Palladium–catalysed transannular C–H functionalization of alicyclic amines

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Discovering pharmaceutical candidates is a resource-intensive enterprise that frequently requires the parallel synthesis of hundreds or even thousands of molecules. C–H bonds are present in almost all pharmaceutical agents. Consequently, the development of selective, rapid and efficient methods for converting these bonds into new chemical entities has the potential to streamline pharmaceutical development1–4. Saturated nitrogen-containing heterocycles (alicyclic amines) feature prominently in pharmaceuticals, such as treatments for depression (paroxetine, amitifadine), diabetes (gliclazide), leukaemia (alvocidib), schizophrenia (risperidone, belaperidone), malaria (mefloquine) and nicotine addiction (cytisine, varenicline)5. However, existing methods for the C–H functionalization of saturated nitrogen heterocycles, particularly at sites remote to nitrogen, remain extremely limited6,7. Here we report a transannular approach to selectively manipulate the C–H bonds of alicyclic amines at sites remote to nitrogen. Our reaction uses the boat conformation of the substrates to achieve palladium-catalysed amine-directed conversion of C–H bonds to C–C bonds on various alicyclic amine scaffolds. We demonstrate this approach by synthesizing new derivatives of several bioactive molecules, including varenicline.

Despite the ubiquity of alicyclic amines, there are very few methods available for the late-stage functionalization of these structures. Late-stage functionalization approaches are particularly valuable in the context of drug development, because they enable the rapid synthesis of analogues to optimize pharmacokinetic properties. Functionalization of C–H bonds using transition-metal catalysis offers a powerful approach for the late-stage functionalization of bioactive molecules1–4, and recent progress in this field has led to thousands of new synthetic methods for selective C–H functionalization in a variety of molecular contexts2–4,8,9. However, methods for the C–H functionalization of saturated nitrogen heterocycles remain extremely limited6,7, and are dominated by functionalization of the highly activated C–H bonds α to nitrogen10–14 (Fig. 1b, left) or of C–H bonds on exocyclic alkyl groups15,16 (Fig. 1b, right). By contrast, here we describe an approach for achieving the C–H functionalization of alicyclic amine cores at sites remote from nitrogen (Fig. 1c) via nitrogen–directed transannular C–H activation.

We envisioned that coordination of the nitrogen of an alicyclic amine such as piperidine to palladium could enable selective transannular amine-directed conversion of C–H bonds to C–C bonds on various alicyclic amine scaffolds. We demonstrate this approach by synthesizing new derivatives of several bioactive molecules, including varenicline.

Figure 1 | Relevance of alicyclic amines and strategies for their late-stage functionalization. a. Representative pharmaceutical agents containing alicyclic amines. b. Previous synthetic approaches for the late-stage functionalization of alicyclic amines. R, R1, generic substituents; FG, functional group. c. Proposed approach for late-stage transannular C–H functionalization of alicyclic amines.
required boat conformation, (2) the requirement for cleavage of an unactivated secondary C(sp²)–H bond and (3) the potential susceptibility of the basic amine towards α-oxidation or N-oxidation. With these considerations in mind, we initially selected 3-azabicyclo[3.1.0]hexane (2) as a test substrate (Fig. 2b). We anticipated that the bicyclic core of 2 would prearrange it in a boat-like conformation and that the high s character of the cyclopropyl C–H bonds should lower the barrier for C–H activation relative to a typical secondary C(sp³)–H site.

The palladium (Pd)-catalysed reaction of 2 with 4-iodobiphenyl provided only traces of C–H arylated products under a variety of conditions. However, when a second coordinating group (an amide derived from a p-CF₃C₆F₄ aniline; Fig. 2c, 3) was appended to nitrogen, the reaction afforded 4a in modest to excellent yield. No products derived from C–H functionalization of the methyl groups of the fluoroamide directing group were observed in this reaction. This finding is in marked contrast to other reported applications of this directing group, in which C–H functionalization at β-methyl sites is strongly favoured and complementarity of our approach that uses bidentate coordination of a sp³-hybridized nitrogen of an alicyclic amine substrate along with the fluoroamide to achieve selectivity (that is, transannular secondary C(sp³)–H functionalization).

The use of 10 mol% of Pd(OAc)₂ (Ac = acetate) and 1 equivalent of AgOAc (an additive commonly used to promote C–H arylation) provided 17% of 4a (Fig. 2c, entry 1). The modest yield of 4a under these conditions is due to competing formation of aminal 5, which is thought to arise from α-oxidation of 3 to the corresponding iminium followed by intramolecular trapping with the amide nitrogen. The Ag additive mediates this transformation, and aminal 5 was obtained in 41% yield in the absence of Pd (Fig. 2c, entry 4). The role of the Ag carboxylate salt in these transformations is to regenerate the Pd carboxylate catalyst by abstraction of iodide from the Pd centre. As such, we hypothesized that the Ag salt could be replaced by a non-oxidizing metal carboxylate. A survey of alkali metal pivalate salts revealed that CsO(Piv = pivalate) delivers the arylated product 4a while suppressing the formation of aminal 5 (Fig. 2c, entry 8). Under the optimal conditions, 4a was obtained in 92% yield as a single detectable stereoisomer (Fig. 2c, entry 12). X-ray crystallographic characterization of 4a confirmed that the aryl group is installed on the concave face of the azabicycle (Fig. 3a).

This transannular C–H arylation reaction proceeds in high yield with aryl iodides bearing electron-donating, electron-neutral and electron-withdrawing substituents (products 4a–h, Fig. 3a). Many traditionally sensitive functional groups are compatible with this system, including aryl bromides, unprotected phenols and aromatic aldehydes (products 4f–h). Both electron-deficient and electron-rich nitrogen heterocycles can be installed (products 4i and 4j). Furthermore, a derivative of the amino acid phenylalanine can be coupled to the bicyclo[3.1.0] scaffold (product 4k). Aryl bromides could also be used as the arylating reagent, albeit with reduced efficiency; for example, the
Figure 3 | Transannular C–H arylation of 3-azabicyclo[3.1.0]hexane core. a, Scope of C–H arylation with respect to the aryl iodide. Top, reaction studied; bottom, isolated products. Reaction to give 4c with PhBr was conducted using 20 equiv. of PhBr; yield determined by gas chromatography. Reaction to give 4j was conducted under modified conditions.

b, Relevant steps in overall transformation: installation of directing group, C–H arylation and SmI₂-mediated removal of directing group (Aryl = biphenyl). PivCl, pivaloyl chloride; TEA, triethylamine.

c, C–H arylation applied to amitifadine. Top left, structure of amitifadine; top right, reaction studied; bottom, isolated products. All yields are reported for pure isolated material. See Supplementary Information for full details.

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The directing group can be removed in high yield via reductive cleavage with samarium diiodide (SmI₂). A 52% overall yield is obtained for the three relevant steps involved in converting 2 to 6 (81% for installation of the directing group, 80% for C–H arylation with 4-iodobiphenyl and 80% for removal of the directing group; Fig. 3b).

A particularly useful application of this method is in the late-stage derivatization of bioactive molecules. Selective C–H functionalization reactions on complex molecular scaffolds provide valuable opportunities for streamlining analogue generation and thereby accelerating structure–activity relationship studies 4,8. The bicyclo[3.1.0] scaffold appears in numerous pharmaceutical candidates, including the serotonin–noradrenaline–dopamine reuptake inhibitor amitifadine (7) 26,27.

**Figure 4 | Transannular C–H arylation of alicyclic amines.** a, Scope of the C–H arylation reaction with respect to the amine. Top, reaction studied; bottom, isolated products. b, Application of this reaction to the derivatization of varenicline. Top left, structure of varenicline; top right, reaction studied; bottom, structure of varenicline derivatives. Reaction to give 14d was conducted under modified conditions. c, Application of this reaction to the derivatization of cytisine. Left, structure of cytisine (15); right, reaction studied. Yields are reported for pure isolated products. See Supplementary Information for full details.

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As shown in Fig. 2c, appending our directing group to 7 enables transannular C–H arylation to deliver the new amidofadine derivatives 9a–d. We next sought to expand this reaction from model substrate 3 to piperidine 10 (Fig. 2a). A thermodynamically unfavourable chair–boat isomerization of the piperidine ring in 10 is required before C–H activation (Fig. 2a) and is expected to add at least 6 kcal mol−1 to the activation barrier relative to substrate 3 (ref. 28). Under the conditions optimized for 3, the piperidine substrate 10 afforded only 12% yield of the C–H arylation product 11a. However, increasing the temperature and removing the solvent led to a substantially improved 44% yield of 11a (Fig. 4a). Amines derived from starting material 10 and product 11a were formed as side products of this reaction (see Supplementary Fig. 2 for full details), but the reaction mixture could be cleanly converted to a mixture of starting material 10 and product 11a via treatment with NaBH₄. Using this work-up procedure, product 11a was isolated in 55% yield (Fig. 4a). Analogous conditions enabled the transannular C–H arylation of a variety of alicyclic amine derivatives, affording products of mono- or diaryl (11b–i; Fig. 4a). The structures of 11b–i were established via a combination of NMR spectroscopy and X-ray crystallography.

Although the yields of 11b–i are moderate in some cases, the de novo synthesis of many of these products would be challenging using traditional synthetic routes. The utility of this transformation is demonstrated in the late-stage C–H arylation of varenicline (12, Fig. 4b), a drug used to treat nicotine addiction. The fluoroamide group was appended to 12 to afford 13 in 81% yield. Under our standard C–H arylation conditions, 13 underwent transannular C–H arylation with a variety of aryl iodides to afford 14a–e. The structure of 14a was assigned by X-ray crystallography (Fig. 4b), which confirms that the aryl group is installed in an axial orientation. This point is particularly noteworthy because the synthesis of this stereoisomer would be challenging using other synthetic approaches29. The C–H arylation of 13 with 4-iodo-o-xylene was conducted using 77 mg and 2.5 g of substrate, with nearly identical yields of 14e (43% and 38% isolated yield, respectively). On the basis of the established synthesis of varenicline, an independent synthesis of these analogues by more traditional methods would require parallel multistep sequences30. In a similar fashion, our method proved effective for the late-stage C–H functionalization of the natural product cytisine (15, a treatment for nicotine addiction), converting 16 to 17 in 25% yield (Fig. 4c). Again, the aryl group is selectively installed at the axial position in this transformation.

We have reported the transannular C–H arylation of a variety of alicyclic amines. The reaction exhibits high functional-group tolerance and enables the synthesis of new amino-acid derivatives (4k) as well as analogues of the pharmaceutical candidate amidofadine (9a–d), the drug varenicline (14a–e) and the natural product cytisine (17). We anticipate that a similar approach will ultimately be useful for the remote C–H functionalization of diverse cyclic and acyclic secondary amine scaffolds.

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