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Palladium-Catalyzed Arylation of Endocyclic 1-Azaallyl Anions: Concise Synthesis of Unprotected Enantioenriched *cis*-2,3-Diarylpiperidines

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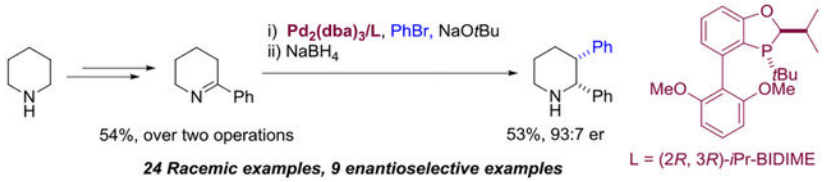
Abstract

Unprotected *cis*-2,3-diarylpiperidines are synthesized through an unprecedented palladium-catalyzed cross-coupling reaction between aryl halides and elusive endocyclic 1-azaallyl anions. These intermediates are generated *in situ* by the deprotonation of 2-aryl-1-piperideines, precursors that are readily prepared in two operations from simple piperidines. An asymmetric version of this reaction with (2*R*, 3*R*)-*i*Pr-BI-DIME as the ligand provides products in moderate to good yields and enantioselectivities. This study significantly expands the synthetic utility of endocyclic 1-azaallyl anions.

Graphical Abstract



Unprotected *cis*-2,3-diarylpiperidines are synthesized from readily available piperidines in only three operations. The key step is a palladium-catalyzed cross-coupling reaction between aryl halides and endocyclic 1-azallyl anions, elusive intermediates derived from the *in situ* deprotonation of 2-aryl-1-piperideines. This cross-coupling reaction can be achieved enantioselectively with a chiral mono-phosphine ligand.

Keywords

piperidines; endocyclic 1-azaallyl anions; endocyclic imines; arylation; palladium catalysis

3-Arylpiperidines are core structures found in various bioactive molecules (Figure 1).[1] However, the synthesis of piperidines containing aryl substituents at the 3-position remains

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challenging.[2–3] Known methods usually involve the de novo synthesis of piperidine rings from linear precursors,[4] or functional group transformations of piperidines already containing a substituent at the 3-position.[5] Catalytic hydrogenations of 3-arylpyridines[6] and direct C–H bond functionalizations of *N*-protected piperidines[7] have also been reported. The majority of these established methods utilize costly reagents, require lengthy syntheses of substrates, and ultimately provide *N*-protected products. In addition, enantioselective syntheses of 3-arylpiperidines remain scarce.[8] Here we report a new approach to the β-arylation of piperidines, along with an asymmetric variant.

In 2020, we reported a convenient one-pot procedure for the direct β-C–H bond functionalization of unprotected alicyclic amines, involving alkylation of endocyclic 1-azaallyl anions (metalloenamines).[9] Prior to our investigation, these elusive intermediates had rarely been studied in a synthetic context.[10] As summarized in Scheme 1a, endocyclic 1-azaallyl anions were generated by deprotonation of the corresponding imines with lithium diisopropylamide (LDA), followed by regioselective S_N2 reaction with alkyl halides, and then reduction. The imines themselves were obtained in situ by treatment of Li-amides with a ketone oxidant. This strategy enabled the synthesis of unprotected 3-alkyl-substituted alicyclic amines in a single operation. However, this method cannot directly be applied to the synthesis of 3-aryl-substituted azacycles. To expand the synthetic utility of endocyclic 1-azaallyl anions, we proposed employing these intermediates in transition metal-catalyzed cross-coupling reactions with aryl halides. The resulting 3-aryl-substituted endocyclic imines can then be readily converted to the corresponding amines. Related work involving acyclic 1-azaallyl anions has been reported by Barluenga and co-workers.[11] These researchers developed a palladium-catalyzed synthesis of indoles from *ortho*-dibromoarenes and acyclic 1-azaallyl anions generated *in situ* by the deprotonation of the corresponding imines (Scheme 1b). Subsequent studies on reactions with 1-azaallyl anions exclusively utilized acyclic variants, while the majority of transformations are annulations proceeding with concurrent functionalization of the nitrogen atom.[12] Our envisioned cross-coupling reaction with endocyclic 1-azaallyl anions is arguably significantly more challenging when compared with those of acyclic 1-azaallyl anions (Scheme 1c). While acyclic imines can be readily prepared by the condensation of carbonyl compounds and primary amines, there is a dearth of modular methods for the preparation of requisite endocyclic imine precursors containing various ring substituents. Further, due to the significant amount of ring strain experienced by medium-sized endocyclic 1-azaallyl anions,[13] these species may not be sufficiently stable under cross-coupling reaction conditions where high temperatures are often needed. The regioselectivity of the coupling step is another concern, since 1-azaallyl anions are ambident nucleophiles.

Our study commmenced with the development of a modular synthesis of 2-aryl-1-piperideines **1** (Scheme 2), motivated by the notion that a 2-aryl group can stabilize not only endocyclic 1-azaallyl anion intermediates, but the corresponding imine precursors as well. Requisite imines can thus be isolated and used as substrates in pure form, thus avoiding potential side reactions and simplifying reaction setup and development. Unprotected 2-arylpiperidines were first prepared in a single operation from readily available piperidines utilizing our previously reported method for the facile α-C–H

bond functionalization of unprotected cyclic amines using simple ketones to oxidize *N*-lithiated cyclic amines to imines.[14–16] Subsequent *N*-chlorination of unprotected 2-arylpiperidines with *N*-chlorosuccinimide (NCS) and regioselective dehydrohalogenation with potassium hydroxide provided 2-aryl-1-piperideines in overall acceptable yields.[17] An initial test of the cross-coupling reaction between 2-phenyl-1-piperideine and chlorobenzene (PhCl) employed sodium *tert*-butoxide (NaO*t*Bu) as the base, tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$) as the catalyst and XPhos as the ligand in 1,4-dioxane at 50 °C. Gratifyingly, *cis*-2,3-diphenylpiperidine (±)-**2a** was obtained in 44% yield after diastereoselective reduction of initially formed 2,3-diphenyl-1-piperideine. However, bis-arylation product **3** was identified as the major product (Table 1, entry 1). Shortening the reaction time from 6 to 3 hours led to an increased yield of (±)-**2a**, while simultaneously reducing the amount of **3** (Table 1, entry 2). Weaker bases such as K_3PO_4 and Cs_2CO_3 failed to promote the reaction (Table 1, entries 3–4), likely due to inefficient formation of the 1-azaallyl anion intermediate. A variety of phosphine ligands were evaluated next (Table 1, entries 5–14). Most Buchwald-type ligands[18] tested provided the desired product (±)-**2a**, but offered no improvements over XPhos. Several bidentate phosphine ligands failed to provide observable amounts of product. A decreased yield of (±)-**2a** was obtained from a reaction performed in a 1:1 mixture of 1,4-dioxane and toluene (Table 1, entry 15). Considering that the formation of one equivalent of **3** consumes two equivalents of PhCl, conditions were evaluated where PhCl was used as the limiting reagent in an effort to improve the ratio of (±)-**2a** to **3**. Interestingly, when PhCl was used as the limiting reagent and the reaction performed in a 1:1 mixture of 1,4-dioxane and toluene, the yield of the desired product increased compared with the reaction in neat 1,4-dioxane, and, as we anticipated, the amount of bis-arylation product **3** dramatically decreased (Table 1, entries 16–17). These results indicate that the first coupling reaction occurs regioselectively at the C-terminus of the endocyclic 1-azaallyl anion intermediate, pior to the second coupling reaction at the nitrogen atom. Extension of the reaction time to 4 hours and the addition of 4 Å molecular sieves further improved the yield of the desired product (±)-**2a** (Table 1, entries 18–20).

The substrate scope of the arylation was then explored (Scheme 3). Chloroarenes and chloroalkenes readily underwent reactions with endocyclic 1-azaallyl anions generated *in situ* by the deprotonation of various 2-aryl-1-piperideines. Following reduction, unprotected *cis*-2,3-diarylpiperidines were obtained in generally moderate to good yields and excellent diastereoselectivities. Readily separable bis-arylation side products were observed in most cases. To suppress the formation of these undesired materials and to improve the yields of product **2**, increased amounts of imines and base were utilized for some substrates. Reactions employing 3-chloropyridine and quinoline were performed at room temprature, since these electrophiles were more reactive than chlorobenzenes and chloroalkenes. Due to the presence of a vicinal aryl group, this reaction was sensitive to sterics. Sterically congested substrates usually gave unsatisfactory reaction outcomes. For the reduction step, the hydride attacked intermediate 2,3-diaryl-1-piperideines from the opposite face of the 3-aryl groups to avoid steric hindrance and form 2,3-*cis* products, however, the diastereoselectivity of this step was also influenced by additional ring-substituents in the substrates (products (±)-**2u**–**2x**). Moreover, the triisopropylsilyloxy (TIPSO) group might

also act as a directing group for the imine reduction forming 2,6-*trans* product (±)-**2v**. Endocyclic 2-aryl imine precursors derived from alicyclic amines with other ring sizes were also examined, but unfortunately failed to provide desired products. Parent 1-piperideine lacking 2-substitution is prone to trimerize and cannot be isolated in the form of monomer.[19] The trimer, however, was found to be unreactive under typical conditions. 1-Piperideines with 2-alkyl substituents were also evaluated briefly. However, deprotonation of these substrates is known to occur selectively at the exocyclic *α*-position to form exocyclic 1-azaallyl anions due to reduced ring strain compared to their endocyclic counterparts.[13] The cross-coupling reaction between an exocyclic 1-azaallyl anion and chlorobenzene gave a product corresponding to *N*-phenylation.[20]

We next sought to develop an asymmetric version of the title reaction (Scheme 4).[21] Enantioenriched unprotected *cis*-2,3-diarylpiperidines were obtained in moderate to good yields and enantioselectivities when (2*R*, 3*R*)-*i*Pr-BI-DIME[22] was used as the ligand in place of XPhos. It was found that the replacement of chloroarenes with bromoarenes, and a reduction in the amount of NaO*t*Bu from 2 equivalents to 1.5 equivalents provided superior enantioselectivities. The BI-DIME ligand exhibited lower reactivity than XPhos. Thus, 2 equivalents of imines were needed to improve yields, although this led to slightly reduced enantiomeric ratios as illustrated in the synthesis of (2*R*, 3*R*)-**2a** and (2*R*, 3*R*)-**2d**. As indicated by the results, base-catalyzed racemization of intermediate 2,3-diaryl-1-piperideines might take place to only a minor extent. Whereas considering the formation of small amounts of the bis-arylation side products were observed for the enantioselective reactions as well, it cannot rule out the possibility that deprotonated 2,3-diaryl-1-piperideines undergo a second *N*-arylation via the intermediacy of enamines. In this scenario, the base-catalyzed isomerization led to decreased yields rather than enantiopurities of the desired products.

Cis-2,3-diarylpiperidine products obtained from the Pd-catalyzed arylation of endocyclic 1-azaallyl anions could be further functionalized regioselectively at the *α'*-position. For example, *α'*-phenylation of (±)-**2a** with phenyl lithium as the nucleophile provided compound (±)-**4** in 59% yield (Scheme 5, eq 1), and Lewis acid promoted *α'*-benzylation of (±)-**2a** with benzyl Grignard reagent gave (±)-**5** in 47% yield (Scheme 5, eq 2). Excellent diastereoselectivities were observed for both transformations. It is noteworthy that product (±)-**4** could not be obtained through 3-arylation of 2,6-diphenyl-1-piperideine. The situation is identical for product (±)-**5**. While the reasons for this are not entirely clear, one possible explanation might be a reduced nucleophilicity of the corresponding 1-azaallyl anion intermediates. The late-stage *α'*-functionalization of *cis*-2,3-diarylpiperidines thus provides an alternative method to access compounds such as (±)-**4** and (±)-**5**. Another example for the modification of the arylation product is the regioselective decarboxylative alkylation with *β*-ketoacid **7**, which provided compound (±)-**6** in 45% yield and also with excellent diastereoselectivity (Scheme 5, eq 3).

In conclusion, we have developed an unprecedented Pd-catalyzed cross-coupling reaction between aryl halides and endocyclic 1-azaallyl anions generated *in situ* by the deprotonation of readily prepared 2-aryl-1-piperideines. Unprotected enantioenriched *cis*-2,3-diarylpiperidines were obtained through a concise sequence of reactions from

cheap commercially available piperidines. Further expansion of the substrate scope and the improvement of enantioselectivities are the subject of ongoing studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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[20]. See the Supporting Information for details.

[21]. See the Supporting Information for a more detailed evaluation of the reaction conditions.

[22]. a)Tang W, Patel ND, Xu G, Xu X, Savoie J, Ma S, Hao M-H, Keshipeddy S, Capacci AG, Wei X, Zhang Y, Gao JJ, Li W, Rodriguez S, Lu BZ, Yee NK, Senanayake CH, Org. Lett 2012, 14, 2258; [PubMed: 22497425] b)Xu G, Fu W, Liu G, Senanayake CH, Tang W, J. Am. Chem. Soc 2014, 136, 570; [PubMed: 24147559] c)Li C, Chen D, Tang W, Synlett 2016, 27, 2183;d)Xu G, Senanayake CH, Tang W, Acc. Chem. Res 2019, 52, 1101. [PubMed: 30848882]

[23]. Deposition number 2261423 (for *p*-bromobenzenesulfonyl-protected (*2R*, *3R*)-**2a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

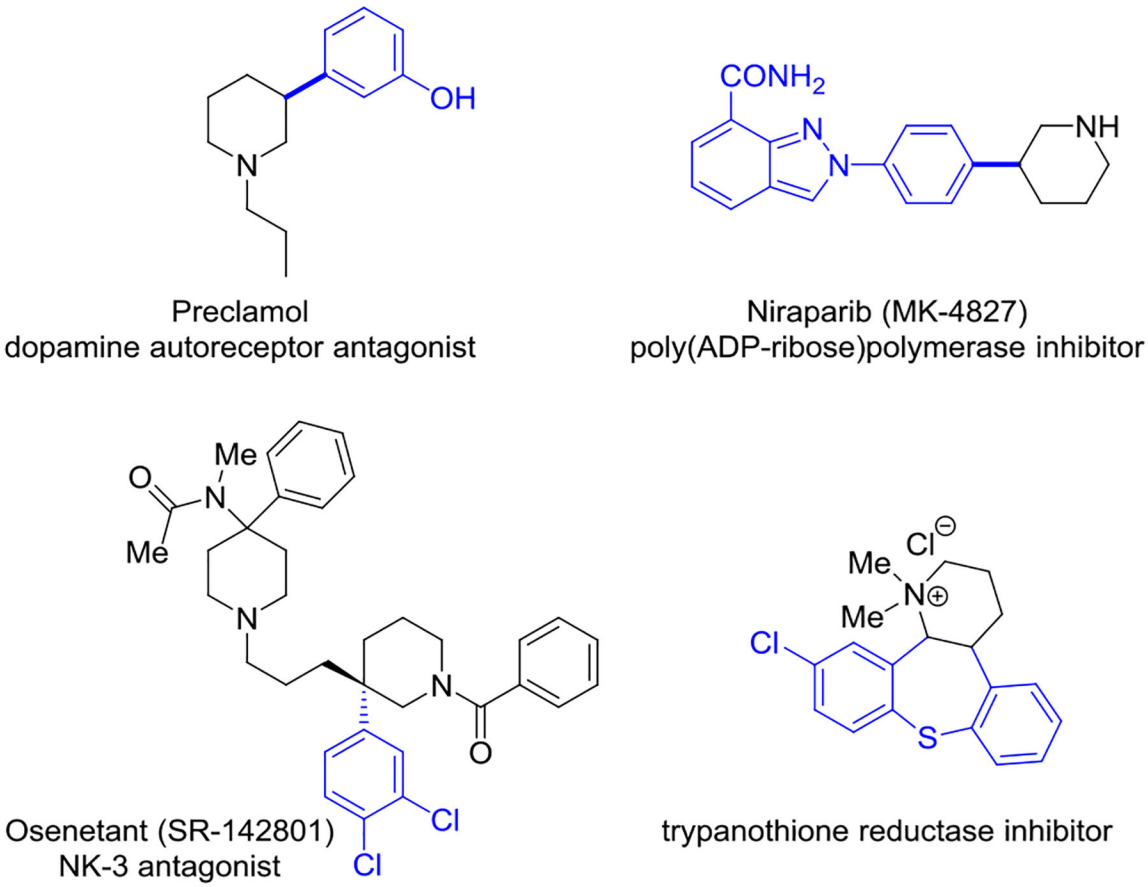
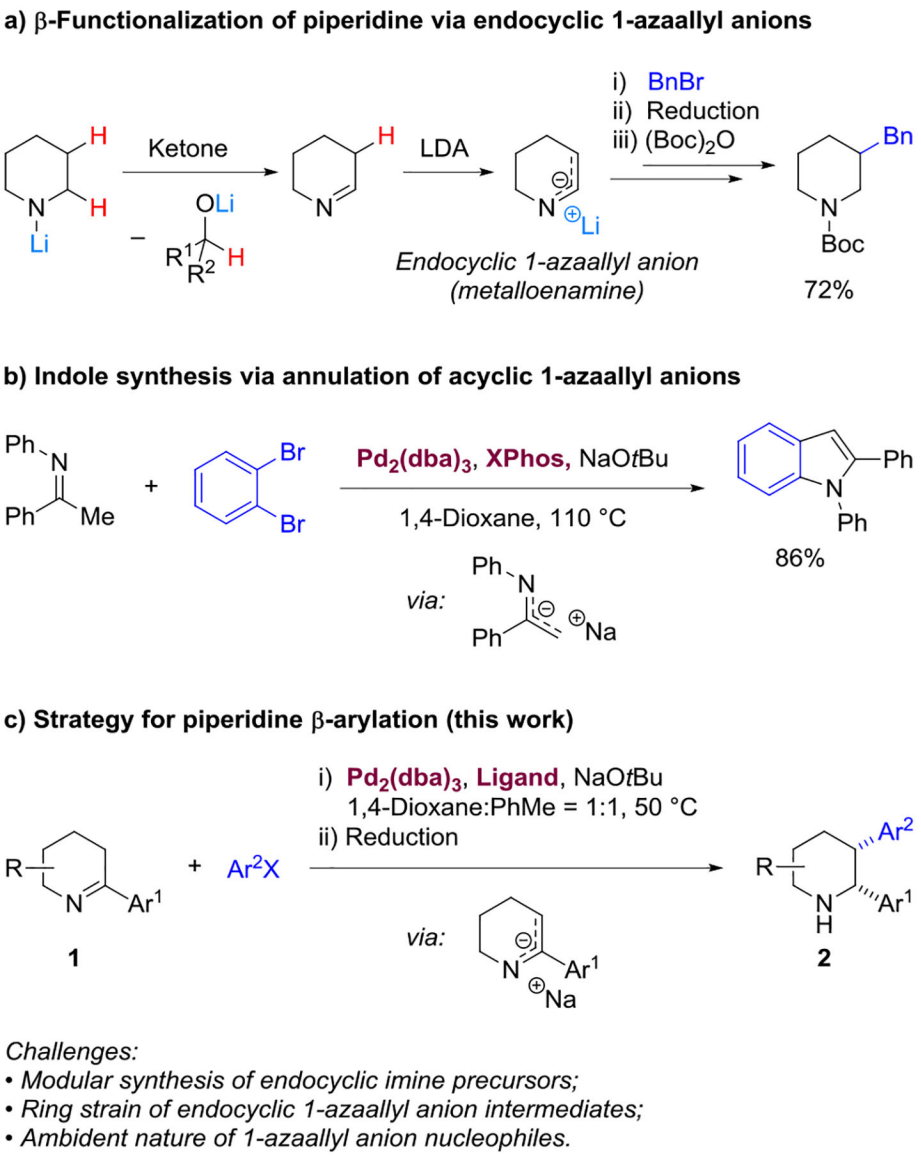
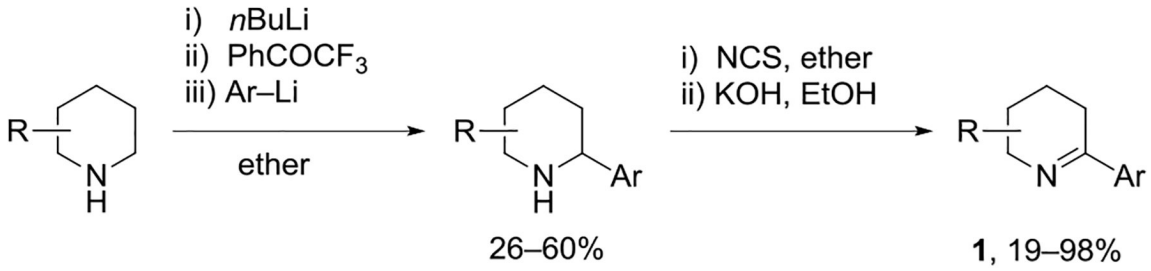


Figure 1.
Representative bioactive molecules containing 3-arylpiperidine core structures.

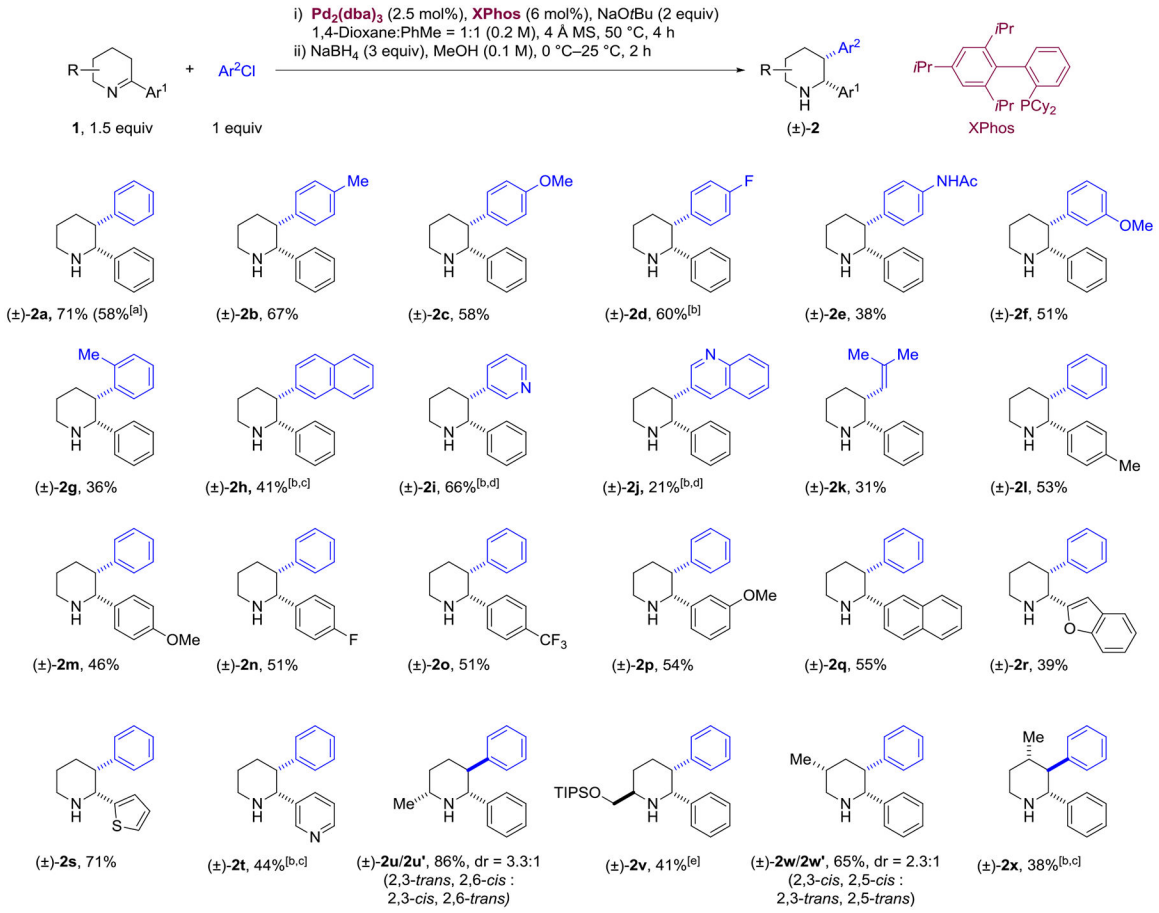


Scheme 1.

Proposed synthesis of unprotected *cis*-2,3-diarylpiperidines through Pd-catalyzed cross-coupling of endocyclic 1-azaallyl anions and aryl halides and relevant precedent.

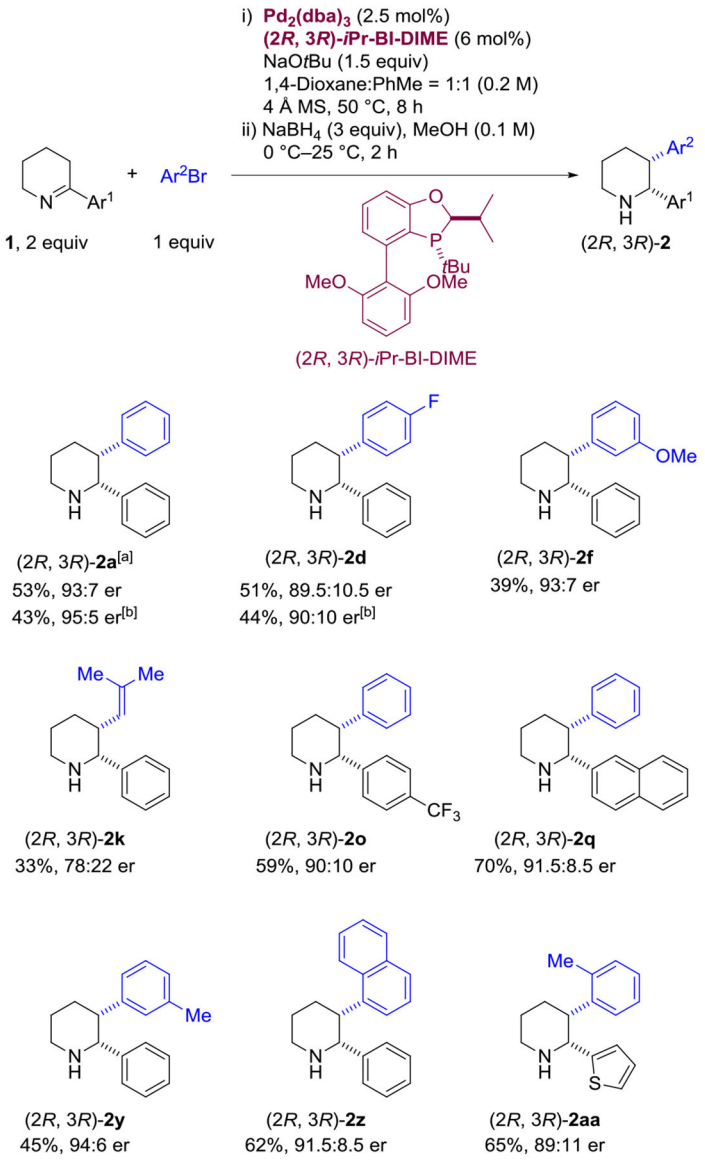


Scheme 2.
Modular synthesis of 2-aryl-1-piperideines.



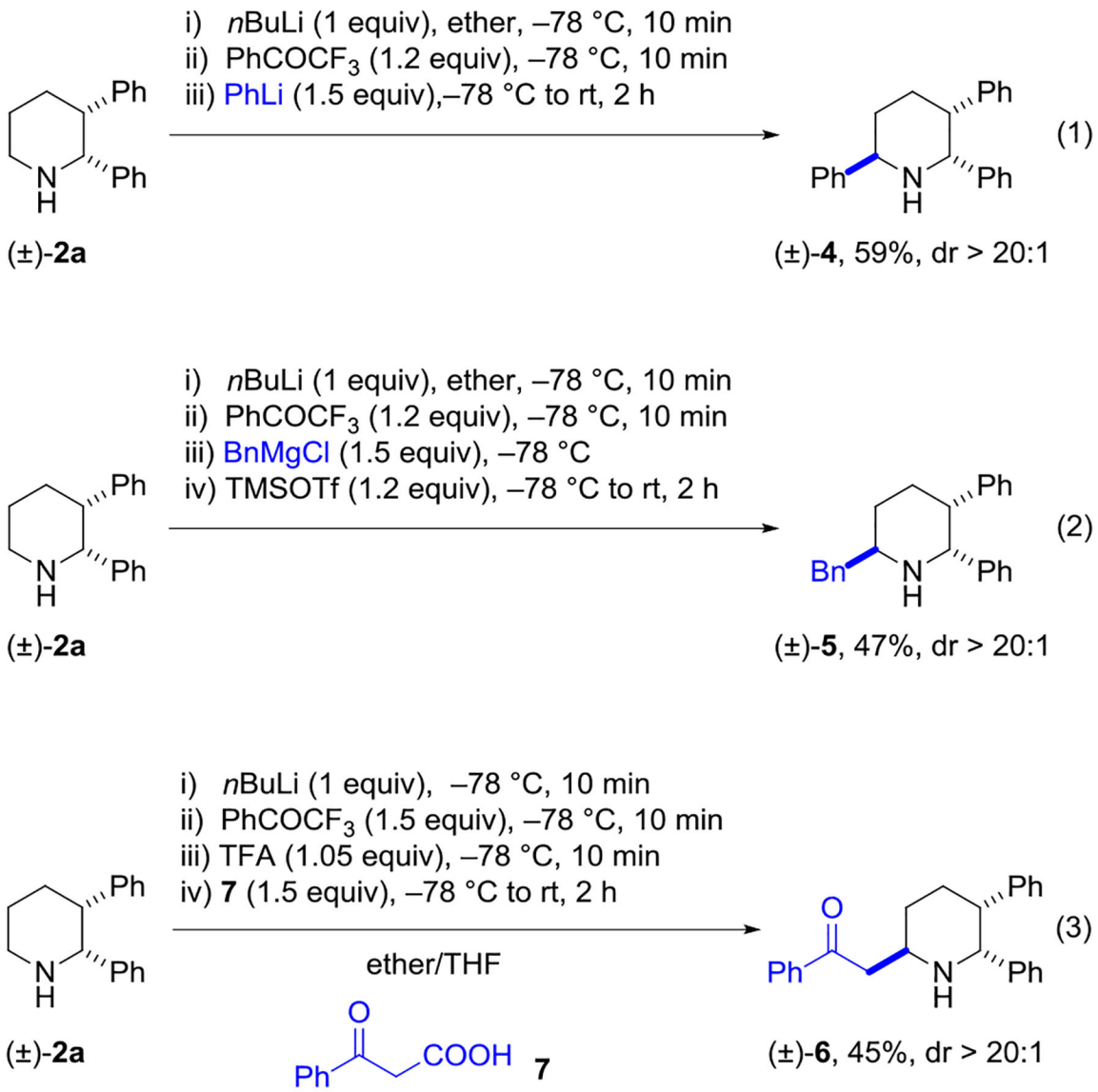
Scheme 3.

Substrate scope for Pd-catalyzed arylation of endocyclic 1-azaallyl anions forming unprotected *cis*-2,3-diarylpiperidines. Reactions were performed on a 0.2 mmol scale. Yields correspond to isolated yields of products. Diastereomeric ratios are >20:1 unless otherwise specified. [a] The reaction was performed on a 2 mmol scale. [b] Imines were used in 2 equiv. [c] NaO*t*Bu was used in 4 equiv. [d] Reactions were performed at 25 °C. [e] The imine was used as the limiting reagent, and PhCl was used in 2 equiv.



Scheme 4.

Pd-Catalyzed enantioselective arylation of endocyclic 1-azaallyl anions forming unprotected enantioenriched *cis*-2,3-diarylpiperidines. Reactions were performed on a 0.2 mmol scale. Yields correspond to isolated yields of the unprotected products, and enantiomeric ratios were determined with Boc-protected (2*R*, 3*R*)-**2**. Diastereomeric ratios are >20:1 for all substrates. [a] The absolute configuration was determined by X-ray diffraction of *p*-bromobenzenesulfonyl-protected product. [b] 1.5 Equiv of the imine was used.

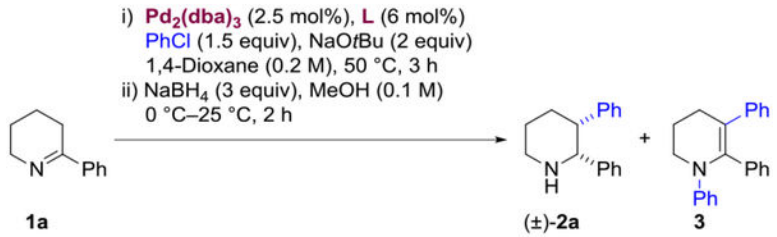


Scheme 5.

α'-C–H bond functionalization of (±)-*cis*-2,3-diphenylpiperidine.

Table 1.

Evaluation of reaction conditions for Pd-catalyzed arylation of 2-phenyl-1-piperideine forming *cis*-2,3-diphenylpiperidine.[a]



Entry	Ligand[b]	Yield of (±)-2a (%)	Yield of 3 (%)[c]
1[d]	XPhos	44	68
2	XPhos	54	60
3[e]	XPhos	NR	NR
4[f]	XPhos	NR	NR
5	Ph-XPhos	29	ND
6	*t*Bu-XPhos	Trace	Trace
7	RuPhos	35	ND
8	SPhos	36	ND
9	Cy-JohnPhos	12	ND
10	PCy_3	Trace	Trace
11	(±)-BINAP	NR	NR
12	dppf	NR	NR
13	XantPhos	NR	NR
14	dppe	NR	NR
15[g]	XPhos	21	61
16[h]	XPhos	55	30
17[g,h]	XPhos	59	32
18[g,h,i]	XPhos	64	ND
19[g,h,j]	XPhos	56	ND
20[g,h,i,k]	XPhos	71	28

[a] Reactions were performed on a 0.2 mmol scale. Yields correspond to isolated yields of products. Diastereomeric ratio (dr) of (±)-**2a** is >20:1 for all entries. NR: no reaction. ND: not determined.

[b] See the Supporting Information for the chemical structures of the ligands.

[c] The yield of **3** is calculated based on the fact that two equivalents of PhCl are needed to form one equivalent of **3**.

[d] The reaction time was 6 hours.

[e] K_3PO_4 was used as the base.

[f] Cs_2CO_3 was used as the base.

[g] A mixture of 1,4-dioxane and toluene (1:1) was used as the solvent.

[h] PhCl was used as the limiting reagent and the imine was used in 1.5 equiv.

[i] The reaction time was 4 hours.

[j] The reaction time was 5 hours.

[k] 4 Å molecular sieves (50 mg) was added.