013).[2] To date, few methodologies exist to synthesize β-arylated piperidines. Most reported procedures are based on functionalization via a cross-coupling reaction involving the corresponding β-(pseudo)halo- or metalated piperidines.[3] In addition, these protocols generally involve the use of a strong base and are therefore not directly applicable on (protected) aminopiperidines. The direct C(sp^3)-H functionalization of the piperidine scaffold is only poorly explored and most research has focused on α-arylation.[4,5] β-C(sp^3)-H arylation in pipecolinic acid has been reported via the installation of a removable directing group (DG)[6] through amide formation with 8-aminoquinoline or $CF_3C_4F_4NH_2$.[7] This was extended to γ-C(sp^3)-H arylation via the use of regioisomeric piperidine-3-carboxylic acid using the same concept.[7b] These DGs allow arylation (C3 or C4), though stereospecificity has only been accomplished with the DG at C2. While our work was in progress, one example of γ-arylation on piperidine was reported using a $CF_3C_4F_4NH_2$-based DG on N1.[8] This is the first example featuring remote directed functionalization in piperidines. The described C4-arylation requires 30 equiv of ArI, indicating the challenging nature of remote functionalization of saturated heterocycles. We wondered whether C5(sp^3)-H arylation could be achieved with a DG at C3. Readily available N1-protected 3-aminopiperidines could be equipped with a bidentate DG via amide formation with 2-picolinic acid and used as substrates in a direct C5(sp^3)-H arylation to access the corresponding 3,5-disubstituted piperidines. 5-Arylated 3-aminopiperidine derivatives are promising building blocks for drug discovery, as has been shown by their reported biological activities (ERK inhibitors and PAR-1 antagonists).[9] Moreover, an aminopiperidine fragment can be found in a

high number of natural products and APIs.[10] Additionally, this fragment introduces a high degree of three-dimentionality, which further increases its medicinal relevance.[11] The classical approach to prepare these molecules involves 5-bromonicotinic acid and starts from 3-picoline, and the amino moiety is only formed in a late stage (Scheme 1A).[12] Generally, a variety of methods has been reported for the synthesis of substituted 3-aminopiperidines, but these are typically lenghty or do not deliver the desired stereoselectivity.[13] Our approach is based on unsubstituted 3-aminopiperidine, which can be obtained from ornithine, by lactamization and subsequent reduction (Scheme 1B).[14] *L*-Ornithine can easily be accessed from naturally occurring *L*-arginine by hydrolysis and allows for the formation of enantiopure (3*S*)-3-aminopiperidine and, consequently, the exploitation of the chiral pool.[15] In fact, both enantiomers can be obtained from *L*-arginine.[16] Besides the renewable aspect, the classical approach is also more elaborate requiring eight steps versus six steps. As the aryl introduction step involves 5-bromonicotinic acid (step 3 of 8) versus N1-protected 3-(picolinoylamino)piperidine (step 5 of 6), the new route is also more attractive for library design, where such variation preferentially occurs at a late stage in the synthetic pathway.

Scheme 1. Synthetic Approaches toward 1-Protected 3-Amino-5-arylpiperidines



Scheme 2. Direct C5-Arylation of Cyclohexylamine 1 and 3-Aminopiperidine 3a Equipped with a Picolinoyl Group

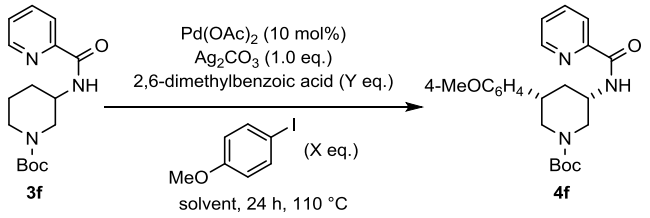


As a starting point, a literature protocol involving the use of a picolinoylamino DG[17] was selected because of its previously reported success on saturated carbocycles, namely, cyclohexylamine **1**.[18] Interestingly, no directed C5(sp^3)-H functionalization on 3-substituted

saturated heterocycles, such as cyclic amines, has hitherto been reported. Due to the coordinating properties of the heteroatom, heterocycles are considered challenging substrates for transition-metal catalysis, in comparison to the corresponding carbocycles.[19] When 3-aminopiperidine substrate **3a**, carrying a benzoyl protective group (PG) at N1 and a picolinoylamino DG at C3, was subjected to these literature conditions, no reaction product **4a** was formed (Scheme 2). This exemplifies the detrimental influence which a methylene-to-N−PG replacement can have on the reaction. We hypothesized that the PG has an effect on the arylation reaction through intramolecular coordination potentially blocking catalysis, and therefore opted to test a representative set of PGs, avoiding or at least reducing such unfavorable interaction (see the Supporting Information (SI)). Both benzyl- and carbamoyl- type groups also did not yield any reaction product. However, when a pivaloyl or a tosyl group was used, C5-arylated product was formed in ~20% yield (25%−29% conversion of substrate). Finally, a variety of alkoxycarbonyl groups was screened, giving a conversion of substrate **3** of 10%−70% and delivering the desired reaction product **4** in 7%−43% yield. Clearly, changing the PG on the piperidine nitrogen atom has a significant effect on the efficiency of the reaction. Based on the obtained results, a Boc PG was selected for further optimization (43% yield, 70% conversion). In addition, 1-Boc-3-aminopiperidine is commercially available. Other Ag salts were considered, but Ag_2CO_3 gave the highest conversion and yield, and was selected for further studies (see the SI). The effect of substituents on the pyridine moiety of the DG (4-OMe, 5-CF_3, 5-NO_2) were subsequently investigated (see the SI).[18a] Although conversion was noted in all cases, no improvement in yield was observed and the unsubstituted pyridine was therefore retained for further optimization. Next, the effect of a carboxylic acid additive on the conversion was explored as such species are believed to play a key role in C−H activation (concerted palladation-deprotonation).[20] Thus, a variety of aliphatic and aromatic acids were screened (see the SI). The addition of 2,6-dimethylbenzoic acid proved to be the most optimal, as an increase of more than 20% in mass balance and yield of **4f** was noted (Table 1, entries 1 and 2). Solvents other than *t*-BuOH were also studied, but they did not deliver a better result (entries 3 and 4). Interestingly, omitting the solvent altogether did not hinder the reaction, as an analogous conversion (71%) was found, although a higher aryl halide loading was employed to allow for a homogeneous reaction mixture (entries 2 and 5). Increasing the reaction temperature from 110 °C to 120 °C did not improve the conversion when *t*-BuOH was used as solvent (entries 2 and 6), but the same variation under solvent-free conditions showed a notable increase in yield of **4f** from 69% to 81% (entries 5 and 7). At this stage, the acid additive effect was rescreened, and its important role in the reaction was confirmed (entries 7 and 8). In pursuit of achieving a full conversion, the 4-iodoanisole loading was increased further (entries 9−14). In parallel with this modification, the amount of acid additive was reduced and ultimately 0.25 equiv was found to be optimal without significant loss of conversion and product yield (entries 12−14). Finally, the use of 6.0 equiv of 4-iodoanisole and 0.25 equiv of 2,6-dimethylbenzoic acid were found to be optimal, delivering **4f** in 98% ^{1}H NMR and 78% isolated yield, with full conversion of substrate **3f** (entry 13). Interestingly, only one diastereoisomer was isolated.

At this point, several PGs were re-evaluated (see the SI). Although an increased conversion was noted for all cases, none delivered a better result in comparison with a Boc. Applying an excess of the 4-iodoanisole coupling partner, acting as both reagent and solvent, proved to be an elegant way to achieve conversion of the remaining amount of **3f** (19%) toward the desired C5-arylated reaction product **4f** (entries 7 and 13).

Table 1. Optimization of the Direct Pd-Catalyzed C5-Arylation of 1-Boc-3-(picolinoylamino)piperidine (3f) with 4-Iodoanisole[a]



entry	Halide, *X* (equiv)	Acid, *Y* (equiv)	solvent	^{1}H NMR yield (%)[b]	
				3f	**4f**
1	1.5	-	*t*-BuOH	30	43
2	1.5	1.0	*t*-BuOH	29	66
3	1.5	1.0	*t*-AmOH	37	54
4	1.5	1.0	toluene	54	44
5	3.0	1.0	-	29	69
6[c]	1.5	1.0	*t*-BuOH	33	66
7[c]	3.0	1.0	-	19	81
8[c]	3.0	-	-	37	62
9[c]	5.0	1.0	-	15 (6)	85 (70)
10[c]	5.0	0.5	-	12	81
11[c]	5.0	-	-	31	67
12[c]	6.0	0.5	-	8 (0)	90 (80)
13[c]	**6.0**	**0.25**	-	**0 (0)**	**98 (78)**
14[c]	6.0	-	-	20	73

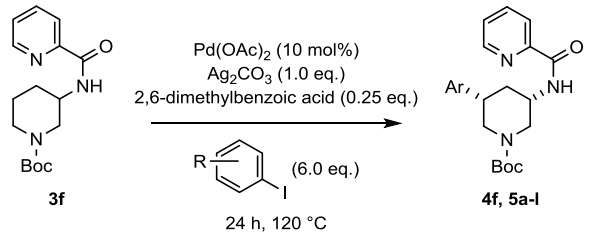
[a] All reactions were performed on 0.4 mmol scale of **3f**. [b] Crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard; isolated yields are given in parentheses. [c] Reaction was performed at 120 °C.

The use of an excess of reagent is no drawback, as 81% of the unreacted 4-iodoanisole could be easily recovered during purification. This recovery is straightforward due to the significantly lower polarity of the aryl iodide versus the reaction product, allowing for a fast and first elution (see the SI). A recovery of 81% implies that only 1.95 equiv are effectively used in the functionalization process.

The aryl iodide scope was subsequently evaluated applying the optimized reaction conditions (Table 2). Gratifyingly, the newly developed synthetic protocol could be successfully applied to

aryl iodides featuring different substituents in the 3- and 4-positions, delivering the corresponding cis reaction products **4f, 5a–l** in moderate to good yields. Both the incorporation of electron-donating (entries 1-4) and electron-withdrawing (entries 11 and 12) substituents was found to be compatible. Only when a CF_3 moiety was present, was a higher aryl halide loading (8.0 equiv) necessary to obtain a satisfactory result (entry 13). Furthermore, the use of halogen groups (bromo, chloro, and fluoro) delivered the desired products **5e–h** without loss of the halide functionality (entries 6-9), allowing one to further post-derivatize these building blocks. Only 2-substituted aryl iodides were found to be incompatible with the developed protocol as exemplified for 1-chloro-2-iodobenzene, presumably due to steric hindrance (entry 10).

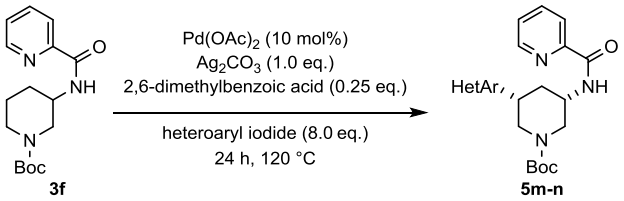
Table 2. Reaction Scope for the Direct Pd-Catalyzed C5-Arylation of 1-Boc-3-(picolinoylamino)piperidine (3f) Using Aryl Iodides[a]

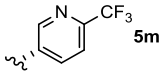
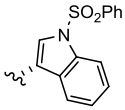


entry	R	product	yield (%)	aryl iodide recovery[b] (%)
1	4-OMe	**4f**	78	81
2	3-OMe	**5a**	68	76
3	4-*t*-Bu	**5b**	70	90
4	4-Me	**5c**	65	55
5	H	**5d**	71	3
6	4-Cl	**5e**	72	80
7	4-Br	**5f**	63	80
8	4-F	**5g**	70	30
9	3-Cl	**5h**	60	37
10[c]	2-Cl	**5i**	(9)	N. D.
11	4-CO_2Me	**5j**	67	75
12	3-CO_2Et	**5k**	62	75
13[d]	4-CF_3	**5l**	71	70
14[e]	4-OMe	**(3*S*,5*S*)-4f**	82	83

[a] All reactions were performed on 0.4 mmol scale of **3f**. [b] Based on the maximum theoretical amount of ArI remaining (5.0 equiv). [c] Screened yield using 1,3,5-trimethoxybenzene as an internal standard. [d] 8.0 equiv of 4-iodobenzotrifluoride were used (the use of 6.0 equiv resulted in 48% **5l** and 22% **3f**). [e] **(3*S*)-3f** was used as substrate. N. D. = not determined.

Table 3. Reaction Scope for the Direct Pd-Catalyzed C5-Heteroarylation of 1-Boc-3-(picolinoylamino)piperidine (3f) Using Heteroaryl Iodides[a]



entry	product	yield (%)	aryl iodide recovery[b] (%)
1	 **5m**	72	84
2[c]	 **5n**	71	95

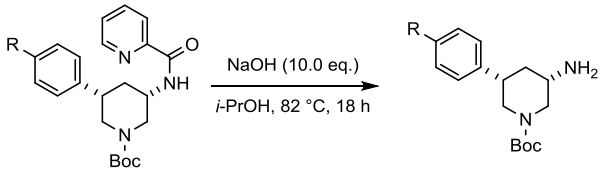
[a] All reactions were performed on 0.4 mmol scale of **3f**. [b] Based on the maximum theoretical amount of ArI remaining (7.0 equiv). [c] *t*-BuOH was used as solvent.

Finally, the arylation of (3*S*)-1-Boc-3-(picolinoylamino)piperidine (**(3*S*)-3f**) with 4-iodoanisole was attempted (entry 14). Herein, enantiopure (3*S*,5*S*)-C5-arylated product **(3*S*,5*S*)-4f** was obtained via diastereospecific arylation demonstrating the real potential of the reported procedure, with respect to the chiral pool (*L*-arginine). Interestingly, 70%−80% of the excess aryl iodide coupling partner was usually recovered during chromatography (Table 2). As observed for **4f**, the ArI elutes fast and first in all cases, allowing for an easy recovery. Moreover, 70−80% of the ArI recovered implies that only 2.5-2.0 equiv are effectively used in the arylation reaction. Only iodo- (entry 5), 1-fluoro-4-iodo- (entry 8), and 1-chloro-3-iodobenzene (entry 9) give a substantially lower recuperation. This is presumably due to their relatively high volatility giving losses during the work up involving rotary evaporation. Challenging heteroaryl iodides were also investigated as coupling partners (Table 3). A first attempt involving 3-iodopyridine did not deliver any desired product, most likely owing to the strong coordinating properties of the pyridine nitrogen towards our Pd-catalyst. We wondered if the use of a less coordinating 3-iodopyridine derivative, carrying an electron-withdrawing substituent such as a trifluoromethyl group at the C2-position, would be more suitable for our arylation protocol. Gratifyingly, this modification allowed for a smooth reaction and delivered **5m** in 72% yield. Additionally, we tested an electron rich azole type system. N-protected 3-iodoindole gave product **5n** in 71% yield. It is noteworthy that both examples also allowed for efficient recovery of the unreacted heteroaryl iodide.

With the new synthetic protocol for direct arylation of the 3-aminopiperidine scaffold in hand, we turned our attention towards the selective removal of the picolinoyl group. Reaction products **4f** and **5l** were selected for this purpose (Scheme 3).

Sodium hydroxide in isopropanol at 82 °C provided smooth amide cleavage without loss of the Boc group.[18b] The corresponding 1-Boc-3-amino-5-arylpiperidines **6** and **7** were obtained as the sole reaction products in good yield. This strategy provides valuable building blocks for further post-functionalization at the C3 amino and N1 (via Boc deprotection) moieties.

Scheme 3. DG Removal in Reaction Product 4f and 5l



4f: R = OMe
5l: R = CF_3

79 % **6**: R = OMe
76 % **7**: R = CF_3

A Pd-catalyzed protocol for the direct remote C5-arylation of 3-aminopiperidine employing a picolinoylamino bidentate DG has been developed. The N1 PG turned out to be crucial to achieve arylation. Addition of catalytic acid and a high reaction concentration are beneficial for the conversion and yield. This new approach permits efficient access to *cis*-3,5-disubstituted piperidines in a direct, regiospecific and stereospecific fashion from commercial 1-Boc-3-aminopiperidine. The versatility of the new method has been successfully demonstrated on a diverse set of aryl iodides, which delivered the anticipated products in moderate to good yields. More challenging heteroaryl iodides could also be employed. The successful use of the chiral pool was shown by the direct C5-arylation of **(3*S*)-3f**. Finally, the utility of the reaction products was demonstrated by smooth orthogonal picolinamide cleavage which allows access to a variety of *cis*-3,5-disubstituted piperidine scaffolds.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b00841.

Experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra. Further details on reaction optimization, purification and obtained stereochemistry are provided (PDF).

AUTHOR INFORMATION

*E-mail: Bert.Maes@uantwerpen.be

The authors declare no competing financial interest.

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